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(54) Title: METHOD FOR PREPARING OREGANIC ACID

(54) Título: PROCEDIMIENTO PARA LA PREPARACIÓN DE ÁCIDO OREGÁNICO

(57) Abstract: The invention relates to a method for obtaining oreganic acid and derivatives thereof, to the intermediate compounds of this synthesis and to the use of said compounds in the preparation of oreganic acid and derivatives thereof.

(57) Resumen: La presente invención se dirige a un procedimiento para la obtención de ácido Oregánico y derivados del mismo, a los compuestos intermedios de esta síntesis y al uso de estos compuestos en la preparación de ácido Oregánico y derivados del mismo.



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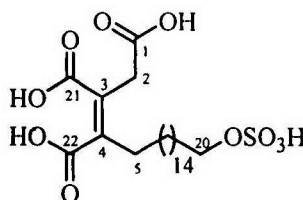
## PROCESS FOR PREPARING OREGANIC ACID

### Field of the Invention

The present invention relates to a new process for the synthesis of oreganic acid and derivatives thereof, to the intermediate compounds of the synthesis and to the use of these compounds in the preparation of oreganic acid and their derivatives.

### State of the Art

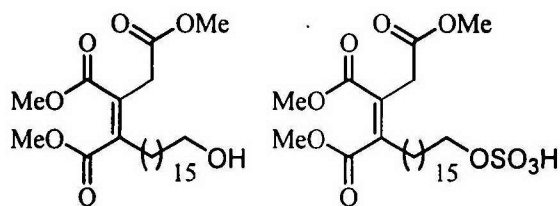
The compound (Z)-3,4-dicarboxy-20-sulfooxy-3-eicosenoic acid, also known as oreganic acid, of formula 1-Z



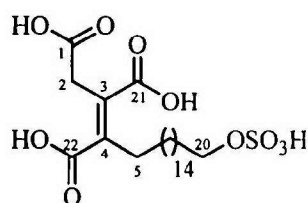
1-Z

is a natural product belonging to the family of alkyl citrates and having a Ras FTase inhibitory activity. The inhibition of the farnesylation process of Ras proteins is considered as an effective mechanism for controlling the growth of tumors promoted by mutated Ras proteins, since said inhibition prevents mutated Ras proteins from being introduced in the cell membrane and being activated, not being able to carry out their biological activity. For a study of the biological activity of oreganic acid see: Silverman, K. C.; Jayasuriya, H.; Cascales, C.; Vilella, D.; Bills, G. F.; Jenkins, R. G.; Singh, S. B.; Lingham, R. B. *Biochem. Biophys. Res. Commun.* **1997**, *232*, 478-481.

Oreganic acid was isolated by Dr. Jayasuriya's group in the year 1996 from an unidentified endophytic fungus (MF 6046), isolated from living leaves of *Berberis oregana* (Berberidaceae) leaves in Lord Ellis Summit, Humboldt Co. California, USA. For the purpose of elucidating the structure of oreganic acid, the trimethylated ester derivative and their corresponding desulfated derivative were prepared.



However, when elucidating their structure, E isomerism was incorrectly assigned to it (see Jayasuriya, H.; Bills, G. F.; Cascales, C.; Zink, D. L.; Goetz, M. A.; Jenkins, R. G.; Silverman, K. C.; Lingham, R. B.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2081-2084)



1-E (incorrect isomerism)

Subsequently, Dr. Gibbs' group represented oreganic acid with a Z (correct) geometry in the tetrasubstituted double bond between the C3-C4 positions (Gibbs, R. A.; Zahn, T. J.; Sebolt-Leopold, J. S. *Curr. Med. Chem.* **2001**, *8*, 1437-1465). Nevertheless, data justifying that the configurational assignment was correct were not provided.

No total synthesis of oreganic acid has been described up until now. In this context, it would be convenient to provide a process for obtaining oreganic acid, which preferably meets the following characteristics:

- using a small number of protecting groups;
- feasible and inexpensive commercial starting substrates;
- a reasonable number of steps;
- non-sophisticated experimental processes; or
- a good final yield.

#### Brief Description of the Invention

The authors of the invention have prepared the first total synthesis described to date of oreganic acid and derivatives thereof. Said synthesis uses simple starting substrates, involves a reasonable number of steps, needs few protecting groups and does not comprises complex transformations. Therefore, it allows obtaining oreganic acid with a good yield, and following conditions which would enable the synthesis at

a large scale and in a short time.

Therefore, a first aspect of the invention relates to a process for obtaining a compound of formula (VIII), an intermediate of organic acid and their derivatives, which already comprises the final backbone of the molecule, which comprises  
5     subjecting a compound of formula (VI) or (VII) to a hydrogenation reaction; or  
   deprotecting the trialkylsilyl group of a compound of formula (XVI).

Additional aspects of the invention are said compounds of formula (VI), (VII) and (XVI), their stereoisomers, or mixtures thereof, intermediates of the synthesis, and processes for obtaining them.

10     An additional aspect of the present invention relates to a process for obtaining compounds of formula (I), their stereoisomers, or mixtures thereof, from compounds of formula (VI), (VII) or (XVI), their stereoisomers, or mixtures thereof through compounds of formula (VIII), their stereoisomers, or mixtures thereof.

15     Additional aspects of the invention relate to compounds of formula (I), (IV), (V), (VI), (VII), (VIII), (IX), (XV), (XVI) and (XVIII) defined herein.

20     Another aspect of the invention corresponds to the use of at least one compound selected from the compounds of formula (II), (III), (IV), (V), (VI), (VII), (VIII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVIII) and (XXIV), their stereoisomers, or mixtures thereof, for the synthesis of compounds of formula (I), their stereoisomers, or mixtures thereof.

#### Detailed Description of the Invention

##### Definitions

25     For the purpose of facilitating the understanding of the present invention, the meanings of several terms and expressions as they are used in the context of the invention are herein included below.

30     "Alkyl" refers to a radical with a hydrocarbon chain which consists of carbon and hydrogen atoms, which does not contain unsaturations and which is attached to the rest of the molecule by means of a single bond. The number of carbon atoms of the alkyl group is specified in each case. For example, when "C<sub>1</sub>-C<sub>4</sub> alkyl" is indicated, it refers to an alkyl group of one, two, three or four carbon atoms, i.e., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl or tert-butyl.

"Aryl" refers to an aromatic substituent, preferably C<sub>6</sub>-C<sub>18</sub>, more preferably C<sub>6</sub>-C<sub>14</sub>, more preferably C<sub>6</sub>-C<sub>10</sub>, which comprises a simple aromatic ring or multiple fused rings in which at least one of them is aromatic. Preferred aryl groups are phenyl or naphthyl, preferably phenyl.

5 "Halogen" means -F, -Cl, -Br or -I.

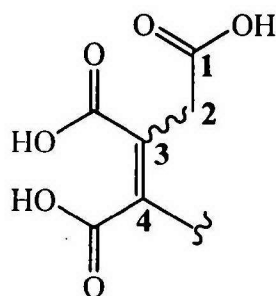
"Trialkylsilyl" is understood as a radical of formula -Si(R')(R'')R''', wherein each of R', R'' and R''' are independently selected from among a phenyl group and a C<sub>1</sub>-C<sub>6</sub> alkyl group. Non-limiting examples of trialkylsilyl groups can be trimethylsilyl, triethylsilyl, tri-*iso*-propylsilyl; dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl.

"Bn" means benzyl (-(CH<sub>2</sub>)-phenyl).

"Leaving group" is an atom or group of atoms activating the carbon to which they are attached against a nucleophilic reagent, such that said nucleophile, or part of said nucleophile, is attached to the molecule and the leaving group is detached therefrom. Leaving groups are known by the person skilled in the art, for example, OTs (tosyl), OMs (mesyl) or halogen.

The references of the present document to substituted groups in the compounds of the present invention refer to the specified moiety which can be substituted in one, two or three available positions with one, two, three suitable groups, which are independently selected from the group consisting of cyano; alkanoyl, such as a C<sub>1</sub>-C<sub>6</sub> alkanoyl group, such as acyl and the like; carboxamido (-(C=O)NH<sub>2</sub>); trialkylsilyl. As a non-limiting example, "substituted alkyl" includes groups such as cyanoethyl, acetylmethyl, carboxamidomethyl (-(CH<sub>2</sub>CONH<sub>2</sub>), 2-trimethylsilylethyl.

25 Throughout the present invention, when positions of the different compounds are mentioned, the numbering followed is:



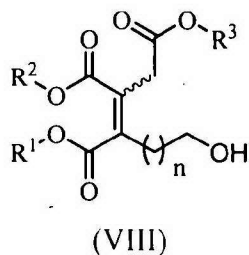
The chain attached to the carbon of position 4 will be referred to as "side chain". As will be discussed below, all the compounds of the present invention containing a double bond between the C3-C4 positions can have said double bond with a *Z* configuration, with an *E* configuration or can be found as mixtures of *Z/E* isomers. The present invention includes said stereoisomers or mixtures thereof, all of them being useful in the synthesis of compounds of formula (I). One of the substituents of said double bond attached by means of a "wavy" bond  $\sim$ , to highlight this possibility.

Unless otherwise indicated, the compounds of the invention also refer to those including compounds which differ only in the presence of one or more isotopically enriched atoms. For example, the compounds having the present structures, with the exception of the substitution of a hydrogen with a deuterium or with tritium, or the substitution of a carbon with a  $^{13}\text{C}$ - or  $^{14}\text{C}$ -enriched carbon, are within the scope of this invention.

The reaction products obtained can be purified, if desired, by means of conventional methods, such as crystallization, chromatography and trituration.

### Synthesis

According to a first aspect, the present invention relates to a process for obtaining a compound of formula (VIII), its stereoisomers or mixtures thereof



wherein

$\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$  are independently selected from substituted or unsubstituted

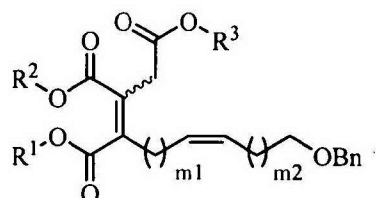
$C_1$ - $C_{20}$  alkyl; and

$n$  is an integer between 2 and 20;

characterized in that it comprises at least one of the following steps (a), (b) or (c)

(a) subjecting a compound of formula (VI), its stereoisomers or mixtures thereof, to

5 a hydrogenation reaction



(VI)

wherein

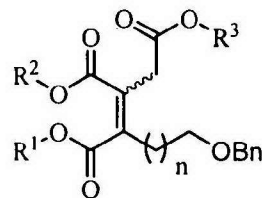
$R^1$ ,  $R^2$  and  $R^3$  are as defined above;

10  $m_1$  is an integer which is selected from 1, 2, 3, 4 and 5; and

$m_2$  is an integer between 0 and 13;

(b) subjecting a compound of formula (VII), its stereoisomers or mixtures thereof, to

a hydrogenation reaction



(VII)

15

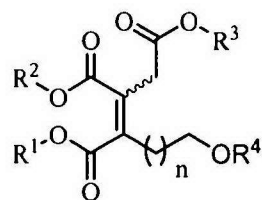
wherein

$n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above;

or

(c) removing the trialkylsilyl group of a compound of formula (XVI), its

20 stereoisomers or mixtures thereof



(XVI)

wherein

n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above; and  
R<sup>4</sup> is a trialkylsilyl group.

In a preferred embodiment, a metal catalyst is added on a solution of a trimer of formula (VI) or (VII) in a suitable solvent, such as 1,4-dioxane for example. Preferably, the solvent is degassed by means of passing a stream of an inert gas. The suspension thus prepared is stirred under a hydrogen atmosphere for a time between 10 and 210 minutes, preferably between 20 and 150 minutes, more preferably between 25 and 80 minutes.

The conditions under which heterogeneous hydrogenation reactions are performed are known for the person skilled in the art. For a review on heterogeneous hydrogenation reactions see, for example: Nishimura, S. *Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons, 2001. Various metal catalysts are used, in which the metal is selected from platinum, palladium, rhodium or ruthenium. Some commercial catalysts of the hydrogenation reaction useful for the purposes of the present invention are, for example, Ni(Ra), Pd/C, Rh(Al<sub>2</sub>O<sub>3</sub>). Among them, the preferred catalyst is Pd/C.

As can be seen, in the case of the compounds of formula (VI), it is thus possible to reduce the double bond of the side chain rather than the conjugated double bond existing between the C3-C4 carbons, and release the end hydroxyl group of the side chain. In the case of the compounds of formula (VII) it is enough to release the end hydroxyl of the side chain. Alternatively, it is possible to only reduce the double bond of the side chain to a compound of formula (VI) to obtain a compound of formula (VII), which can be reduced in the same reaction medium or after isolation, to a compound of formula (VIII). In other words, the reduction of the compounds of formula (VI) to the compounds of formula (VIII) can be performed in a single step, or in two steps through a compound of formula (VII).

For example, conditions under which the compound of formula (VI) is relatively diluted in the reaction medium (0.02-1.5 M), preferably 0.07-1.5 M, and Pd/C of a concentration between 3 and 7%, preferably 5%, favor directly obtaining an alcohol of formula (VIII) as a single product. Preferred embodiments for directly obtaining compounds of formula (VIII) are also those wherein between 0.01-0.1

equivalents, preferably 0.04-0.06 equivalents, of Pd/C are added. According to another preferred embodiment, the solvent is 1,4-dioxane. The reaction time is preferably between 50 and 70 minutes.

5 Preferred conditions for obtaining a compound of formula (VII) from compounds of formula (VI) are those in which the concentration of the compound of formula (VI) in the reaction medium and the concentration of Pd/C is slightly higher. Thus, for example, according to a preferred embodiment the concentration of the compound of formula (VI) in the reaction medium is greater than 0.15 M, preferably of 0.16-0.25 M), more preferably about 0.2M, and Pd/C of a concentration between 8 and 12%, preferably 10%, is used. Preferred embodiments for obtaining 10 compounds of formula (VII) are also those wherein between 0.01-0.1 equivalents, preferably 0.04-0.06 equivalents, of Pd/C are added. According to another preferred embodiment, the solvent is 1,4-dioxane. The reaction time is preferably between 10 and 50 minutes, preferably between 20 and 40 minutes, more preferably about 30 15 minutes.

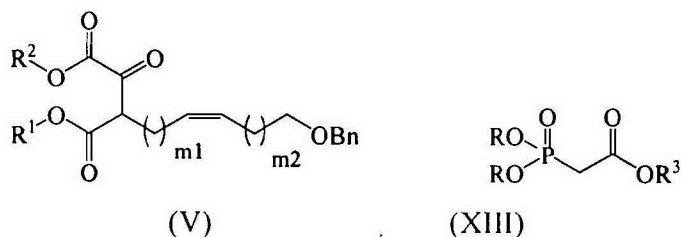
As can be observed, option (c) comprises the removal of the trialkylsilyl group, i.e., the transformation of R<sup>4</sup> into a hydrogen, of a compound of formula (XVI). Said transformation is normally understood as a deprotection and can be performed under different conditions (see for example, Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 2000. pp.: 187-230). According to a preferred 20 embodiment, the trialkylsilyl group is removed from a compound of formula (XVI) to give rise to a compound of formula (VIII) in diluted acidic medium, such as 1% HCl, for example

According to another aspect, the invention relates to compounds of (VI), 25 (VII), or (XVI) as defined above, immediate precursors of the compounds of formula (VIII). According to a preferred embodiment, in the compounds of formula (VII) or (XVI) n is an integer between 8 and 20, preferably between 12 and 17, more preferably between 13 and 16, more preferably n is 15. According to a preferred embodiment, in the compounds of formula (VI) m<sub>1</sub> is an integer which is selected from 2, 3 or 4, preferably m<sub>1</sub> is 3. According to a preferred embodiment, m<sub>2</sub> is an 30 integer which is selected from among 5-12, preferably 8-12, more preferably m<sub>2</sub> is

10.

Said groups  $R^1$ ,  $R^2$  and  $R^3$  act as protecting groups for the acid groups of the compounds of formula (I) and, as seen below, they are removed in the last steps of the synthesis. Therefore, any substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl protecting group, orthogonal to the rest of the protecting groups used in the synthesis (for example, benzyl and trialkylsilyl) is useful for the purposes of the present invention. Preferably, each of  $R^1$ ,  $R^2$  and  $R^3$  is independently selected from a  $C_1$ - $C_4$ , preferably  $C_{1-3}$ , alkyl group more preferably,  $R^1$ ,  $R^2$  and  $R^3$  are methyl groups.

Another aspect of the present invention relates to a process for the synthesis of a compound of formula (VI). Said compound of formula (VI), its stereoisomers or mixtures thereof, can be prepared by reacting a compound of formula (V) with a phosphonate of formula (XIII) in the presence of a base:



wherein

$R^1$  is selected from a substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl; and

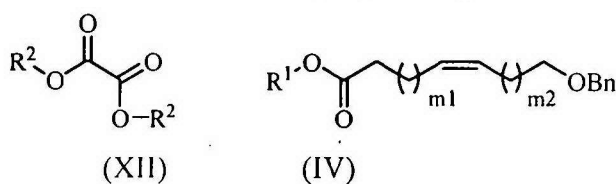
$R$  is selected from  $C_1$ - $C_4$  alkyl substituted or unsubstituted with one or more halogen atoms, benzyl, phenyl and tolyl.

Reactions of this type are known in the state of the art and allow a certain variability in their conditions (for example, see Wittig see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927). The phosphonate is preferably in an excess with respect to the compound of formula (V), more preferably in a proportion between 1.5 to 3 equivalents, still more preferably in a proportion of 2.2 equivalents. As has been mentioned, this transformation furthermore needs the presence of a base, such as lithium bases for example, such as *n*-BuLi, *t*-BuLi, *s*-BuLi, LDA, LiHMDS for example; sodium bases, such as NaH, NaHMDS for example; or potassium bases, such as KHMDS, *t*-BuOK for example. The base is preferably NaH. The amount of base depends on the amount of phosphonate used. Thus, the base is preferably in an excess with respect to the compound of formula (V), more

preferably in a proportion between 1.5-3. In a preferred embodiment, the reaction is performed using THF at room temperature as a solvent.

Depending on the reaction conditions and the specific substituents, the reaction leads to mixtures of the C3-C4 geometric isomers of the compound (VI) in a different ratio. Both isomers are within the scope of the present invention and allow the synthesis of organic acid and its derivatives, as discussed below.

A compound of formula (V) can be prepared by reacting a compound of formula (IV) with an oxalate of formula (XII) in the presence of a base:



wherein

$\text{R}^1$  and  $\text{R}^2$  are independently selected from a substituted or unsubstituted  $\text{C}_1$ - $\text{C}_{20}$  alkyl;

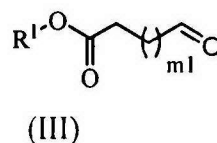
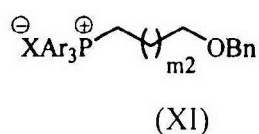
$m_1$  is an integer which is selected from 0, 1, 2, 3, 4 and 5; and

$m_2$  is an integer between 0 and 13.

As has been mentioned, this transformation furthermore needs the presence of a base, such as lithium bases for example, such as *n*-BuLi, *t*-BuLi, *s*-BuLi, LDA, LiHMDS for example; sodium bases, such as NaH, NaHMDS for example; or potassium bases, such as KHMDS, *t*-BuOK for example. The base is preferably NaH.

According to a preferred embodiment, the reaction is suitably performed in a mixture of MeOH/THF, using a temperature of about 70°C.

A compound of formula (IV) can be prepared by reacting a compound (III) with a compound of formula (XI):



wherein

$\text{R}^1$  is selected from a substituted or unsubstituted  $\text{C}_1\text{-C}_{20}$  alkyl,

5  $m_1$  is an integer which is selected from 0, 1, 2, 3, 4 and 5;

$m_2$  is an integer between 0 and 13;

X is a halogen; and

each of the Ar groups is independently selected from among the  $\text{C}_6\text{-C}_{10}$  aryl groups.

10 Experimentally, the treatment of a compound of formula (XI) with a base leads to the formation of the corresponding ylide, which reacts with the compound of formula (III) to obtain a compound of formula (IV).

Preferably, the base used is *n*-BuLi, the aryl is phenyl and the halogen is Br.

15 It is therefore possible to prepare a compound of formula (VI) by means of the following synthetic sequence:

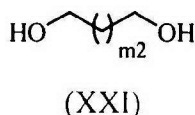
(i) reacting a compound of formula (III) with a compound of formula (XI) to yield a compound of formula (IV)

(ii) reacting said compound of formula (IV) with an oxalate of formula (XII) in the presence of a base to yield a compound of formula (V); and

20 (iii) reacting said compound of formula (V) with a phosphonate of formula (XIII).

The process for the synthesis of a compound of formula (XI) was performed by following the methodology described in García, J.; López, M.; Romeo, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2617-2626, which is incorporated in its entirety by reference. The process comprises the following steps

25 (i) reacting a benzylating agent in the presence of a base with a compound of formula (XXI)



wherein

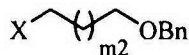
30  $m_2$  is an integer between 0 and 13;

to obtain a compound of formula (XXII)



(XXII)

(ii) reacting said compound of formula (XXII) with a halogenating agent to obtain a compound of formula (XXV)



(XXV)

wherein

$m_2$  is an integer between 0 and 13; and

X is a halogen atom;

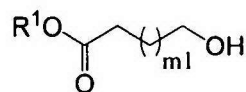
and

(iii) reacting said compound of formula (XXV) in the presence of a triarylphosphorus of formula  $\text{PAR}_3$  to obtain said compound of formula (XI).

According to a particular embodiment, the compound of formula (XXI) is 1,12-dodecanediol. Preferably, the deprotonation of the latter with a base, such as NaH for example, followed by treatment with a benzylating agent, such as BnBr for example, leads to 12-benzyloxy-1-dodecanol (6). Then, in the compound (6), the alcohol is substituted with a halogen. The halogen is preferably bromine. This bromination reaction can be carried out in the presence of  $\text{PPh}_3$  and  $\text{CBr}_4$ .

The halogenated compound of formula (X) is preferably transformed into a compound of formula (XI) by treatment with triphenylphosphine.

The compounds of formula (III) can be prepared by means of the oxidation of alcohols of formula (IIa)



(IIa)

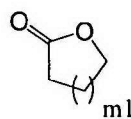
wherein

$\text{R}^1$  is selected from a substituted or unsubstituted  $\text{C}_1\text{-C}_{20}$  alkyl; and

$m$  is an integer which is selected from 0, 1, 2, 3, 4 and 5;

Oxidizing agents for the transformation of alcohols into aldehydes are known by the person skilled in the art (Larock, R. C. *Comprehensive Organic transformations*; John Wiley & Sons: New York, 1999, pp.: 1234-1249). According to a preferred embodiment, said oxidizing agent is selected from the group consisting of PCC (pyridinium chlorochromate),  $\text{MnO}_2$ , and  $\text{DMSO}/(\text{COCl})_2/\text{Et}_3\text{N}$ , preferably PCC.

Said compounds of formula (IIa) can be prepared from compounds of formula (XXIVa)



(XXIVa)

wherein

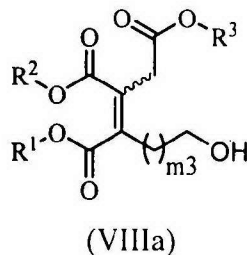
$m$  is an integer which is selected from 0, 1, 2, 3, 4 and 5;

according to the process described in Bosone, E.; Farina, P.; Guazzi, G.; Innocenti, S.; Marotta, V. *Synthesis* **1983**, 942-944, in the presence of an alcohol of formula  $\text{R}^1\text{OH}$ , wherein  $\text{R}^1$  has the meaning indicated above.

According to a particular embodiment, the treatment of  $\epsilon$ -caprolactone (compound of formula (XXIVa) wherein  $m$  is 3) in acidic medium using as a solvent an alcohol of formula  $\text{R}^1\text{OH}$ , preferably wherein  $\text{R}^1$  is a  $\text{C}_1\text{-C}_3$  alkyl, more preferably methanol, leads to the formation of the corresponding compound of formula (IIa), wherein the substituent  $\text{R}^1$  corresponds to the rest of the alcohol used as a solvent. This alcohol of formula (IIa) gives rise to the corresponding compound of formula (III) by means of an oxidation reaction. The oxidizing reagent is preferably PCC.

Alternatively, the side chain of a compound of formula (VIII) can be

elongated to provide a compound of formula (VIII) with a longer chain. According to a preferred embodiment, in the process of the invention the compound of formula (VIII), its stereoisomers or mixtures thereof, is a compound of formula (VIIIa), its stereoisomers or mixtures thereof,



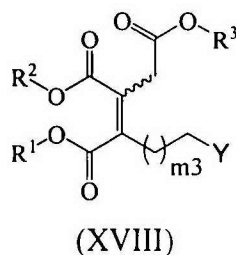
wherein

$R^1$ ,  $R^2$  and  $R^3$  are independently selected from substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl; and

10  $m_3$  is an integer between 2 and 18;

it additionally comprises the following steps

(i) activating as a leaving group the hydroxyl group of a compound of formula (VIIIa), its stereoisomers or mixtures thereof, to form a compound of formula (XVIII), its stereoisomers or mixtures thereof

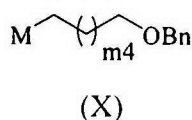


wherein

$m_3$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above; and

Y is selected from  $-OSO_3H$ ,  $OMs$ ,  $-OTs$ , I and Br;

20 (ii) reacting said compound of formula (XVIII), its stereoisomers or mixtures thereof, with a compound of formula (X)



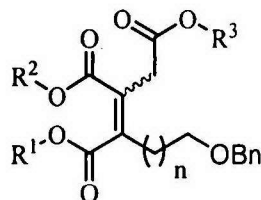
wherein

25 M is a metal; and

$m_4$  is an integer between 0 and 18; and

the relation  $m_3 + m_4 + 2 = n$  is met;

to obtain a compound of formula (VII), its stereoisomers or mixtures thereof



(VII)

wherein

$n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above,

and

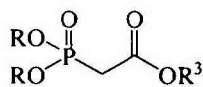
(iii) subjecting said compound of formula (VII), its stereoisomers or mixtures thereof, to a hydrogenation reaction.

In the context of the present invention, preferred leaving groups are those which are active against organometallic reagents (nucleophilic groups) used in the formation of carbon-carbon bonds, preferably Grignard reagents transmetalated or non-transmetalated with Zn, Al, or Cu. Preferred leaving groups are -OTs, -I, -Br, Cl, -SO<sub>3</sub>H. In a preferred embodiment, the leaving group is selected from Br and OTs.

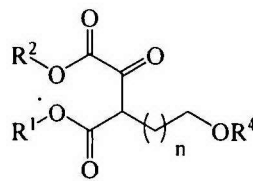
In a preferred embodiment, the hydroxyl group is activated as the corresponding tosylate (OTs) in the presence of a base, such as pyridine for example.

According to another preferred embodiment, the treatment of a compound of formula (VIII) with CBr<sub>4</sub> and PPh<sub>3</sub> gives rise to the compound of formula (XVIII) wherein Y is Br.

The compounds of formula (XVI) can be prepared by reacting a compound of formula (XV) with a phosphonate of formula (XIII) in the presence of a base



(XIII)



(XV)

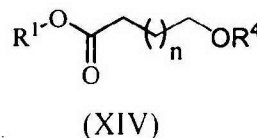
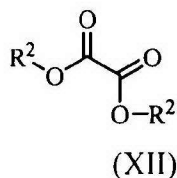
wherein

R is selected from C<sub>1</sub>-C<sub>4</sub> alkyl substituted or unsubstituted with one or more halogen atoms, benzyl, phenyl and tolyl; and

R<sup>3</sup> is selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl; and  
n, R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> are as defined above.

5 The reactions of the compounds of formula (V) or (XV) with the phosphonates of formula (XIII) can give rise to mixtures of Z(cis)/E(trans)-isomers which can be separated, subjected to the following step as a mixture or enriched in the Z(cis)-isomer according to the process described below.

10 The compounds of formula (XV) can in turn be obtained by reacting an oxalate of formula (XII) with a compound of formula (XIV)

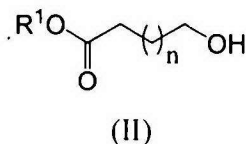


wherein

15 R<sup>2</sup> is selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl; and  
n, R<sup>1</sup> and R<sup>4</sup> are as defined above.

As can be seen, the process followed for the synthesis of the compounds of formula (XIV) and (XV) is similar to the one used to synthesize the compounds of formula (V) and (VI), and the conditions can be the same or similar.

20 According to a particular embodiment, a compound of formula (XIV) is prepared by means of the treatment of an alcohol of formula (II) with a base and a silylating agent



wherein

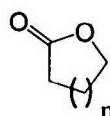
25 R<sup>1</sup> and n are as defined above.

Non-limiting examples of conditions under which this transformation for protecting the hydroxyl group can be carried out can be found in, for example, Dalla, V.; Catteau, J. P. *Tetrahedron* **1999**, *55*, 6497-6510, and the trialkylsilyl groups which can be used in this reaction, as well as reagents suitable for their introduction

and removal, are known for the person skilled in the art (for example see Greene, T. W.; Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons: Hoboken, 2007.

5 According to a particular embodiment, the base used is imidazole and the silylating agent is TBDMSCl.

According to another particular embodiment, the compounds of formula (II) can be prepared by reacting a compound of formula (XXIV) in the presence of an alcohol of formula  $R^1OH$ , wherein  $R^1$  and  $n$  are as defined above

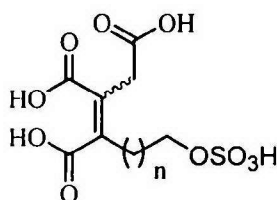


(XXIV).

10

As can be seen, the process followed for the synthesis of the compounds of formula (II) is similar to the one used to synthesize the compounds of formula (IIa), and the conditions can be the same or similar.

15 An additional aspect of the present invention relates to a process for the synthesis of a compound of formula (I),



(I)

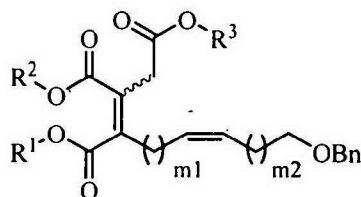
15

wherein  $n$  is an integer between 2 and 20;

20

its stereoisomers or mixtures thereof, characterized in that it comprises at least one of the following steps (ai), (aai) or (aaii)

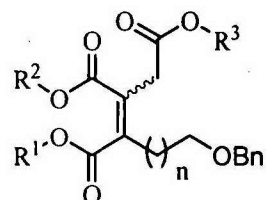
(ai) subjecting a compound of formula (VI), its stereoisomers or mixtures thereof, to a hydrogenation



(VI)

or

(a)ii) subjecting a compound of formula (VII), its stereoisomers or mixtures thereof, to a hydrogenation

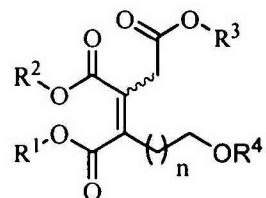


(VII)

5

or

(a)iii) removing the trialkylsilyl group of a compound of formula (XVI), its stereoisomers or mixtures thereof



(XVI)

10

wherein

n is an integer between 2 and 20;

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl;

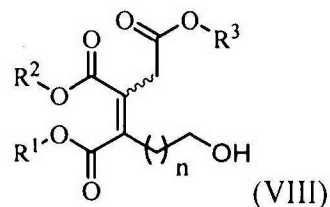
15

m<sub>1</sub> is an integer which is selected from 0, 1, 2, 3, 4 and 5;

m<sub>2</sub> is an integer between 0 and 13; and

R<sup>4</sup> is a trialkylsilyl group;

to obtain a compound of formula (VIII), its stereoisomers or mixtures thereof



(VIII)

20

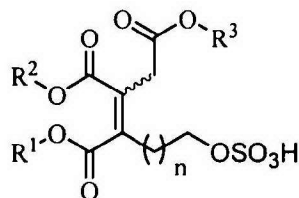
wherein

n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above;

and additionally comprises

(b) reacting said compound of formula (VIII), its stereoisomers or mixtures thereof,

with a sulfating agent to yield a compound of formula (IX), its stereoisomers or mixtures thereof



(IX)

5 wherein

$n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above;

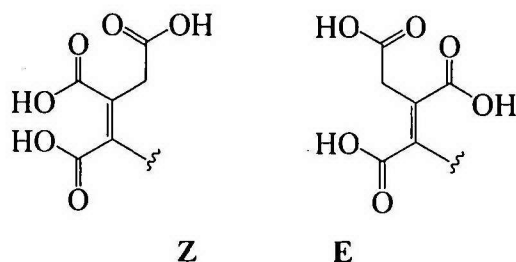
and

(c) hydrolyzing the ester groups of said compound of formula (IX), its stereoisomers or mixtures thereof, to provide the corresponding acid groups.

10 Various sulfating agents are known for the person skilled in the art. The most common are  $SO_3$  and  $HSO_3Cl$ . The sulfating agent is preferably the  $SO_3$  pyridine complex.

The hydrolysis of ester groups to provide the corresponding acid groups is known by the person skilled in the art (see for example, Kocienski, P. J. Protecting Groups; Thieme: Stuttgart, 2000. pp.: 393-425). In this case, they would be conditions inert to the C3-C4 double bond and to the sulfate group present in the compounds of formula (IX). Non-limiting conditions for the purposes of the present invention are preferably those in which the hydrolysis of the compounds of formula (IX) is performed in the presence of an alkali metal or alkaline earth hydroxide, for example in the presence of  $LiOH$ ,  $NaOH$ ,  $Ba(OH)_2$ , or in the presence of  $Na_2S$ .

20 As has been indicated above, both C3-C4 stereoisomers of the compounds described in the present invention, as well as the mixture thereof are included within the present invention.



25

For example, the reduction of a compound of formula (VI)-Z leads to

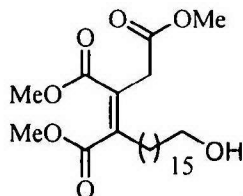
products with a *Z* configuration and the reduction of a compound of formula (VI)-*E* leads to products with a *Z* configuration.

However, it is possible to transform the *E*(*trans*)-isomer into the *Z* (*cis*) isomer into the corresponding *Z*(*cis*)-isomer or enrich a mixture of *Z*(*cis*)/*E*(*trans*)-isomers in the *Z*(*cis*)-isomer by means of exposure to a basic medium. Therefore, according to a preferred embodiment the process of the invention comprises obtaining a compound of formula *cis*-(I), *cis*-(VI), *cis*-(VII), *cis*-(VIII), *cis*-(VIIIa), *cis*-(IX), *cis*-(XVI), *cis*-(XVIa) or *cis*-(XVIII) or the enrichment in the *cis*-isomer of a mixture of *cis*- and *trans*-isomers of a compound of formula (I), (VI), (VII), (VIII), (VIIIa), (IX), (XVI), (XVIa) or (XVIII), by means of the exposure to a basic medium of a compound of formula *trans*-(I), *trans*-(VI), *trans*-(VII), *trans*-(VIII), *trans*-(VIIIa), *trans*-(IX), *trans*-(XVI), *trans*-(XVIa) or *trans*-(XVIII), or a mixture of *cis*- and *trans*-isomers of a compound of formula (I), (VI), (VII), (VIII), (VIIIa), (IX), (XVI), (XVIa) or (XVIII). According to a preferred embodiment, the process of the invention comprises transforming a compound of formula *trans*-(VI), *trans*-(VII), *trans*-(IX) and/or *trans*-(XVI) into the corresponding compound of formula *trans*-(VI), *trans*-(VII), *trans*-(IX) and/or *trans*-(XVI), or in mixtures of the corresponding *cis*/*trans*-isomers. Said basic medium preferably comprises SO<sub>3</sub>·pyridine.

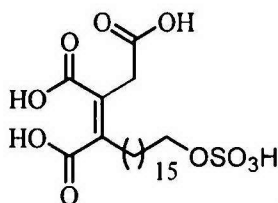
### Compounds

As has already been indicated above, additional aspects of the present invention are compounds of formula (IV), (V), (VI), (VII), (XV), (XVI) and (XVIII), their stereoisomers or mixtures thereof, as defined above.

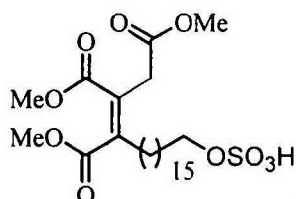
Another additional aspect is a compound of formula (VIII), its stereoisomers or mixtures thereof, as defined above with the exception of a compound of formula



Another additional aspect is a compound of formula (I), its stereoisomers or mixtures thereof, as defined above, except

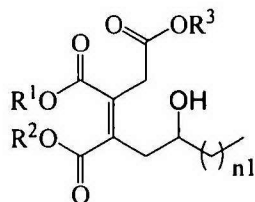


Another additional aspect is a compound of formula (IX), its stereoisomers or mixtures thereof, as defined above, except

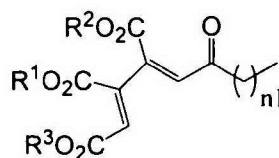


5 Compounds of formula (VIIIb)

An additional aspect of the present invention is aimed at a process for preparing a compound of formula (VIIIb), which comprises reacting a compound of formula (XXX) with a hydride, preferably NaBH<sub>4</sub> (see Burke, S.D.; Danheiser, R.L. *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents*; John Wiley & Sons: Chichester, 1999. pp.: 394-400).



(VIIIb)



(XXX)

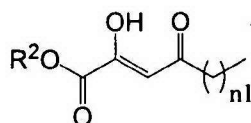
wherein

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl; and

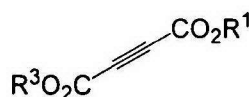
n<sub>1</sub> is an integer between 1 and 16, preferably between 3 and 12, more preferably between 5 and 10, more preferably 8;

According to a preferred embodiment, said compound of formula (XXX) is prepared by reacting a compound of formula (XXXI) with a compound of formula (XXXII) in the presence of a compound of formula PAr<sub>3</sub>, preferably triphenylphosphine, wherein each of the Ar groups is independently selected from a C<sub>6</sub>-C<sub>10</sub> aryl group, and wherein n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above. To see a non-limiting example of conditions for preparing compounds of formula (XXX), see

Yavari, I.; Samzadeh-Kermani, A. R. *Tetrahedron Lett.* **1998**, 39, 6343-6344.

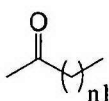


(XXXI)

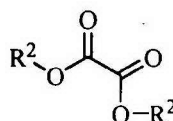


(XXXII)

According to another preferred embodiment, said compound of formula  
5 (XXXI) is prepared by reacting a compound of formula (XXXIII) with an oxalate of  
formula (XII) in the presence of a base, wherein  $n1$  and  $R^2$  are as defined above.



(XXXIII)



(XII)

The compounds of formula (XXXI) can be obtained under the conditions  
10 described in Seki, K.; Isegawa, J.; Fukuda, M.; Ohki, M. *Chem. Pharm. Bull.* **1984**,  
32, 1568-1577; or Ashton, W. T.; Doss, G. A. *J. Heterocycl. Chem.* **1993**, 30, 307-  
311, which are incorporated in their entirety by reference.

In short, this process allows obtaining the derivatives of the oreganic acid of  
15 formula (VIIIb) from commercial starting materials (compounds of formula  
(XXXIII) and (XII)) in a few steps and with a high yield.

### Examples

#### Materials and methods

All the reactions were performed under an argon atmosphere, except those  
20 indicated in each case. The reagents and solvents used are from the companies  
Aldrich, Fluka, Merck, Sigma, Acros, Lancaster, SDS or Scharlau, and were purified  
by usual processes [Armarego, W. L.; Perrin, D. D. *Purification of Laboratory  
Chemicals*; Butterworth-Heinemann: Oxford, 1996] when necessary.

The solvents used were distilled and dried under an argon atmosphere. The  
dioxane was degassed by passing a stream of argon before being used.

25 The purification of the reaction products was performed by column  
chromatography under pressure (flash chromatography), using 60 Merck silica gel (with  
a 230-400 mesh particle size) as a stationary phase and previously distilled solvents as a  
mobile phase. The eluent used is indicated in each case and the ratios of the mixture of  
solvents used are always volume/volume.

The reactions were monitored by thin layer chromatography (TLC), using 60 *F*<sub>254</sub> silica gel chromatography plates marketed by Merck. The plates were developed using iodine vapors, 2% solution of 2,4-dinitrophenylhydrazine in EtOH (with 0.04% by volume of 97% H<sub>2</sub>SO<sub>4</sub>), 10% solution of phosphomolybdic acid in EtOH and UV light viewer (254 and 366 nm).

The general process used to create the H<sub>2</sub> atmosphere necessary for carrying out the hydrogenation reactions consisted of: after performing a vacuum in the reaction flask, a stream of H<sub>2</sub> was connected. The vacuum/H<sub>2</sub> process was repeated twice, and finally two balloons filled with H<sub>2</sub> were connected.

The reactions under high pressure conditions were carried out in Kimble brand glass vials.

The (fully decoupled) <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectra were performed at room temperature in the solvent indicated in each case (CDCl<sub>3</sub> and CD<sub>3</sub>OD) using the following apparatuses: Varian Gemini-200 (200 MHz), Varian INOVA-300 (300 MHz), Bruker Avance-300 (300 MHz) and Varian INOVA-400 (400 MHz). The values of the chemical shifts are expressed in parts per million (δ, ppm), using as an internal reference the residual signal of the solvent: CDCl<sub>3</sub>, 7.26 ppm (<sup>1</sup>H-NMR) and 77.0 ppm (<sup>13</sup>C-NMR); CD<sub>3</sub>OD, 3.31 ppm (<sup>1</sup>H-NMR) and 49.0 ppm (<sup>13</sup>C-NMR).

The melting points (m.p.) were measured in a Reichert brand Kofler microscope.

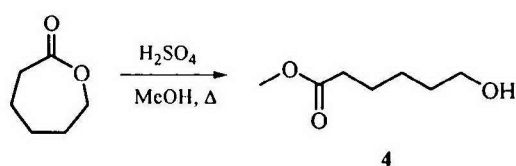
The infrared (IR) spectra were recorded in the Perkin-Elmer spectrophotometer models 681 and FT-IR Spectrum One, and the frequencies (ν) of the absorption maxima are expressed in cm<sup>-1</sup>. The samples were analyzed as films between NaCl crystals or in KBr discs.

The low resolution mass spectra (LRMS) were recorded: (1) by direct injection of the sample into a Hewlett Packard 5973 MSD spectrophotometer using the electron impact (EI) ionization technique with an ionization energy of 70 eV; or (2) in a Hewlett Packard LCMS 1100 MSD spectrophotometer (an HPLC-coupled quadrupole analyzer) using the electrospray chemical ionization technique (API-ES) in positive or negative modes, applying a capillary voltage of 4000 V, a drying

temperature of 330°C and using a [1:1] H<sub>2</sub>O/MeOH mixture with 1% AcOH as a carrier. The data obtained are expressed in mass units (*m/z*) and the values in parenthesis correspond to the relative intensities with respect to the base peak (100%). The molecular peak is specified as M<sup>+</sup>.

5 The elemental analyses (E.A.) were performed with the Perkin-Elmer 240C and Heraeus CHN-O-Rapid analyzers. The data calculated and observed are expressed in percentages.

Example 1. Preparation of methyl 6-hydroxyhexanoate (**4**)

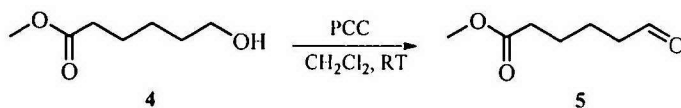


10 A solution of  $\epsilon$ -caprolactone (25 g, 220 mmol) in MeOH (25 ml) was added to a solution of 97% H<sub>2</sub>SO<sub>4</sub> (2.5 ml) in MeOH (25 ml). The mixture was heated under reflux for 30 minutes. After that time, the mixture was neutralized with an aqueous solution of 10% NaOH (17.5 ml) and extracted with AcOEt (3 × 25 ml). The organic phase was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure, obtaining (32 g, quantitative yield) methyl 6-hydroxyhexanoate (**4**), which was used in the following step without purifying.

15 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>).  $\delta$  3.55 (3H, s, -OCH<sub>3</sub>), 3.53 (2H, t, *J* = 6.2 Hz, H-6), 2.22 (2H, t, *J* = 7.2 Hz, H-2), 1.62-1.23 (6H, m, -CH<sub>2</sub>-).

Example 2. Preparation of methyl 5-formylpentanoate (**5**)

20

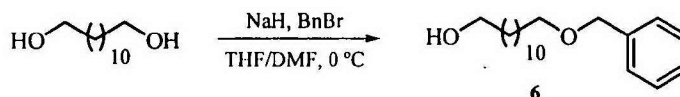


25 PCC (2.65 g, 12.3 mmol) was added to a solution of methyl 6-hydroxyhexanoate (**4**) (1.2 g, 8.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml). The mixture was stirred at room temperature for 2.5 hours. After that time, the solvent was removed under reduced pressure. The residue was suspended in a 1:1 hexane/AcOEt mixture (30 ml) and filtered through silica gel to remove the remains of the reagent, obtaining (1.16 g, quantitative yield) methyl 5-formylpentanoate (**5**), which was used

in the following step without purifying.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 9.71 (1H, m, H-6), 3.61 (3H, s, -OCH<sub>3</sub>), 2.39 (4H, m, H-2, H-5), 1.65 (4H, m, H-3, H-4).

Example 3. Preparation of 12-benzyloxy-1-dodecanol (**6**)



5

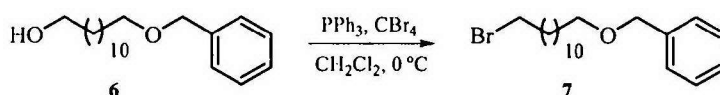
10

15

A solution of 1,12-dodecanediol (5.0 g, 24.7 mmol) in a 2:1 THF/DMF mixture (36 ml) was added to a suspension of NaH (0.595 g, 24.83 mmol) in DMF (18 ml) at 0°C. The mixture was stirred at 0°C for 2 hours. After that time, BnBr (4.42 g, 25.8 mmol) was added at 0°C. The resulting mixture was stirred at room temperature for 4 hours. Then, the mixture was cooled at 0°C and H<sub>2</sub>O (75 ml) was added. The phases were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (5 × 20 ml). The organic phase was washed with sat. NaCl (30 ml), dried with anhydrous MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 10:1), obtaining (3.59 g, yield 50%) 12-benzyloxy-1-dodecanol (**6**), as a transparent oil.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 7.36-7.27 (5H, m, Ar-H), 4.51 (2H, s, -OCH<sub>2</sub>Ph), 3.60 (2H, t, *J* = 6.5 Hz), 3.45 (2H, t, *J* = 6.4 Hz); 1.60 (4H, m), 1.40 (16H, m).

Example 4. Preparation of 12-benzyloxy-1-bromododecane (**7**)



20

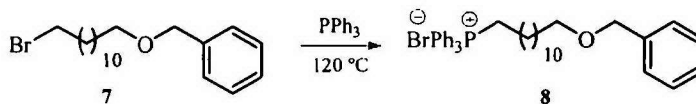
25

CBr<sub>4</sub> (3.34 g, 10.08 mmol) was added to a solution of 12-benzyloxy-1-dodecanol (**6**) (2.36 g, 8.06 mmol) and PPh<sub>3</sub> (2.64 g, 10.08 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 ml) at 0°C. The mixture was stirred at room temperature for 30 minutes. After that time, the solvent was removed under reduced pressure. The residue was suspended in hexane (115 ml) and stirred at room temperature for 30 minutes. After that time, the mixture was filtered under vacuum and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/CH<sub>2</sub>Cl<sub>2</sub>, 2:1), obtaining (2.45 g, yield 86%) 12-benzyloxy-1-bromododecane (**7**), as a transparent oil.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 7.35 (5H, m, Ar-H), 4.48 (2H, s, -OCH<sub>2</sub>Ph), 3.45

(2H, t,  $J = 6.5$  Hz), 3.35 (2H, t,  $J = 6.5$  Hz), 1.85 (2H, m, -CH<sub>2</sub>-), 1.58 (2H, m, -CH<sub>2</sub>-), 1.36-1.15 (16H, m, -CH<sub>2</sub>-).

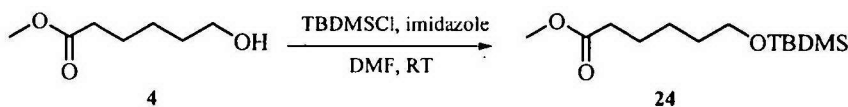
**Example 5.** Preparation of [12-benzyloxydodec-1-yl]triphenylphosphonium bromide (**8**)



A mixture of 12-benzyloxy-1-bromododecane (**7**) (1.58 g, 4.44 mmol) and PPh<sub>3</sub> (1.28 g, 4.89 mmol) was heated in a Kimble at 120°C for 3 hours. After that time, the product was purified by a chromatographic column (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1), obtaining (2.5 g, yield 91%) [12-benzyloxydodec-1-yl]triphenylphosphonium bromide (**8**), as a transparent oil.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 7.70 (15H, m), 7.22 (5H, m, Ar-H), 4.52 (2H, s, -OCH<sub>2</sub>Ph), 3.80 (2H, m, H-1), 3.38 (2H, t,  $J = 6.5$  Hz, H-12), 1.55 (4H, m, -CH<sub>2</sub>-), 1.36-1.15 (16H, m, -CH<sub>2</sub>-).

**Example 6.** Preparation of methyl 6-(*tert*-butyldimethylsilyloxy)hexanoate (**24**)

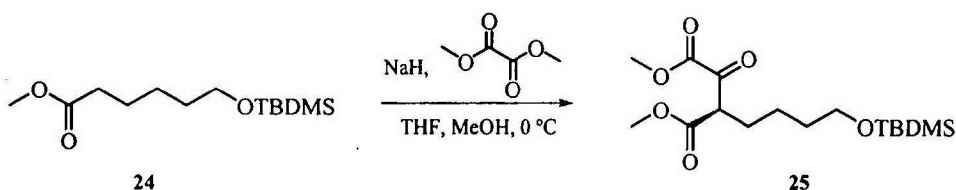


A solution of TBDMSCl (7.16 g, 46.08 mmol) in DMF (10 ml) was added to a solution of methyl 6-hydroxyhexanoate (**4**) (5.613 g, 38.40 mmol) and imidazole (3.13 g, 46.08 mmol) in DMF (50 ml) at 0°C. The mixture was stirred at room temperature for 24 hours. After that time, H<sub>2</sub>O (80 ml) and AcOEt (40 ml) were added. The phases were separated, and the aqueous phase was extracted with AcOEt (3 × 20 ml). The organic phase was washed with sat. CuSO<sub>4</sub> (2 × 30 ml) and sat. NaCl (2 × 30 ml), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 25:1), obtaining (6.46 g, yield 73%) methyl 6-(*tert*-butyldimethylsilyloxy)hexanoate (**24**) as a colorless oil.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 3.56 (3H, s, -OCH<sub>3</sub>), 3.49 (3H, t,  $J = 6.2$  Hz, H-6), 2.21 (2H, t,  $J = 7.6$  Hz, H-2), 1.61-1.20 (6H, m, -CH<sub>2</sub>-), 0.78 (9H, s, *tert*-BuSi), -0.06 (6H, s, (Me)<sub>2</sub>Si).

**Example 7.** Preparation of methyl *rac*-(*R*)-7-(*tert*-butyldimethylsilyloxy)-3-

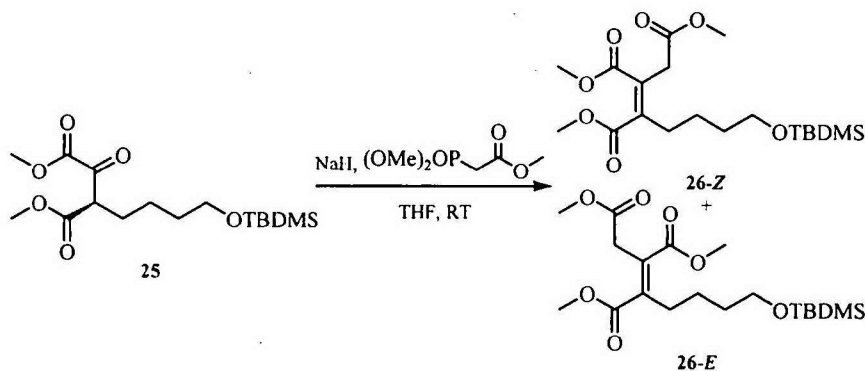
(methoxycarbonyl)-2-oxoheptanoate (**25**)



MeOH (0.23 ml) was added to a suspension of NaH (0.507 g, 21.11 mmoles) in THF (9.2 ml) at 0°C. The mixture was stirred until it reached room temperature. Then, dimethyl oxalate (2.29 g, 19.19 mmoles) and methyl 6-(*tert*-butyldimethylsilyloxy)hexanoate (**24**) (5.0 g, 19.19 mmoles) were added. The resulting mixture was heated under reflux for 3 hours. After that time, H<sub>2</sub>O (10 ml) and an aqueous solution of 10% HCl were added until neutral pH. The phases were separated, and the aqueous phase was extracted with AcOEt (3 × 10 ml). The organic phase was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 25:1), obtaining (4.41 g, yield 67%) methyl *rac*-(*R*)-7-(*tert*-butyldimethylsilyloxy)-3-(methoxycarbonyl)-2-oxoheptanoate (**25**), as a transparent oil.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 3.92 (1H, t, *J* = 6.8 Hz, H-3), 3.78 (3H, s, -OCH<sub>3</sub>), 3.62 (3H, s, -OCH<sub>3</sub>), 3.49 (2H, t, *J* = 5.9 Hz, H-7), 1.87-1.41 (6H, m, -CH<sub>2</sub>-), 0.77 (9H, s, *tert*-BuSi), -0.07 (6H, s, (Me)<sub>2</sub>Si).

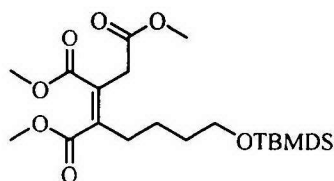
**Example 8.** Reaction of methyl *rac*-(*R*)-7-(*tert*-butyldimethylsilyloxy)-3-(methoxycarbonyl)-2-oxoheptanoate (**25**) with methyl (dimethoxyphosphoryl)acetate



A solution of methyl (dimethoxyphosphoryl)acetate (0.105 g, 0.57 mmoles) in THF (0.3 ml) was added to a suspension of NaH (0.013 g, 0.57 mmoles) in THF

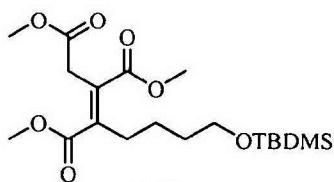
(2.3 ml). The mixture was stirred at room temperature until H<sub>2</sub> was no longer evolved. Then, a solution of methyl *rac*-(*R*)-7-(*tert*-butyldimethylsilyloxy)-3-(methoxycarbonyl)-2-oxoheptanoate (**25**) (0.100 g, 0.29 mmoles) in THF (0.3 ml) was added. The resulting mixture was stirred at room temperature for 24 hours. After that time, Celite was added and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 15:1), obtaining (0.063 g, yield 54%) methyl (*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,4-bis(methoxycarbonyl)-3-octenoate (**26-Z**) and (0.024 g, yield 21%) methyl (*E*)-8-(*tert*-butyldimethylsilyloxy)-3,4-bis(methoxycarbonyl)-3-octenoate (**26-E**), both as a transparent oil.

Methyl (*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,4-bis(methoxycarbonyl)-3-octenoate (**26-Z**)

**26-Z**

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 3.67 (3H, s, -OCH<sub>3</sub>), 3.62 (3H, s, -OCH<sub>3</sub>), 3.57 (3H, s, -OCH<sub>3</sub>), 3.48 (2H, m, H-8), 3.29 (2H, s, H-2), 2.26 (2H, m, H-5), 1.40 (4H, m, -CH<sub>2</sub>-), 0.76 (9H, s, *tert*-BuSi), -0.08 (6H, s, (Me)<sub>2</sub>Si).

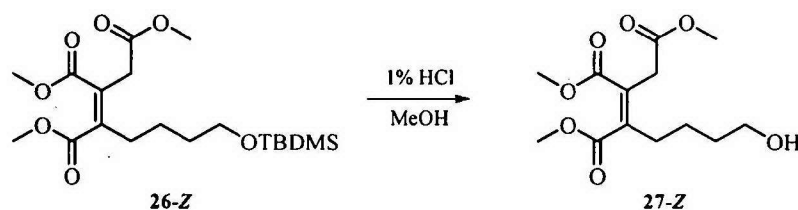
Methyl (*E*)-8-(*tert*-butyldimethylsilyloxy)-3,4-bis(methoxycarbonyl)-3-octenoate (**26-E**)

**26-E**

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>). δ 3.67 (6H, s, -OCH<sub>3</sub>), 3.57 (3H, s, -OCH<sub>3</sub>), 3.49 (2H, m; H-8), 3.41 (2H, s, H-2), 2.53 (2H, m, H-5), 1.41 (4H, m, -CH<sub>2</sub>-), 0.77 (9H, s, *tert*-BuSi), -0.07 (6H, s, (Me)<sub>2</sub>Si).

Example 9. Preparation of methyl (*Z*)-8-hydroxy-3,4-bis(methoxycarbonyl)-3-

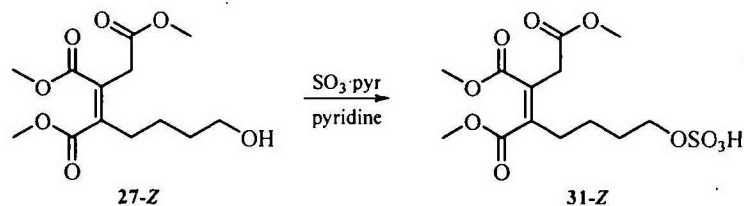
octenoate (**27-Z**)



A solution of methyl (*Z*)-8-(*tert*-butyldimethylsilyloxy)-3,4-bis(methoxycarbonyl)-3-octenoate (**26-Z**) (0.100 g, 0.24 mmol) in HCl (1% in MeOH, 1 ml) was stirred at room temperature for 2 hours. After that time, the mixture was neutralized with an aqueous solution of 10% NaHCO<sub>3</sub> (1 ml), and CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added. The phases were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 2 ml). The organic phase was washed with sat. NaCl (2 ml), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure, obtaining (0.065 g, yield 95%) methyl (*Z*)-8-hydroxy-3,4-bis(methoxycarbonyl)-3-octenoate (**27-Z**) as a colorless oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>). δ 3.79 (3H, s, -OCH<sub>3</sub>), 3.73 (3H, s, -OCH<sub>3</sub>), 3.69 (3H, s, -OCH<sub>3</sub>), 3.63 (2H, t, *J* = 6.0 Hz, H-8), 3.42 (2H, s, H-2), 2.40 (2H, t, *J* = 7.4 Hz, H-5), 1.58 (4H, m, -CH<sub>2</sub>-).

Example 10. Preparation of methyl (*Z*)-3,4-bis(methoxycarbonyl)-8-sulfooxy-3-octenoate (**31-Z**)



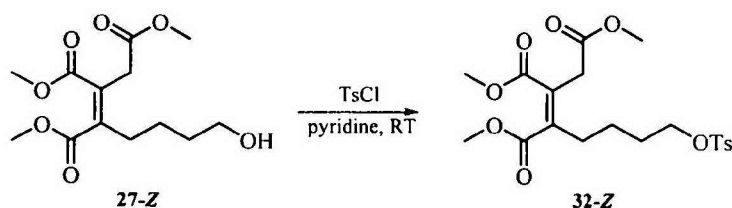
SO<sub>3</sub>·pyr (0.276 g, 1.73 mmol) was added in small portions to a solution of methyl (*Z*)-8-hydroxy-3,4-bis(methoxycarbonyl)-3-octenoate (**27-Z**) (0.100 g, 0.34 mmol) in pyridine (6.5 ml). The mixture was stirred at room temperature for 24 hours. After that time, the solvent was removed under reduced pressure. The residue was suspended in a 1:1 H<sub>2</sub>O/MeOH mixture (2 ml), neutralized with an aqueous solution of 0.5M KOH and the solvent was removed under reduced pressure. The product was purified by trituration with MeOH, obtaining (0.126 g, quantitative yield) methyl (*Z*)-3,4-bis(methoxycarbonyl)-8-sulfooxy-3-octenoate (**31-Z**), as a

white solid.

**IR** (BrK):  $\nu$  3457, 3075, 2955, 1726, 1638, 1489, 1437, 1261, 1201, 1008, 756, 683  $\text{cm}^{-1}$ .

**<sup>1</sup>H-NMR** (200 MHz,  $\text{CDCl}_3$ ).  $\delta$  4.11 (2H, t,  $J = 6.0$  Hz, H-8), 3.78 (3H, s,  $-\text{OCH}_3$ ), 3.73 (3H, s,  $-\text{OCH}_3$ ), 3.69 (3H, s,  $-\text{OCH}_3$ ), 3.42 (2H, s, H-2), 2.40 (2H, t,  $J = 7.4$  Hz, H-5), 1.60 (4H, m,  $-\text{CH}_2-$ ).

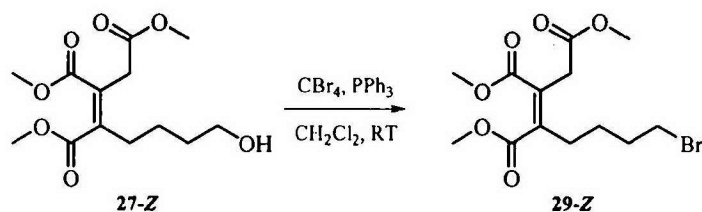
Example 11. Preparation of methyl (*Z*)-3,4-bis(methoxycarbonyl)-8-(*p*-toluenesulfonyl)-3-octenoate (**32-Z**)



A solution of methyl (*Z*)-8-hydroxy-3,4-bis(methoxycarbonyl)-3-octenoate (**27-Z**) (0.100 g, 0.347 mmoles) in pyridine (1 ml) was added to a solution of TsCl (0.099 g, 0.52 mmoles) in pyridine (1 ml) at 0°C. The mixture was stirred at 0°C for 2 hours. After that time,  $\text{H}_2\text{O}$  (4 ml) was added. The phases were separated, and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 4$  ml). The organic phase was washed with an aqueous solution of 10% HCl ( $\times 2$ , until an acidic pH), with  $\text{H}_2\text{O}$  (4 ml), with sat.  $\text{NaHCO}_3$  (4 ml) and with sat. NaCl (4 ml), dried with anhydrous  $\text{MgSO}_4$ , filtered and the solvent was removed under reduced pressure, obtaining (0.110 g, yield 72%) methyl (*Z*)-3,4-bis(methoxycarbonyl)-8-(*p*-toluenesulfonyl)-3-octenoate (**32-Z**), as a colorless oil.

**<sup>1</sup>H-NMR** (200 MHz,  $\text{CDCl}_3$ ).  $\delta$  7.79 (2H, d,  $J = 8.3$  Hz, Ar-H), 7.36 (2H, d,  $J = 8.3$  Hz, Ar-H), 4.02 (2H, t,  $J = 6.1$  Hz, H-8), 3.79 (3H, s,  $-\text{OCH}_3$ ), 3.75 (3H, s,  $-\text{OCH}_3$ ), 3.71 (3H, s,  $-\text{OCH}_3$ ), 3.39 (2H, s, H-2), 2.47 (3H, s,  $-\text{CH}_3$ ), 2.36 (2H, t,  $J = 7.6$  Hz, H-5), 1.80-1.45 (4H, m,  $-\text{CH}_2-$ ).

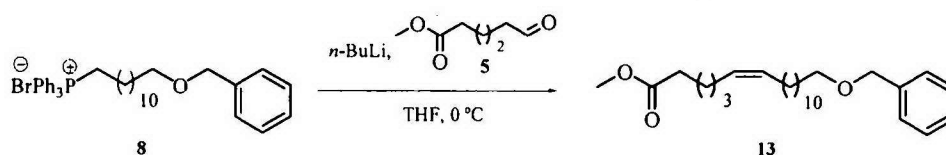
Example 12. Preparation of methyl (*Z*)-8-bromo-3,4-bis(methoxycarbonyl)-3-octenoate (**29-Z**)



A solution of PPh<sub>3</sub> (0.341 g, 1.30 mmoles) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added to a solution of methyl (*Z*)-8-hydroxy-3,4-bis(methoxycarbonyl)-3-octenoate (**27-Z**) (0.300 g, 1.04 mmoles) and CBr<sub>4</sub> (0.431 g, 1.30 mmoles) in CH<sub>2</sub>Cl<sub>2</sub> (6.5 ml) at 0°C. The mixture was stirred at room temperature for 2 hours. After that time, Celite was added and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 4:1), obtaining (0.218 g, yield 60%) methyl (*Z*)-8-bromo-3,4-bis(methoxycarbonyl)-3-octenoate (**29-Z**), as a colorless oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>). δ 3.80 (3H, s, -OCH<sub>3</sub>), 3.74 (3H, s, -OCH<sub>3</sub>), 3.70 (3H, s, -OCH<sub>3</sub>), 3.42 (2H, s, H-2), 3.39 (2H, t, *J* = 6.6 Hz, H-8), 2.39 (2H, t, *J* = 7.9 Hz, H-5), 1.88 (2H, m, -CH<sub>2</sub>-), 1.62 (2H, m, -CH<sub>2</sub>-).

**Example 13.** Preparation of methyl (*Z*)-18-benzyloxy-6-octadecenoate (**13**)



*n*-BuLi (0.545 g, 8.52 mmoles) was added to a solution of [12-benzyloxydodec-1-yl]triphenylphosphonium bromide (**8**) (3.71 g, 6.0 mmoles) in THF (85 ml) at 0°C. The mixture was stirred at 0°C for 45 minutes. After that time, a solution of methyl 5-formylpentanoate (**5**) (0.952 g, 8.34 mmoles) in THF (2 ml) was added at 0°C. The mixture was stirred at room temperature for 1 hour. After that time, the reaction mixture was cooled at 0°C and sat. NH<sub>4</sub>Cl was added (30 ml). The phases were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (4 × 15 ml). The organic phase was dried with anhydrous MgSO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 20:1), obtaining (2.61 g, yield 53%) methyl (*Z*)-18-benzyloxy-6-octadecenoate (**13**), as a transparent oil.

**IR** (NaCl): ν 3004, 2926, 2854, 1741, 1496, 1454, 1435, 1362, 1204, 1170, 1102,

1028, 734, 697  $\text{cm}^{-1}$ .

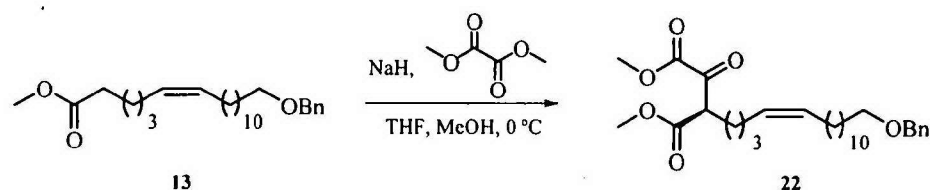
$^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ ).  $\delta$  7.30 (5H, m, Ar-H), 5.39 (1H, dt,  $J = 7.0, 10.9$  Hz, H-6 or H-7), 5.30 (1H, dt,  $J = 8.3, 10.9$  Hz, H-7 or H-6), 4.50 (2H, s,  $\text{CH}_2\text{Ph}$ ), 3.66 (3H, s,  $-\text{OCH}_3$ ), 3.46 (2H, t,  $J = 6.5$  Hz, H-18), 2.31 (2H, t,  $J = 7.5$  Hz, H-2), 1.96 (4H, m, H-5, H-8), 1.63 (4H, m,  $-\text{CH}_2-$ ), 1.34 (18H, m,  $-\text{CH}_2-$ ).

$^{13}\text{C-NMR}$  (50MHz,  $\text{CDCl}_3$ ).  $\delta$  174.1, 138.6, 130.9, 130.4, 129.0, 128.2, 127.5, 127.3, 72.7, 70.4, 51.3, 33.9, 29.7, 29.6, 29.5, 29.5, 29.4, 29.2, 29.1, 29.0, 27.1, 26.7, 26.1, 24.5, 24.3.

**LRMS(EI)**:  $m/z$  402( $\text{M}^+$ , 2), 371(1), 342(0), 311(14), 279(37), 261(16), 195(3), 91(100).

**E.A.** ( $\text{C}_{26}\text{H}_{42}\text{O}_3$ ): Found: C, 77.50, H, 10.45; Calculated: C, 77.56, H, 10.51.

**Example 14.** Preparation of methyl *rac*-(*Z,R*)-19-benzyloxy-3-(methoxycarbonyl)-2-oxo-7-nonadecenoate (**22**)



MeOH (0.022 ml) was added to a suspension of NaH (0.044 g, 1.87 mmoles) in THF (1 ml) at  $0^\circ\text{C}$ . The mixture was stirred until it reached room temperature. Then, dimethyl oxalate (0.221 g, 1.87 mmoles) and methyl (*Z*)-18-benzyloxy-6-octadecenoate (**13**) (0.685 g, 1.70 mmoles) were added. The resulting mixture was heated under reflux for 4 hours. After that time,  $\text{H}_2\text{O}$  (10 ml) and an aqueous solution of 10% HCl were added until neutral pH. The phases were separated, and the aqueous phase was extracted with AcOEt ( $3 \times 7$  ml). The organic phase was dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 15:1), obtaining (0.70 g, yield 85%) methyl *rac*-(*Z,R*)-19-benzyloxy-3-(methoxycarbonyl)-2-oxo-7-nonadecenoate (**22**), as a transparent oil.

**IR** (NaCl):  $\nu$  3454, 3005, 2926, 2853, 1735, 1657, 1495, 1454, 1436, 1361, 1249, 1100, 815, 735, 697  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ ).  $\delta$  7.29 (5H, m, Ar-H), 5.37 (1H, dt,  $J = 6.1, 10.7$  Hz,

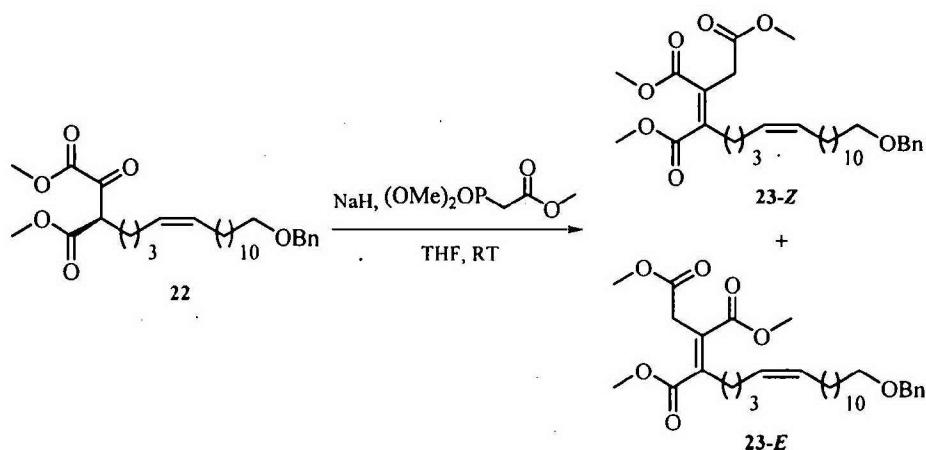
H-7 or H-8), 5.31 (1H, dt,  $J = 6.8, 10.7$  Hz, H-8 or H-7), 4.50 (2H, s,  $-\text{CH}_2\text{Ph}$ ), 4.03 (1H, t,  $J = 6.8$  Hz, H-3), 3.88 (3H, s,  $-\text{OCH}_3$ ), 3.72 (3H, s,  $-\text{OCH}_3$ ), 3.46 (2H, t,  $J = 6.5$  Hz, H-19), 1.97 (6H, m,  $-\text{CH}_2-$ ), 1.65-1.23 (20H, m,  $-\text{CH}_2-$ ).

$^{13}\text{C-NMR}$  (75MHz,  $\text{CDCl}_3$ ).  $\delta$  188.5, 169.3, 160.7, 138.6, 130.8, 130.3, 128.2, 127.4, 127.3, 72.7, 70.4, 53.7, 53.1, 52.4, 29.6, 29.5, 29.4, 29.4, 29.3, 29.2, 29.0, 27.1, 27.0, 26.9, 26.7, 26.6, 26.1.

**LRMS(EI)**:  $m/z$  488( $\text{M}^+$ , 0), 457(0), 397(2), 347(8), 287(30), 237(9), 91(100).

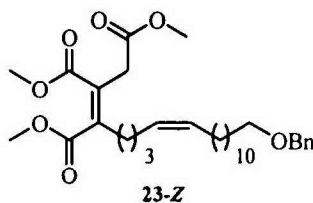
**E.A.** ( $\text{C}_{29}\text{H}_{44}\text{O}_6$ ): Found: C, 71.20, H, 9.00; Calculated: C, 71.28, H, 9.08.

**Example 15.** Reaction of methyl *rac*-(*Z,R*)-19-benzyloxy-3-(methoxycarbonyl)-2-oxo-7-nonadecenoate (**22**) with methyl (dimethoxyphosphoryl)acetate



A solution of methyl (dimethoxyphosphoryl)acetate (1.11 g, 6.12 mmoles) in THF (3.2 ml) was added to a suspension of NaH (0.147 g, 6.12 mmoles) in THF (10.6 ml). The mixture was stirred at room temperature until  $\text{H}_2$  was no longer evolved. Then, a solution of methyl *rac*-(*Z,R*)-19-benzyloxy-3-(methoxycarbonyl)-2-oxo-7-nonadecenoate (**22**) (1.36 g, 2.78 mmoles) in THF (3.2 ml) was added. The resulting mixture was stirred at room temperature for 24 hours. After that time, Celite was added and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 10:1), obtaining (0.754 g, yield 50%) methyl (3*Z*,8*Z*)-20-benzyloxy-3,4-bis(methoxycarbonyl)-3,8-eicosadienoate (**23-Z**) and (0.261 g, yield 18%) methyl (3*E*,8*Z*)-20-benzyloxy-3,4-bis(methoxycarbonyl)-3,8-eicosadienoate (**23-E**), both as a transparent oil.

Methyl (3*Z*,8*Z*)-20-benzyloxy-3,4-bis(methoxycarbonyl)-3,8-eicosadienoate (**23-Z**)



**IR** (NaCl):  $\nu$  3448, 3003, 2926, 2853, 1735, 1645, 1495, 1454, 1435, 1314, 1268, 1198, 1169, 1099, 1027, 797, 736, 698  $\text{cm}^{-1}$ .

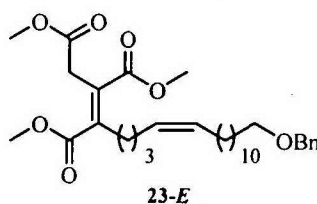
**$^1\text{H-NMR}$**  (300MHz,  $\text{CDCl}_3$ ).  $\delta$  7.29 (5H, m, Ar-H), 5.39 (1H, dt,  $J = 6.6, 10.5$  Hz, H-8 or H-9), 5.35 (1H, dt,  $J = 6.8, 10.5$  Hz, H-9 or H-8), 4.50 (2H, s,  $-\text{OCH}_2\text{Ph}$ ), 3.79 (3H, s,  $-\text{OCH}_3$ ), 3.73 (3H, s,  $-\text{OCH}_3$ ), 3.69 (3H, s,  $-\text{OCH}_3$ ), 3.46 (2H, t,  $J = 6.5$  Hz, H-20), 3.40 (2H, s, H-2), 2.34 (2H, m,  $-\text{CH}_2-$ ), 2.02 (4H, m,  $-\text{CH}_2-$ ), 1.65-1.23 (20H, m,  $-\text{CH}_2-$ ).

**$^{13}\text{C-NMR}$**  (75MHz,  $\text{CDCl}_3$ ).  $\delta$  169.7, 169.3, 166.2, 145.6, 138.4, 130.9, 128.5, 127.9, 127.9, 127.2, 125.4, 72.5, 70.1, 52.0, 51.8, 51.8, 33.4, 30.5, 29.5, 29.4, 29.3, 29.2, 29.2, 29.0, 27.2, 27.0, 26.4, 25.9.

**LRMS(EI)**:  $m/z$  544( $\text{M}^+$ , 0), 512(2), 485(2), 453(2), 389(23), 329(8), 198(45), 166(50), 91(100).

**E.A.** ( $\text{C}_{32}\text{H}_{48}\text{O}_7$ ): Found: C, 70.45, H, 9.00; Calculated: C, 70.56, H, 8.88.

Methyl (3*E*,8*Z*)-20-benzyloxy-3,4-bis(methoxycarbonyl)-3,8-eicosadienoate (**23-E**)



**IR** (NaCl):  $\nu$  3436, 3000, 2926, 2853, 1741, 1435, 1251, 1201, 1169, 1101, 1014, 735, 697  $\text{cm}^{-1}$ .

**$^1\text{H-NMR}$**  (300MHz,  $\text{CDCl}_3$ ).  $\delta$  7.31 (5H, m, Ar-H), 5.37 (1H, dt,  $J = 7.0, 10.9$  Hz, H-8 or H-9), 5.33 (1H, dt,  $J = 8.3, 10.9$  Hz, H-9 or H-8), 4.50 (2H, s,  $-\text{OCH}_2\text{Ph}$ ), 3.78 (6H, s,  $-\text{OCH}_3$ ), 3.68 (3H, s,  $-\text{OCH}_3$ ), 3.51 (2H, s, H-2), 3.46 (2H, t,  $J = 6.5$  Hz, H-20), 2.58 (2H, m,  $-\text{CH}_2-$ ), 2.07 (4H, m,  $-\text{CH}_2-$ ), 1.65-1.23 (20H, m,  $-\text{CH}_2-$ ).

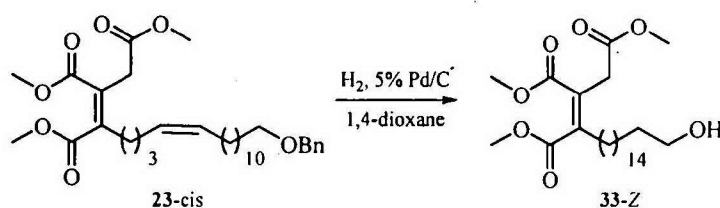
**$^{13}\text{C-NMR}$**  (75MHz,  $\text{CDCl}_3$ ).  $\delta$  170.4, 168.6, 167.4, 146.5, 143.7, 138.6, 131.0, 130.6, 128.7, 128.5, 128.1, 127.4, 127.2, 72.7, 70.3, 51.9, 51.8, 51.6, 36.4, 29.6,

29.5, 29.4, 29.4, 29.3, 29.2, 29.0, 28.5, 27.1, 26.8, 26.0.

**LRMS(EI):**  $m/z$  544( $M^+$ , 0), 512(1), 453(3), 421(8), 389(26), 357(13), 198(21), 91(100).

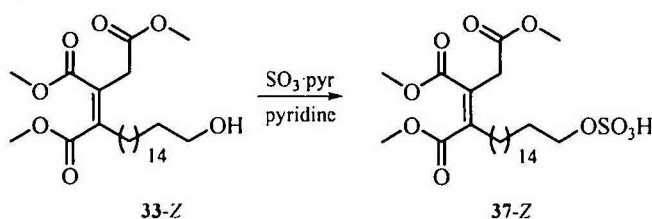
**E.A. (C<sub>32</sub>H<sub>48</sub>O<sub>7</sub>):** Found: C, 70.50, H, 9.05; Calculated: C, 70.56, H, 8.88.

5 **Example 16.** Preparation of methyl (Z)-20-hydroxy-3,4-bis(methoxycarbonyl)-3-eicosadienoate (**33-Z**)



Pd/C (0.042 g, 5% by weight, 0.02 mmoles) was added to a solution of methyl (3Z,8Z)-20-benzyloxy-3,4-bis(methoxycarbonyl)-3,8-eicosadienoate (**23-Z**) (0.217 g, 0.398 mmoles) in 1,4-dioxane (4.33 ml). The mixture was stirred under an argon atmosphere at room temperature for 1 hour. After that time, the mixture was filtered through Celite with AcOEt and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 3:1), obtaining (0.149 g, yield 82%) methyl (Z)-20-hydroxy-3,4-bis(methoxycarbonyl)-3-eicosenoate (**33-Z**), as a white solid.

15 **Example 17.** Preparation of methyl (Z)-3,4-bis(methoxycarbonyl)-20-sulfooxy-3-eicosenoate (**37-Z**)



SO<sub>3</sub>·pyr (0.181 g, 1.11 mmoles) was added in small portions to a solution of methyl (Z)-20-hydroxy-3,4-bis(methoxycarbonyl)-3-eicosenoate (**33-Z**) (0.102 g, 0.22 mmoles) in pyridine (4.2 ml). The mixture was stirred at room temperature for 2 hours. After that time, the solvent was removed under reduced pressure. The residue was suspended in a 1:1 H<sub>2</sub>O/MeOH mixture (2 ml), neutralized with an aqueous solution of 0.5M KOH and the solvent was removed under reduced pressure. The product was purified by trituration with MeOH, obtaining (0.119 g, quantitative

yield) methyl (*Z*)-3,4-bis(methoxycarbonyl)-20-sulfooxy-3-eicosenoate (**37-Z**), as a white solid.

**m.p.:** 129-130°C.

**IR (BrK):**  $\nu$  3452, 2923, 2852, 1733, 1643, 1436, 1255, 1217, 1065, 1008, 773, 619, 577  $\text{cm}^{-1}$ .

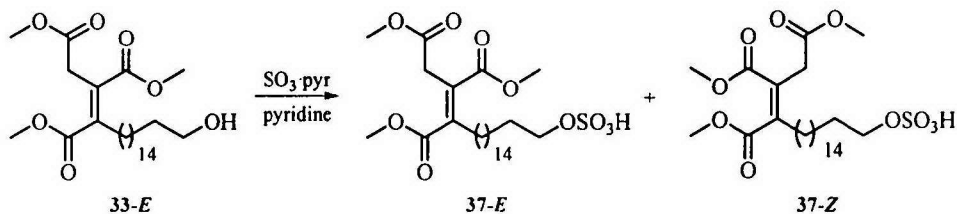
**$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  4.10 (2H, m, H-20), 3.79 (3H, s,  $-\text{OCH}_3$ ), 3.73 (3H, s,  $-\text{OCH}_3$ ), 3.69 (3H, s,  $-\text{OCH}_3$ ), 3.41 (2H, s, H-2), 2.33 (4H, m,  $-\text{CH}_2-$ ), 1.60-1.24 (26H, m,  $-\text{CH}_2-$ ).

**$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  170.2, 169.7, 166.7, 146.1, 125.4, 69.8, 52.3, 52.1, 33.7, 31.3, 29.9, 29.5, 29.3, 27.5, 25.8.

**LRMS(EI):**  $m/z$  536( $\text{M}^+$ , 0), 518(13), 486(6), 458(10), 426(5), 346(7), 287(6), 198(44), 166(88), 55(100).

**E.A. ( $\text{C}_{25}\text{H}_{44}\text{O}_{10}\text{S}$ ):** Found: C, 56.00, H, 8.30; Calculated: C, 55.95, H, 8.26.

**Example 18.** Reaction of methyl (*E*)-20-hydroxy-3,4-bis(methoxycarbonyl)-3-eicosenoate (**33-E**) with SO<sub>3</sub>·pyr

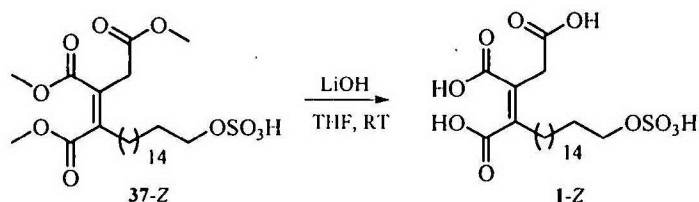


SO<sub>3</sub>·pyr (0.181 g, 1.11 mmoles) was added in small portions to a solution of methyl (*E*)-20-hydroxy-3,4-bis(methoxycarbonyl)-3-eicosenoate (**33-E**) (0.102 g, 0.22 mmoles) in pyridine (4.2 ml). The mixture was stirred at room temperature for 2 hours. After that time, the solvent was removed under reduced pressure. The residue was suspended in a 1:1 H<sub>2</sub>O/MeOH mixture (2 ml), was neutralized with an aqueous solution of 0.5M KOH and the solvent was removed under reduced pressure. The product was purified by trituration with MeOH, obtaining (0.119 g, quantitative yield) a mixture of methyl (*E*)-3,4-bis(methoxycarbonyl)-20-sulfooxy-3-eicosenoate (**37-E**) and methyl (*Z*)-3,4-bis(methoxycarbonyl)-20-sulfooxy-3-eicosenoate (**37-Z**) in a 2:3 ratio, respectively, as a white solid.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>). δ 4.10 (2H, m, H-20 **37-Z**), 3.97 (2H, m, H-20 **37-E**), 3.79 (3H, s, -OCH<sub>3</sub> **37-Z**), 3.78 (6H, s, -OCH<sub>3</sub> **37-E**), 3.73 (3H, s, -OCH<sub>3</sub> **37-Z**), 3.69 (3H, s, -OCH<sub>3</sub> **37-Z**), 3.68 (3H, s, -OCH<sub>3</sub> **37-E**), 3.50 (2H, s, H-2 **37-E**), 3.41 (2H, s, H-2 **37-Z**), 2.60 (4H, m, -CH<sub>2</sub>- **37-E**), 2.33 (4H, m, -CH<sub>2</sub>- **37-Z**), 1.60-1.24 (26H, m, -CH<sub>2</sub>- **37-Z**, **37-E**).

LRMS(EI): *m/z* 536(M<sup>+</sup>, 0), 518(13), 486(6), 458(10), 426(5), 346(7), 287(6), 198(44), 166(88), 55(100).

**Example 19.** Preparation of (*Z*)-3,4-dicarboxy-20-sulfooxy-3-eicosenoic acid (**1-Z**)



An aqueous solution of 1 M LiOH (3.3 ml) to a solution of methyl (*Z*)-3,4-bis(methoxycarbonyl)-20-sulfooxy-3-eicosenoate (**37-Z**) (0.059 g, 0.11 mmoles) in THF (4.7 ml) was added. The mixture was stirred at room temperature for 1 hour.

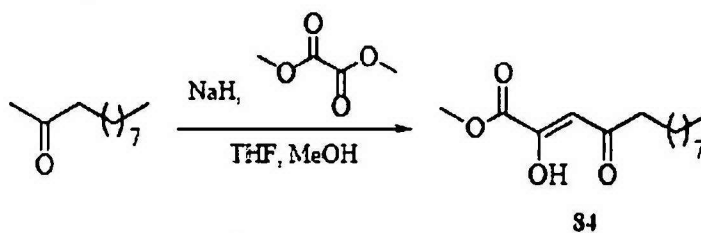
After that time, H<sub>2</sub>O (5 ml) was added. The phases were separated. The aqueous phase was washed with AcOEt (2 × 5 ml), acidified with an aqueous solution of 10% HCl and extracted with AcOEt (3 × 5 ml). The extraction organic phase was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure, obtaining (0.048 g, yield 88%) (Z)-3,4-dicarboxy-20-sulfooxy-3-eicosenoic acid (**1-Z**), as a white solid.

**m.p.:** 63-65 °C.

**IR** (NaCl):  $\nu$  3436, 2919, 2849, 1771, 1732, 1644, 1464, 1190, 1052 cm<sup>-1</sup>.

**<sup>1</sup>H-NMR** (300MHz, CD<sub>3</sub>OD).  $\delta$  3.88 (2H, t,  $J$  = 6.5 Hz, H-20), 3.61 (2H, s, H-2), 2.23 (2H, m, -CH<sub>2</sub>-), 1.55-1.18 (28H, m, -CH<sub>2</sub>-).

**Example 20:** Preparation of methyl (Z)-2-hydroxy-4-oxo-2-tridecenoate (**84**)



MeOH (0.5 ml) was added to a suspension of NaH (0.253 g, 10.57 mmoles) in THF (5 ml) at 0°C. The mixture was stirred until reaching room temperature. Then, dimethyl oxalate (1.14 g, 9.69 mmoles) and a solution of 2-undecanone (1.5 g, 8.8 mmoles) in THF (3 ml) were added. The resulting mixture was heated at 60°C for 5 hours. After that time, AcOEt (10 ml) and an aqueous solution of 10% HCl (10 ml) were added. The phases were separated, and the aqueous phase was extracted with AcOEt (3 × 10 ml). The organic phase was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 100:1), obtaining (1.18 g, yield 52%) methyl (Z)-2-hydroxy-4-oxo-2-tridecenoate (**84**), as a colorless oil.

**IR** (NaCl):  $\nu$  2922, 2853, 1739, 1720, 1648, 1543, 1437, 1018 cm<sup>-1</sup>.

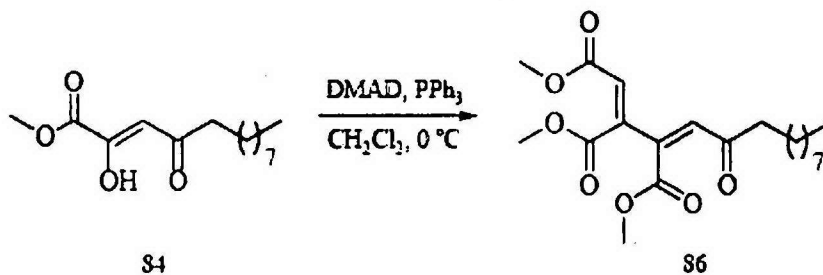
**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>).  $\delta$  6.35 (1H, s, H-3), 3.88 (3H, s, -OCH<sub>3</sub>), 2.46 (2H, t,  $J$  = 7.1 Hz, H-5), 1.63 (2H, m, H-6), 1.25 (12H, broad s, -CH<sub>2</sub>-), 0.86 (3H, m, -CH<sub>3</sub>).

**<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>).  $\delta$  203.3, 166.3, 162.6, 101.6, 53.0, 48.8, 31.7, 29.3, 29.1, 29.0, 24.8, 23.3, 20.9, 14.0.

**LRMS(EI):**  $m/z$  256( $M^+$ , 0), 197(100), 168(1), 155(12), 144(12).

**E.A.** ( $C_{14}H_{24}O_4$ ): Found: C, 65.50, H, 9.50; Calculated: C, 65.60, H, 9.44.

**Example 21:** Preparation of methyl (2Z,4Z)-3,4-bis(methoxycarbonyl)-6-oxo-2,4-pentadecadienoate (**86**)



5

A solution of DMAD (0.138 g, 0.97 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 ml) was added to a solution of methyl (Z)-2-hydroxy-4-oxo-2-tridecenoate (**84**) (0.250 g, 0.97 mmol) and  $\text{PPh}_3$  (0.255 g, 0.97 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 ml) at  $0^\circ\text{C}$ . The mixture was stirred at room temperature for 24 hours. After that time, the solvent was removed under reduced pressure. The crude reaction product was dissolved in toluene (10 ml), and the mixture was heated under reflux for 6 hours. Then, the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 6:1), obtaining (0.240 g, yield 64%) methyl (2Z,4Z)-3,4-bis(methoxycarbonyl)-6-oxo-2,4-pentadecadienoate (**86**), as a colorless oil.

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**IR** (NaCl):  $\nu$  3428, 2952, 2928, 2851, 1727, 1695, 1436, 1254, 1029  $\text{cm}^{-1}$ .

**$^1\text{H-NMR}$**  (300 MHz,  $\text{CDCl}_3$ ).  $\delta$  6.32 (1H, s, H-5), 6.11 (1H, s, H-2), 3.91 (3H, s,  $-\text{OCH}_3$ ), 3.88 (3H, s,  $-\text{OCH}_3$ ), 3.75 (3H, s,  $-\text{OCH}_3$ ), 2.54 (2H, t,  $J = 7.3$  Hz, H-7), 1.62 (2H, m, H-8), 1.24 (12H, broad s,  $-\text{CH}_2-$ ), 0.86 (3H, t,  $J = 6.1$  Hz,  $-\text{CH}_3$ ).

20

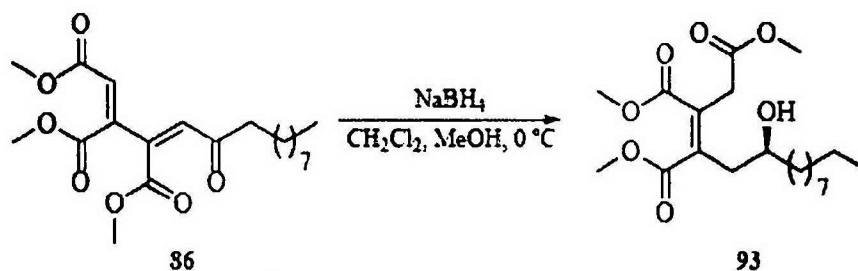
**$^{13}\text{C-NMR}$**  (75 MHz,  $\text{CDCl}_3$ ).  $\delta$  198.3, 166.2, 165.9, 164.4, 142.8, 138.9, 129.9, 124.5, 53.1, 53.0, 52.4, 38.6, 31.8, 29.3, 29.2, 29.0, 28.8, 23.5, 22.6, 14.0.

**LRMS(EI):**  $m/z$  382( $M^+$ , 1), 351(4), 323(90), 291(11), 265(3), 255(10), 227(32), 196(100).

**E.A.** ( $C_{20}H_{30}O_7$ ): Found: C, 62.90, H, 8.00; Calculated: C, 62.81, H, 7.91.

**Example 22:** Reaction of methyl (2Z,4Z)-3,4-bis(methoxycarbonyl)-6-oxo-2,4-pentadecadienoate (**86**) with  $\text{NaBH}_4$

25



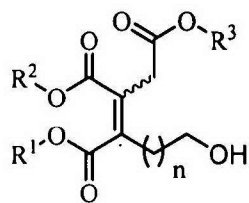
NaBH<sub>4</sub> (0.009 g, 0.244 mmol) was added to a solution of methyl (2Z,4Z)-3,4-bis(methoxycarbonyl)-6-oxo-2,4-pentadecadienoate (**86**) (0.360 g, 0.941 mmol) in a 5:2 CH<sub>2</sub>Cl<sub>2</sub>/MeOH mixture (21 ml) at 0°C. The mixture was stirred at 0°C for 1 hour. After that time, sat. NH<sub>4</sub>Cl (10 ml) was added. The phases were separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 ml). The organic phase was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure. The product was purified by a chromatographic column (hexane/AcOEt, 4:1), obtaining (0.020 g, yield 6%) methyl *rac*-(Z,R)-3,4-bis(methoxycarbonyl)-6-hydroxy-3-pentadecenoate (**93**), as a colorless oil.

**<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>). δ 3.80 (3H, s, -OCH<sub>3</sub>), 3.74 (3H, s, -OCH<sub>3</sub>), 3.70 (3H, s, -OCH<sub>3</sub>), 3.66 (1H, m, H-6), 3.46 (2H, s, H-2), 2.48 (2H, d, *J* = 6.0 Hz, H-5), 1.64-1.43 (4H, m, -CH<sub>2</sub>-), 1.25 (16H, broad s, -CH<sub>2</sub>-), 0.86 (3H, m, -CH<sub>3</sub>).

**LRMS(EI)**: *m/z* 386(M<sup>+</sup>, 0), 353(0), 320(2), 295(1), 265(0), 235(1), 198(91), 166(100), 139(28), 111(10).

**CLAIMS**

1.- A process for obtaining a compound of formula (VIII), its stereoisomers or mixtures thereof



(VIII)

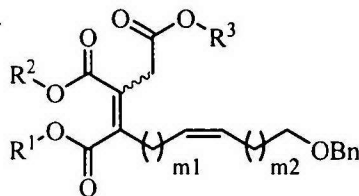
wherein

$R^1$ ,  $R^2$  and  $R^3$  are independently selected from substituted or unsubstituted  $C_1-C_{20}$  alkyl; and

$n$  is an integer between 2 and 20;

characterized in that it comprises at least one of the following steps (a), (b) or (c)

(a) subjecting a compound of formula (VI), its stereoisomers or mixtures thereof, to a hydrogenation reaction



(VI)

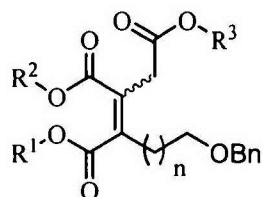
wherein

$R^1$ ,  $R^2$  and  $R^3$  are as defined above;

$m_1$  is an integer which is selected from 1, 2, 3, 4 and 5; and

$m_2$  is an integer between 0 and 13;

(b) subjecting a compound of formula (VII), its stereoisomers or mixtures thereof, to a hydrogenation reaction



(VII)

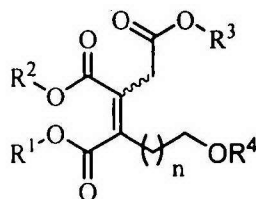
wherein

$n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above;

or

(c) removing the trialkylsilyl group of a compound of formula (XVI), its stereoisomers or mixtures thereof

5



(XVI)

wherein

$n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above; and

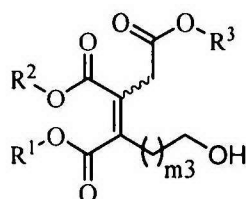
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$R^4$  is a trialkylsilyl group.

2.- The process according to claim 1, wherein said hydrogenation uses Pd/C as a catalyst and 1,4-dioxane as a solvent.

3.- The process according to any of claims 1 or 2, wherein the compound of formula (VIII), its stereoisomers or mixtures thereof, is a compound of formula (VIIIa), its stereoisomers or mixtures thereof,

15



(VIIIa)

wherein

$R^1$ ,  $R^2$  and  $R^3$  are independently selected from substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl; and

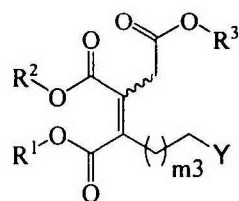
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$m_3$  is an integer between 2 and 18;

which additionally comprises the following steps

(i) activating as a leaving group the hydroxyl group of a compound of formula (VIIIa), its stereoisomers or mixtures thereof, to form a compound of formula (XVIII), its stereoisomers or mixtures thereof

25



(XVIII)

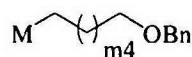
wherein

$m_3$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above; and

5

$Y$  is selected from  $-\text{OSO}_3\text{H}$ ,  $-\text{OMs}$ ,  $-\text{OTs}$ ,  $\text{I}$  and  $\text{Br}$ ;

(ii) reacting said compound of formula (XVIII), its stereoisomers or mixtures thereof, with a compound of formula (X)



(X)

10

wherein

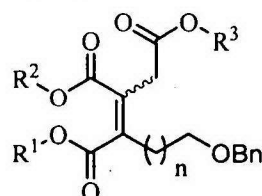
$M$  is a metal, preferably selected from among Grignard reagents transmetalated or non-transmetalated with  $\text{Zn}$ ,  $\text{Al}$ , or  $\text{Cu}$ ; and

$m_4$  is an integer between 0 and 18; and

the relation  $m_3 + m_4 + 2 = n$  is met;

15

to obtain a compound of formula (VII), its stereoisomers or mixtures thereof



(VII)

wherein

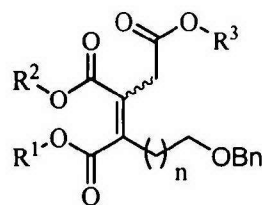
$n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined above,

20

and

(iii) subjecting said compound of formula (VII), its stereoisomers or mixtures thereof, to a hydrogenation reaction.

4.- A compound of formula (VII)



(VII)

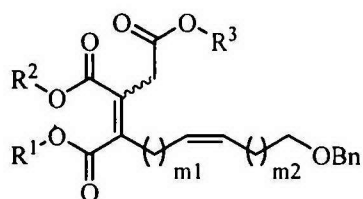
wherein

$n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined in claim 1;

5 its stereoisomers or mixtures thereof.

5.- A process for the synthesis of a compound of formula (VII) as defined in claim 4, its stereoisomers or mixtures thereof, characterized in that it comprises the selective hydrogenation of the double bond of the compound of formula (VI), as defined in claim 1, its stereoisomers or mixtures thereof.

10 6.- A compound of formula (VI)



(VI)

wherein

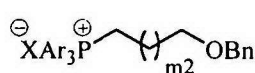
$m_1$ ,  $m_2$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined in claim 1;

15 its stereoisomers or mixtures thereof.

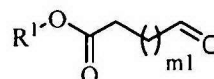
7.- A process for obtaining a compound of formula (VI) as defined in claim 6, its stereoisomers or mixtures thereof, characterized in that it comprises the following steps

(i) reacting a compound of formula (III) with a compound of formula (XI), to yield a compound of formula (IV)

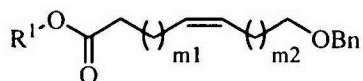
20



(XI)



(III)



(IV)

wherein

$R^1$  is selected from a substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl,

$m_1$  is an integer which is selected from 1, 2, 3, 4 and 5;

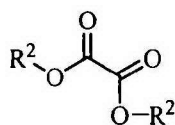
5  $m_2$  is an integer between 0 and 13;

X is a halogen; and

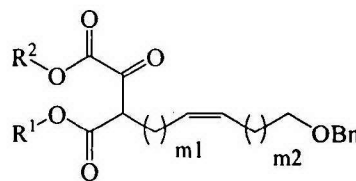
each of the Ar groups is independently selected from among  $C_6$ - $C_{10}$  aryl groups.

(ii) reacting said compound of formula (IV) with an oxalate of formula (XII) in the presence of a base to yield a compound of formula (V)

10



(XII)



(V)

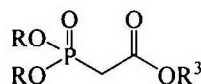
wherein

$m_1$ ,  $m_2$ ,  $R^1$  and  $R^2$  are as defined above;

15

and

(iii) reacting said compound of formula (V) with a phosphonate of formula (XIII)



(XIII)

wherein

20

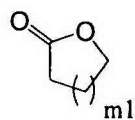
$R^1$  is selected from a substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl; and

R is selected from  $C_1$ - $C_4$  alkyl substituted or unsubstituted with one or more halogen atoms, benzyl, phenyl and tolyl.

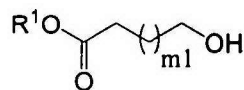
8.- The process according to claim 7, characterized in that the preparation of said compound of formula (III) comprises the steps of

25

(i) reacting a compound of formula (XXIVa) in the presence of an alcohol of formula  $R^1OH$  to yield a compound of formula (IIa)



(XXIVa)



(IIa)

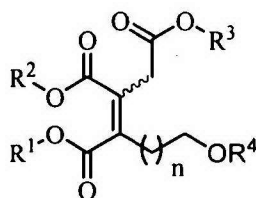
wherein

$R^1$  is selected from a substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl; and  
 5  $m_1$  is an integer which is selected from 0, 1, 2, 3, 4 and 5;

and

(ii) oxidizing the primary hydroxyl of the compound of formula (IIa) to aldehyde.

9.- A compound of formula (XVI), its stereoisomers or mixtures thereof



(XVI)

wherein

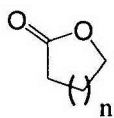
$n$  is an integer between 2 and 20;

$R^1$ ,  $R^2$  and  $R^3$  are independently selected from a substituted or unsubstituted  
 15  $C_1$ - $C_{20}$  alkyl; and

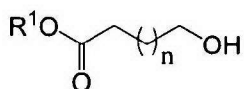
$R^4$  is a trialkylsilyl group;

10.- A process for the synthesis of a compound of formula (XVI) as defined  
 in claim 9, its stereoisomers or mixtures thereof, characterized in that it comprises  
 the steps of

(i) reacting a compound of formula (XXIV) in the presence of an alcohol of formula  
 20  $R^1OH$  to yield a compound of formula (II)



(XXIV)

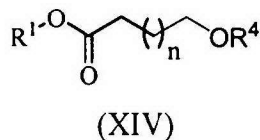


(II)

wherein

$R^1$  is selected from a substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl; and  
 25  $n$  is an integer between 2 and 20;

(ii) protecting the free hydroxyl group of said compound of formula (II) with a trialkylsilyl to obtain a compound of formula (XIV)

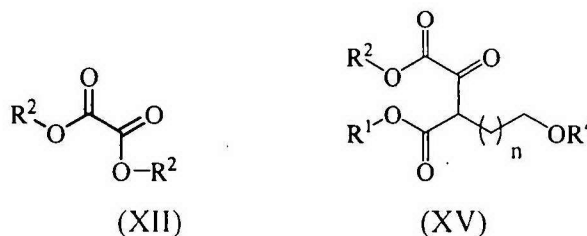


5 wherein

$\text{R}^1$  and  $n$  are as defined above; and

$\text{R}^4$  is a trialkylsilyl group;

(iii) reacting said compound of formula (XIV) with an oxalate of formula (XII) in the presence of a base to obtain a compound of formula (XV)



10

wherein

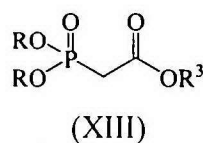
$\text{R}^2$  is selected from a substituted or unsubstituted  $\text{C}_1\text{-C}_{20}$  alkyl; and

$n$ ,  $\text{R}^1$  and  $\text{R}^4$  are as defined above;

15

and

(iv) reacting said compound of formula (XV) with a phosphonate of formula (XIII) in the presence of a base



20

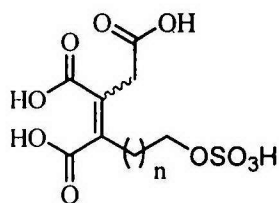
wherein

$\text{R}$  is selected from a substituted or unsubstituted  $\text{C}_1\text{-C}_4$  alkyl with one or more halogen atoms, benzyl, phenyl and tolyl; and

$\text{R}^3$  is selected from a substituted or unsubstituted  $\text{C}_1\text{-C}_{20}$  alkyl.

25

11.- A process for the synthesis of a compound of formula (I),



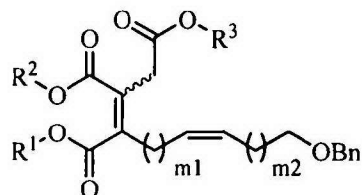
(I)

wherein n is an integer between 2 and 20;

its stereoisomers or mixtures thereof, characterized in that it comprises at least one of the following steps (ai), (aii) or (aiii)

5

(ai) subjecting a compound of formula (VI), its stereoisomers or mixtures thereof, to a hydrogenation

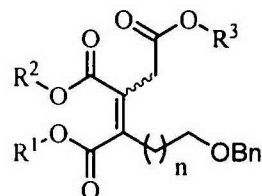


(VI)

10

or

(aii) subjecting a compound of formula (VII), its stereoisomers or mixtures thereof, to a hydrogenation



(VII)

15

or

(aiii) removing the trialkylsilyl group of a compound of formula (XVI), its stereoisomers or mixtures thereof



(XVI)

20

wherein

n is an integer between 2 and 20;

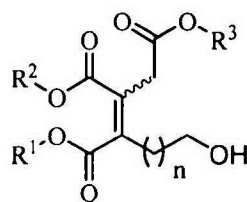
R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl;

m1 is an integer which is selected from 0, 1, 2, 3, 4 and 5;

5 m2 is an integer between 0 and 13; and

R<sup>4</sup> is a trialkylsilyl group;

to obtain a compound of formula (VIII), its stereoisomers or mixtures thereof



(VIII)

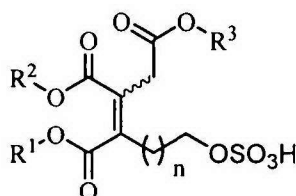
10 wherein

n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above;

and additionally comprises

(b) reacting said compound of formula (VIII), its stereoisomers or mixtures thereof, with a sulfating agent to yield a compound of formula (IX), its stereoisomers or mixtures thereof

15



(IX)

wherein

n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above;

20 and

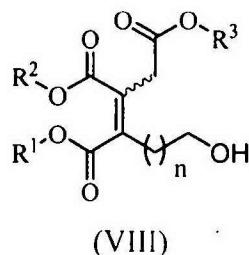
(c) hydrolyzing the ester groups of said compound of formula (IX), its stereoisomers or mixtures thereof, to provide the corresponding acid groups.

25

12.- The process according to any of the previous claims, which comprises obtaining a compound of formula cis-(I), cis-(VI), cis-(VII), cis-(VIII), cis-(VIIIa), cis-(IX), cis-(XVI), cis-(XVIa) or cis-(XVIII) or the enrichment in the cis-isomer of a mixture of cis- and trans-isomers of a compound of formula (I), (VI), (VII), (VIII),

(VIIIa), (IX), (XVI), (XVIa) or (XVIII), by means of the exposure to a basic medium of a compound of formula trans-(I), trans-(VI), trans-(VII), trans-(VIII), trans-(VIIIa), trans-(IX), trans-(XVI), trans-(XVIa) or trans-(XVIII), or a mixture of cis- and trans-isomers of a compound of formula (I), (VI), (VII), (VIII), (VIIIa), (IX), (XVI), (XVIa) or (XVIII).

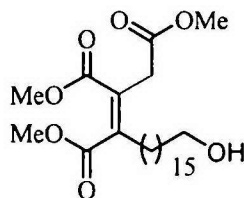
13.- A compound of formula (VIII), its stereoisomers or mixtures thereof



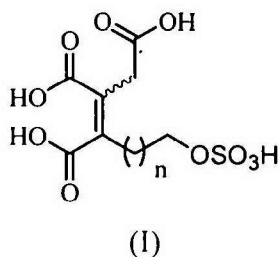
wherein

$R^1$ ,  $R^2$  and  $R^3$  are independently selected from substituted or unsubstituted  $C_1$ - $C_{20}$  alkyl; and  
 $n$  is an integer between 0 and 20;

with the exception of a compound of formula

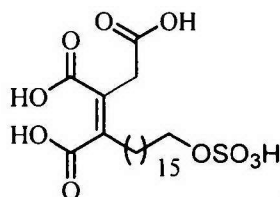


14.- A compound of formula (I), its stereoisomers or mixtures thereof,

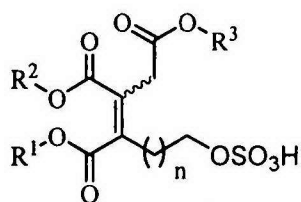


wherein  $n$  is an integer between 2 and 20;

except



15.- A compound of formula (IX), its stereoisomers or mixtures thereof

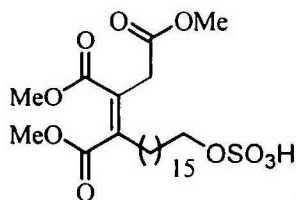


(IX)

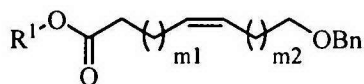
wherein

- 5            n is an integer between 2 and 20; and  
              R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from a substituted or unsubstituted  
              C<sub>1</sub>-C<sub>20</sub> alkyl;

except



10            16.- A compound of formula (IV), its stereoisomers or mixtures thereof

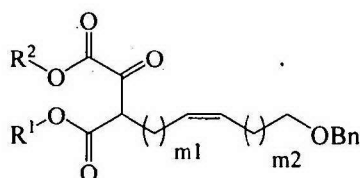


(IV)

wherein

- R<sup>1</sup> is selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl,  
 15            m<sub>1</sub> is an integer which is selected from 0, 1, 2, 3, 4 and 5;  
              m<sub>2</sub> is an integer between 0 and 13.

17.- A compound of formula (V), its stereoisomers or mixtures thereof



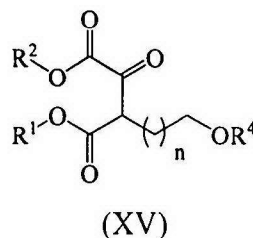
(V)

20            wherein

- R<sup>1</sup> and R<sup>2</sup> are selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl,  
              m<sub>1</sub> is an integer which is selected from 0, 1, 2, 3, 4 and 5;

m2 is an integer between 0 and 13.

18.- A compound of formula (XV), its stereoisomers or mixtures thereof



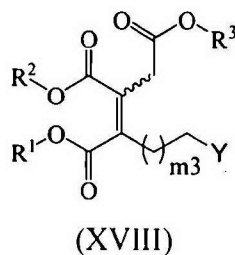
5 wherein

n is an integer between 2 and 20;

R<sup>1</sup> and R<sup>2</sup> are independently selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl; and

R<sup>4</sup> is a trialkylsilyl group.

10 19.- A compound of formula (XVIII), its stereoisomers or mixtures thereof



wherein

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are independently selected from a substituted or unsubstituted C<sub>1</sub>-C<sub>20</sub> alkyl;

15 m3 is an integer between 2 and 18; and

Y is selected from -OSO<sub>3</sub>H, OTs and Br.

20 20.- Use of at least one compound selected from the compounds of formula (II), (III), (IV), (V), (VI), (VII), (VIII), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVIII) and (XXIV) as defined in the previous claims, their stereoisomers or mixtures thereof, for the synthesis of a compound of formula (I), its stereoisomers or mixtures thereof.