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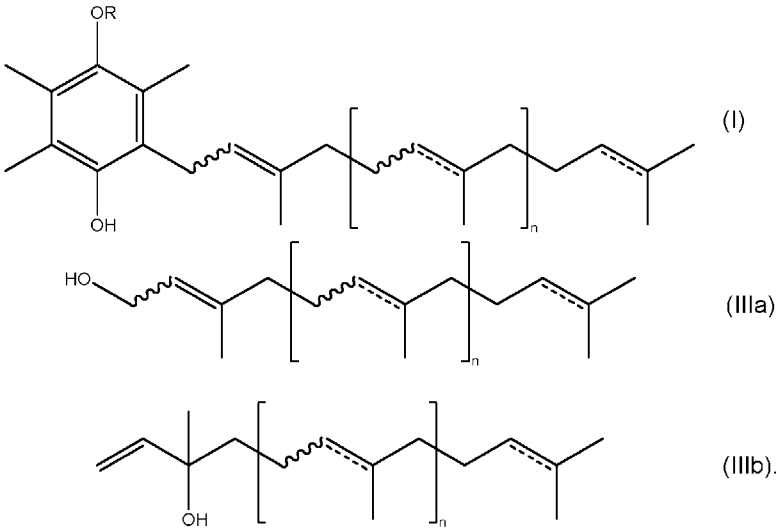
(54) Title: COUPLING OF 2,3,5-TRIMETHYLHYDROQUINONE AND UNSATURATED ALCOHOLS



(57) Abstract: The present invention relates to the formation of compound of the formula (I) by reacting 2,3,6-trimethylhydroquinone or a protected derivative thereof with the unsaturated alcohol of formula (IIIa) or (IIIb) in the presence of $Gd(OTf)_3$ or $Tm(OTf)_3$ or $Al(OTf)_3$ or $Y(OTf)_3$ or $Fe(OTf)_2$ or camphorsulfonic acid or $BiCl_3$ as acidic catalyst.

WO 2022/229213 A1

[Continued on next page]

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COUPLING OF 2,3,5-TRIMETHYLHYDROQUINONE AND UNSATURATED ALCOHOLS

Technical Field

The present invention relates to the field of the synthesis of chromanes and chromenes, particularly, of 3,4-dehydrotocotrienols, tocotrienols and tocopherols.

Background of the invention

Chromane compounds comprising olefinic carbon-carbon double bonds are an important class of chemicals. Particularly, α-tocotrienol is an highly important member of this class.

The corresponding compound having a saturated side chain, i.e. α-tocopherol, is known to be prepared from 2,3,6-trimethylhydroquinone and isophytol in the presence of Lewis and/or Brønsted acids.

For example, WO 2004/063182 A1 discloses the formation of α-tocopheryl acetate from 2,3,6-trimethylhydroquinone-1-acetate and isophytol in the presence of a large variety of metal triflates. Isophythol has only one carbon-carbon double bond which is used for the coupling reaction, however, has no further double bond(s) which might lead to secondary ring formations, i.e. ring formation in the side chain.

WO 2004/046126 A1 discloses the formation of α-tocopheryl acetate from 2,3,6-trimethylhydroquinone-1-acetate and isophytol in the presence of a large variety of sulfonic acids, particularly triflic acid or p-toluenesulfonic acid. As isophythol is used, no secondary ring formation is possible.

EP 949255 A1 discloses the coupling of TMHQ with isophythol using sulfuric acid or a few sulfonic acids, particularly triflic acid or p-toluenesulfonic acid.

However, it has been shown that the use of those acidic catalysts are generally not suitable for the reaction of 2,3,6-trimethylhydroquinone (TMHQ) or its protected form with the respective unsaturated alcohols, such as geranyl-geraniol or farnesol, because undesired cyclic compounds are formed.

This finding is completely in line with Kabbe and Heitzer, *Synthesis* **1978**, *12*, 888-889, who has reported that using the known synthetic pathway for vitamin

E (i.e. α-tocopherol) from TMHQ and isophytol is not suitable for the synthesis of tocotrienols (i.e. from TMHQ and geranyllinalool) because the isoprenoid side chain undergoes acid-catalyzed secondary ring closure reactions.

The synthesis of tocotrienol and its precursors, however, is still of great importance.

Summary of the invention

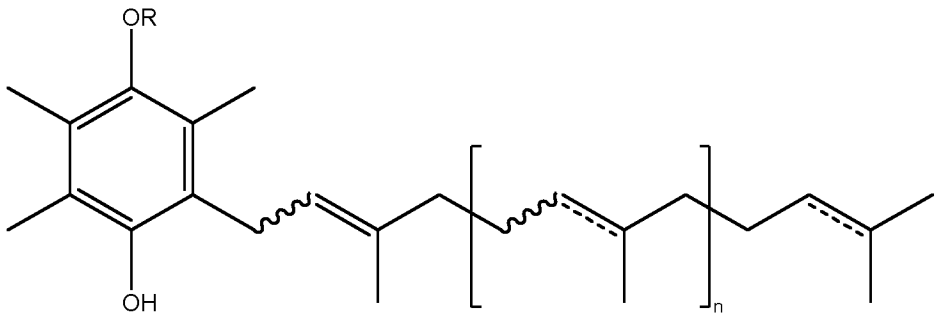
Therefore, the problem to be solved by the present invention is to find a suitable process for the manufacturing of the compound of the formula (I) from TMHQ or its protected form with unsaturated alcohols of the formula (IIIa) or (IIIb).

It has been very surprising that despite the teaching of the prior art, a few members of the metal triflates and sulfonic acids are suitable catalysts for this reaction and yield the compound of formula (I) in high yield and selectivity, particularly with low tendency of forming cyclic compounds by the isoprenoid side chains as side products.

Further aspects of the invention are subject of further independent claims. Particularly preferred embodiments are subject of dependent claims.

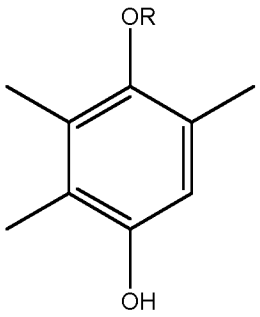
Detailed description of the invention

In a first aspect, the present invention relates to a process of manufacturing the compound of the formula (I)

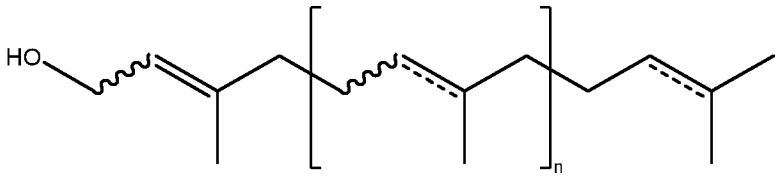


(I)

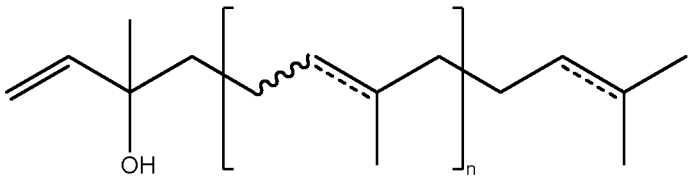
comprising a step of reacting a compound of the formula (II) with a compound of the formula (IIIa) or (IIIb)



(II)



(IIIa)



(IIIb)

in the presence of an acidic catalyst being

either

$Gd(OTf)_3$ or $Tm(OTf)_3$ or $Al(OTf)_3$ or $Y(OTf)_3$ or $Fe(OTf)_2$

or

camphorsulfonic acid;

or

$BiCl_3$;

wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R represents hydrogen or R' which is a phenol protecting group;

OTf represents trifluoromethanesulfonate;

and

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond, with the proviso that at least one of the bonds having dotted lines represents a carbon-carbon double bond;

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration.

It is preferred, that any wavy lines when linked to a carbon-carbon double bond is in the *E*-configuration.

For sake of clarity, some terms used in the present document are defined as follows:

In the present document, a "C_{x-y}-alkyl" group is an alkyl group comprising x to y carbon atoms, i.e., for example, a C_{1-3}-alkyl group is an alkyl group comprising 1 to 3 carbon atoms. The alkyl group can be linear or branched. For example $-CH(CH_3)-CH_2-CH_3$ is considered as a C_4-alkyl group.

An "aralkyl" group is an alkyl group which is substituted by an aryl group.

Accordingly, in the present document, a "C_{x-y}-aralkyl" group is an aralkyl group comprising x to y carbon atoms, i.e., for example, a C_{7-16}-aralkyl group is an aralkyl group comprising 7 to 16 carbon atoms. The aralkyl group can be linear or branched. For example, benzyl group ($-CH_2-C_6H_5$) is considered as a C_7-aralkyl group.

In case identical labels for symbols or groups are present in several formulae, in the present document, the definition of said group or symbol made in the context of one specific formula applies also to other formulae which comprises the same said label.

The term "independently from each other" in this document means, in the context of substituents, moieties, or groups, that identically designated substituents, moieties, or groups can occur simultaneously with a different meaning in the same molecule.

In the present document, any dotted line in formulae represents the bond by which a substituent is bound to the rest of a molecule.

In the present document any bond having dotted line (------) in a chemical formula represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond.

Any wavy line in any formula of this document represents a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the Z or in the E-configuration. It is preferred in all molecules that the carbon-carbon double bond is in the E-configuration.

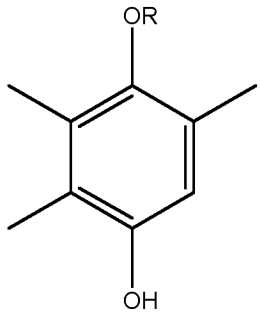
The term "OTf", as used in this document, means trifluoromethanesulfonate.

The "pK_a" is commonly known as negative decadic logarithm of the acid dissociation constant ($pK_a = -\log_{10} K_a$). When the organic acid has several protons the pK_a as used in this document relates to the dissociation constant of the last

proton. For example, for a base having two basic sites the "pka" relates to pK_{a2}. The pK_a are measured at standard temperature and pressure.

Compound of the formula (II)

The compound of formula (II) is either 2,3,5-trimethyl hydroquinone (=2,3,5-trimethylbenzene-1,4-diol, TMHQ) (R=H) or the mono-protected derivative thereof (R≠H; R=R').



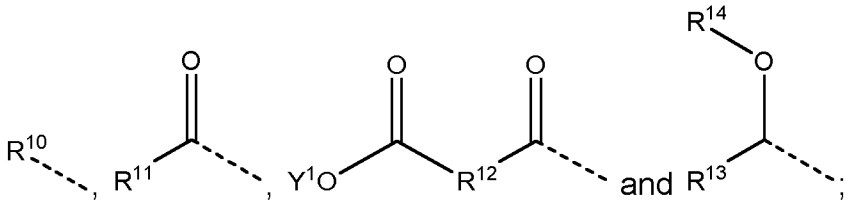
(II)

A phenol protecting group is a group which protects the phenolic group (OH) in any of the formulae in this document having R=H in said formulae and the protecting group can be easily removed, i.e. by state-of-the-art methods, resulting to the respective compound with the free phenolic group again.

The phenol protecting group R' is introduced by a chemical reaction of the compound of the respective formula having H as R with a protecting agent.

The protecting agents leading to the corresponding phenol protecting groups are known to the person skilled in the art, as well as the chemical process and conditions for this reaction. If, for example, the phenol protecting group forms with the rest of the molecule an ester, the suitable protecting agent is for example an acid, an anhydride, or an acyl halide.

The phenol protecting group R' is particularly selected from the groups consisting of



wherein R^{10} and R^{11} represent independently from each other a C_{1-15}-alkyl or a fluorinated C_{1-15}-alkyl or a C_{1-15}-cycloalkyl or a C_{7-15}-aralkyl group;

R^{12} represents a C_{1-15}-alkylene or a C_{6-15}-alkylene group;

and wherein either

R^{13} represents a C_{1-15}-alkyl group or an alkyleneoxyalkyl group or a polyoxyalkylene group;

R^{14} represents hydrogen or a C_{1-15}-alkyl group;

or

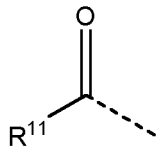
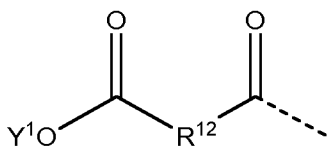
R^{13} and R^{14} represent together a C_{3-7}-alkylene group forming a 5 to 7 membered ring;

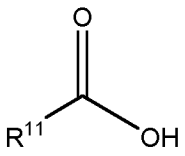
and wherein the single dotted line represents the bond by which said substituent is bound to the rest of a molecule.

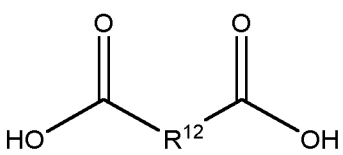
If R' is equal to R^{10}, the respective compound is an ether, which can be formed by the reaction of the respective protecting agent with the phenolic group (OH). In this case, the protecting agent may be for example an alkylation agent such as the respective C_{1-15}-alkyl or fluorinated C_{1-15}-alkyl or C_{1-15}-cycloalkyl or C_{7-15}-aralkyl halide, particularly iodide.

In one of the preferred embodiments R^{10} is a methyl group.

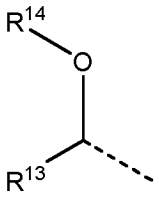
In another preferred embodiment R^{10} is a C_{7-15}-aralkyl group, preferably a benzyl group or a substituted benzyl group, particularly preferred a benzyl group.

If R' is represented by  or , the respective compound is an ester of a carboxylic acid or dicarboxylic acid, which can be formed by the reaction of the respective protecting agent with the phenolic group (OH). In this case, the protecting agent may be for example an anhydride or halide of the respective carboxylic acid (1) or dicarboxylic acid (2).

(1) 

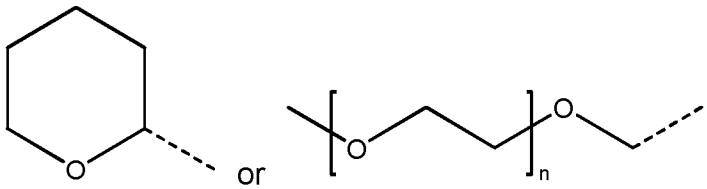
(2) 

If the compound of the respective formula is an ester of a carboxylic acid or dicarboxylic acid, it is preferred that R' is an C_{1-7}-acyl, preferably acetyl, trifluoroacetyl, propionyl or benzoyl group, or a substituted benzoyl group.



If R' is , the respective compound is an acetal, which can be formed by the reaction of the respective protecting agent with the phenolic group (OH). In this case, the protecting agent may be for example, a respective aldehyde, alkyl halide, e.g. $MeO(CH_2)_2OCH_2Cl$, or an enol ether, e.g. 3,4-dihydro-*2H*-pyran.

In this case, the substituent R' is preferably



or with n=0 or 1.

In some instances, acetals are also called “ethers”, particularly in the cases mentioned above: methoxymethyl ether (MOM-ether), β-methoxyethoxy-methyl ether (MEM-ether) or tetrahydropyranyl ether (THP-ether).

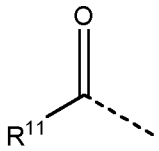
In another preferred embodiment, the respective compound is an ester of phosphoric acid, pyrophosphoric acid, phosphorous acid, sulphuric acid or sulphurous acid.

Depending on the reaction conditions, the esterification is either complete or partial, leaving some residual acid groups of the respective acid non-esterified.

It is most preferred that the protecting group R' is a benzoyl group or a C_{1-4}-acyl group, particularly acetyl or trifluoroacetyl group, more particularly acetyl group. The molecules in which R' represents an acyl group, particularly an acetyl group, can be easily prepared from the corresponding unprotected molecule by esterification, and the unprotected phenolic compound can be obtained from the corresponding ester by ester hydrolysis.

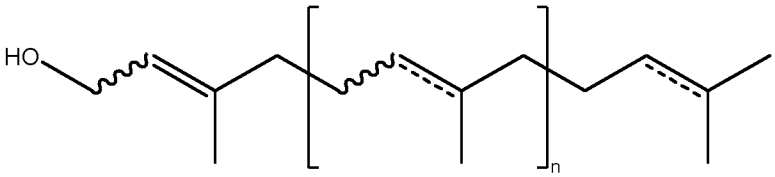
The phenol protecting group can be cleaved by a deprotecting reaction step b), as discussed later.

It is preferred that R' is a phenol protecting group of the formula

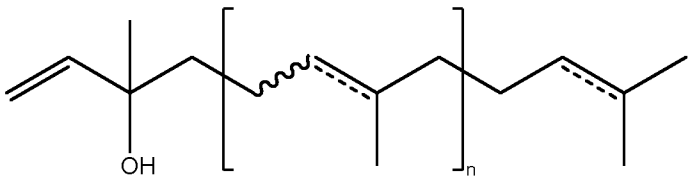


wherein R^{11} is a C_{1-15}-alkyl or a fluorinated C_{1-15}-alkyl or a C_{1-15}-cycloalkyl or a C_{7-15}-aralkyl group, preferably a methyl or a benzyl group.

Compound of the formula (IIIa) or (IIIb)



(IIIa)

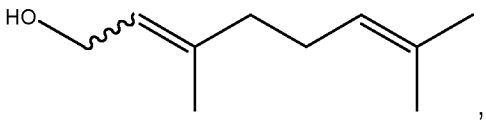


(IIIb)

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12.

It is preferred that n=0 or 1 or 2, preferably 1 or 2, most preferably n = 2.

Examples of preferred compounds of the formula (IIIa) are compounds selected from the group consisting of



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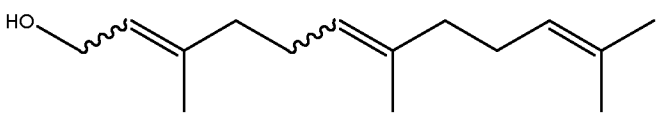

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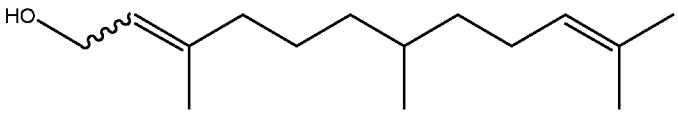

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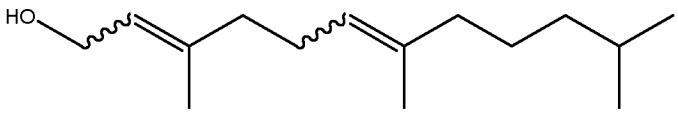

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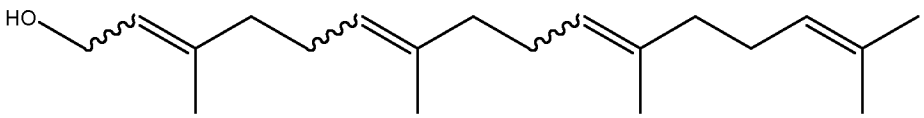

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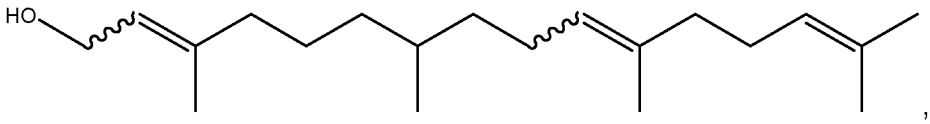
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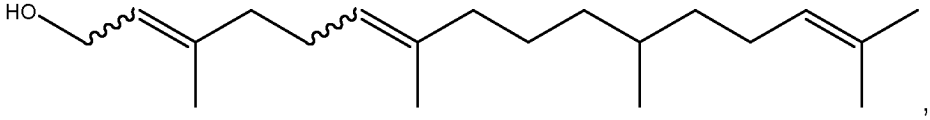
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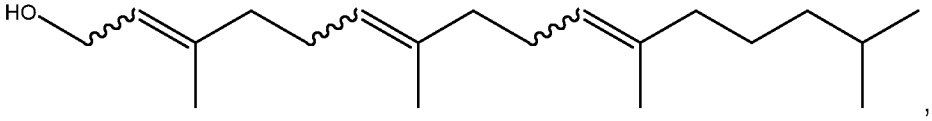
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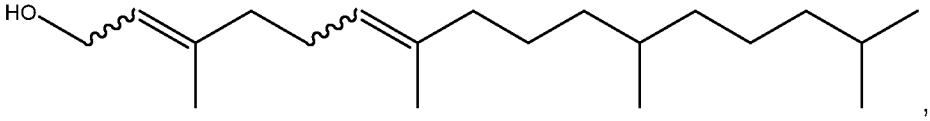
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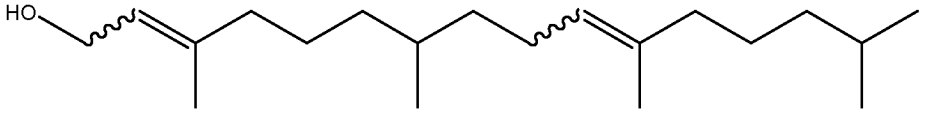
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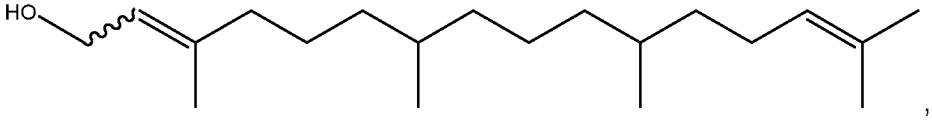
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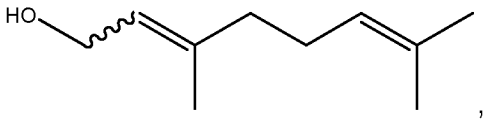
particularly selected from the group consisting of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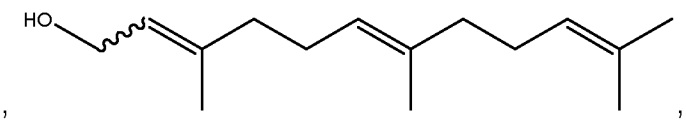
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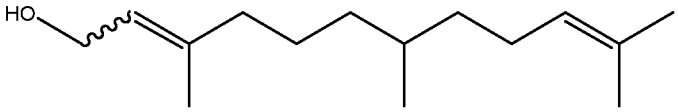
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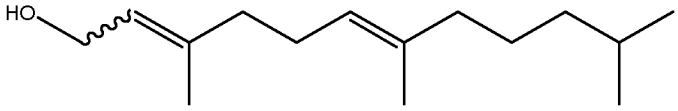
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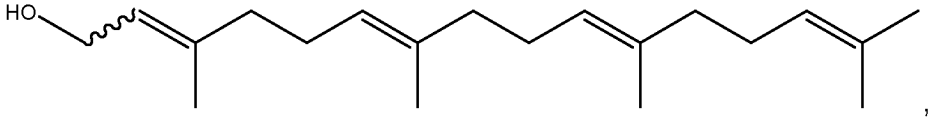
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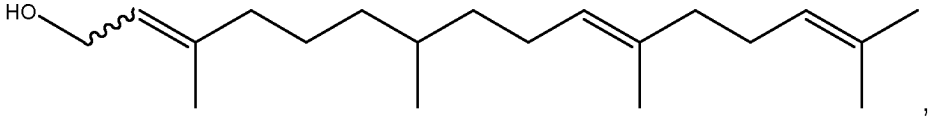
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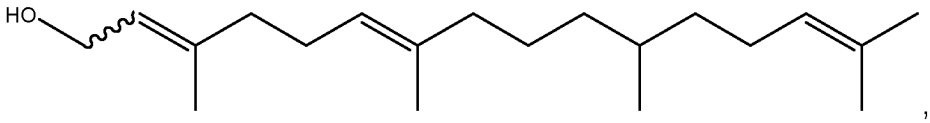
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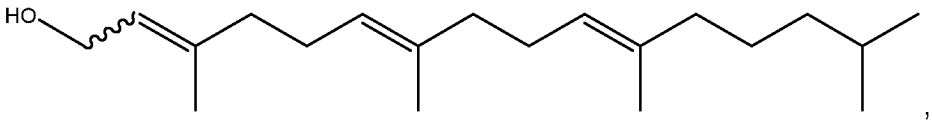
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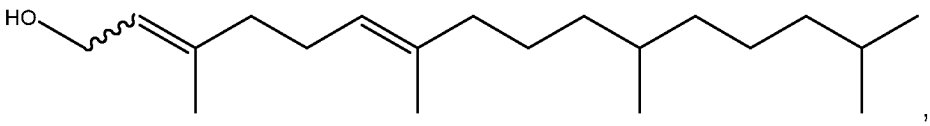

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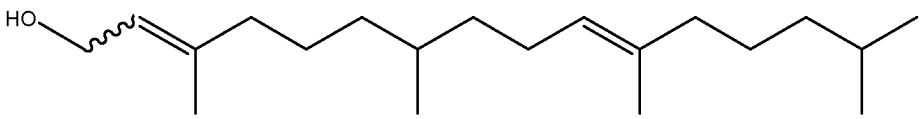

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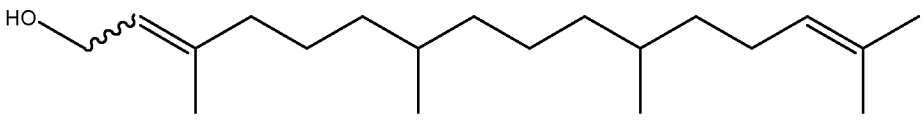
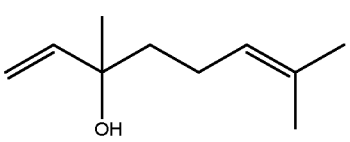


.

It is more preferred that all double bonds are in the *E*-configuration.

Most preferred compounds of formula (IIIa) are 3,7,11-trimethyldodeca-2,6,10-trien-1-ol, preferably (6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol, also known as farnesol; and 3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-ol, preferably (6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-ol, also known as geranylgeraniol. Particularly preferred are (2*E*,6*E*)-farnesol und (2*E*,6*E*,10*E*)—geranylgeraniol.

Examples for preferred compounds of the formula (IIIb) are compounds selected from the group consisting of



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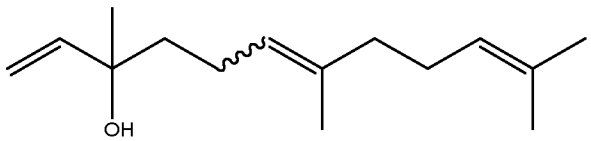

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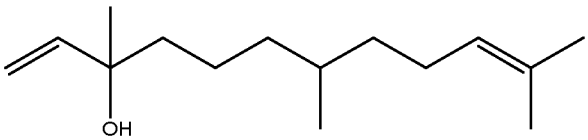

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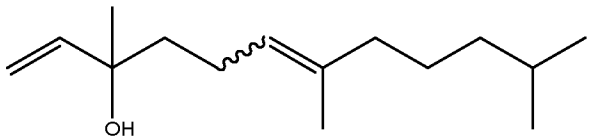

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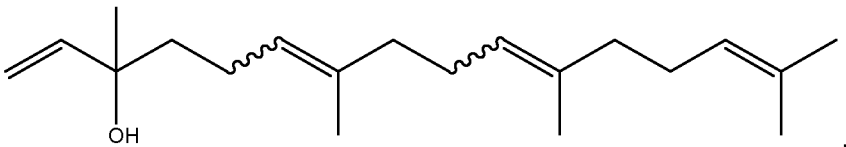

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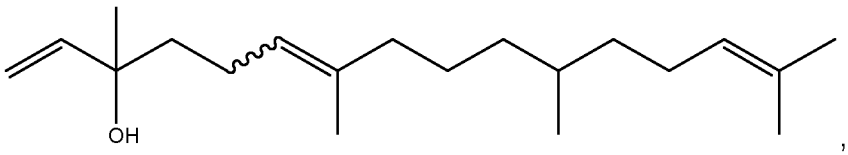

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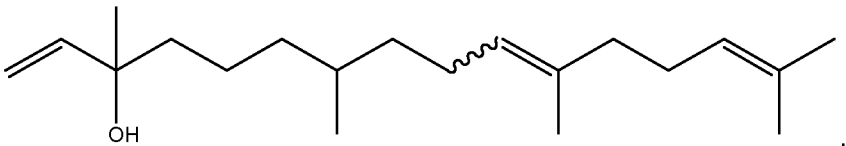

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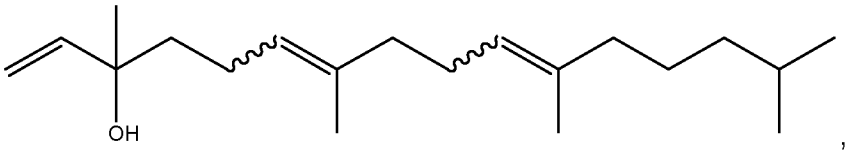

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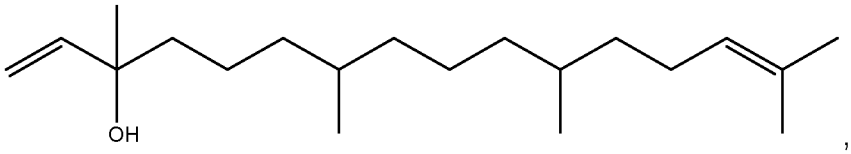

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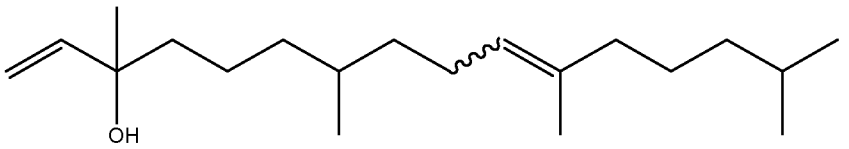

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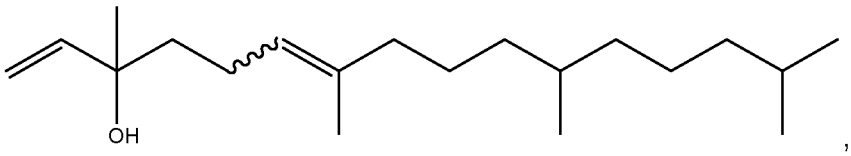

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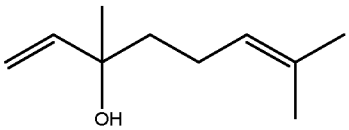
particularly selected from the group consisting of



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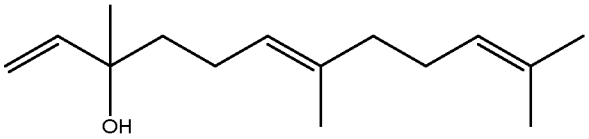

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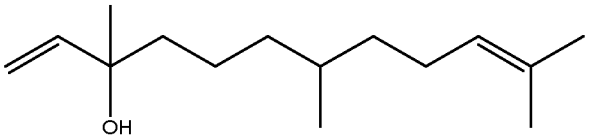

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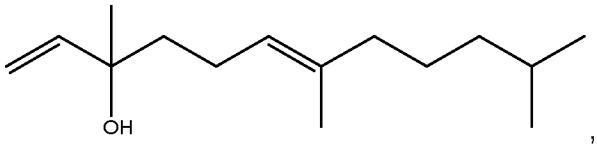

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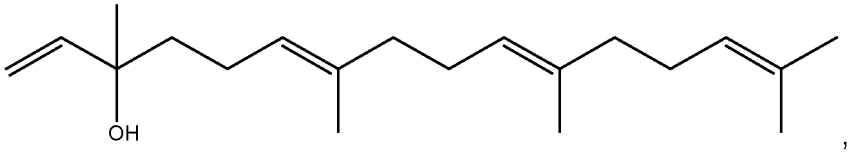

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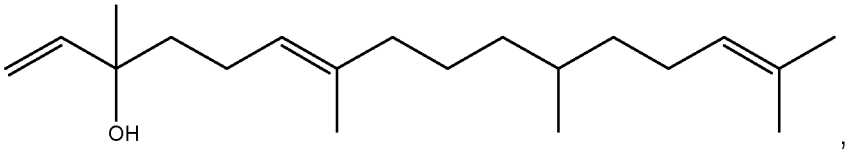

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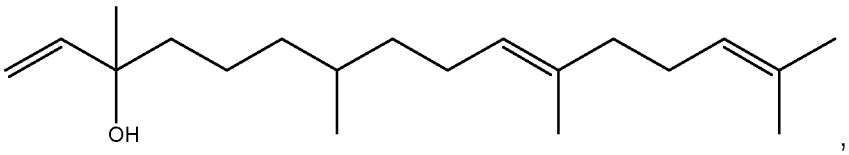

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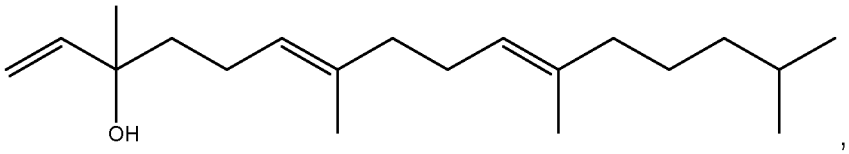

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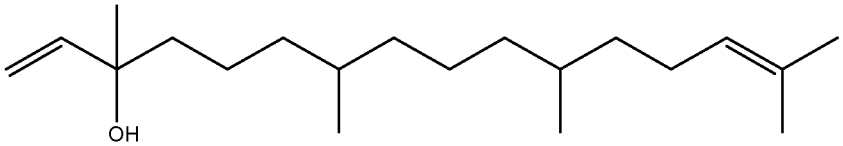

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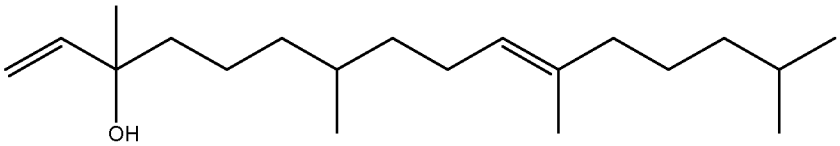

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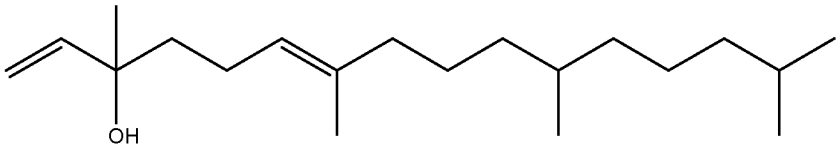


.

Most preferred compounds of formula (IIIb) are 3,7,11-trimethyldodeca-1,6,10-trien-3-ol, preferably (*E*)-3,7,11-trimethyldodeca-1,6,10-trien-3-ol, also known as nerolidol; and 3,7,11,15-tetramethylhexadeca-1,6,10,14-tetraen-3-ol, preferably (6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-1,6,10,14-tetraen-3-ol, also known as geranyllinalool.

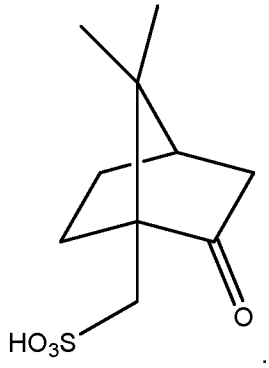
The compound of the formula (IIIa) and (IIIb), particularly geranyllinalool and geranylgeraniol, can either be prepared by known methods in industrial quantities or are also commercially available, for example from Sigma-Aldrich or from natural sources/ bio-based sources, such as disclosed by John A. Hyatt et al., *Organic Process Research and Developmen*t **2002**, *6*, 782-787.

Acidic catalyst

The compound of the formula (II) is reacted with a compound of the formula (IIIa) or (IIIIb) in the presence of a acidic catalyst which is either camphorsulfonic acid or $BiCl_3$ or $Gd(OTf)_3$ or $Tm(OTf)_3$ or $Al(OTf)_3$ or $Y(OTf)_3$ or $Fe(OTf)_2$.

It has been found that only a very small number of Brønsted or Lewis acids are suitable as acidic catalyst for the reaction of this invention.

In one embodiment, the acidic catalyst is camphorsulfonic acid. Camphorsulfonic acid as used in this document is camphor-10-sulfonic acid:



Preferably, camphorsulfonic acid is in its (+) form.

In another embodiment, the acid catalyst is $BiCl_3$.

In another embodiment, the acidic catalyst is the triflate of gadolinium or thulium or aluminum or yttrium or iron. Preferred triflates are $Gd(OTf)_3$ and $Al(OTf)_3$ and $Fe(OTf)_2$.

It is preferred that in above reaction, the molar ratio of the compound of formula (II) to the compound of formula (IIIa) or (IIIb) is in the range of between 3 and 1, preferably between 2.5 and 1.1, more preferably between 2.0 and 1.2.

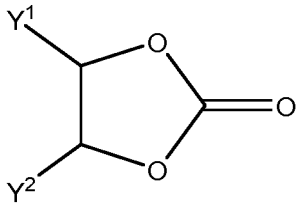
Furthermore, it is preferred that the molar ratio of the compound of the formula (II) to the acidic catalyst is 0.001 mol% to 1 mol%, preferably 0.005 % to 1 mol%, more preferably 0.02 to 1 mol%.

Said reaction is performed at a temperature of between 20 °C and 160°C, preferably between 80 and 120 °C.

Furthermore, the reaction is typically performed at ambient pressure.

It is preferred that said reaction is performed in one embodiment in the presence of a solvent which is a hydrocarbon, preferably toluene, or a C_{5-10} alkane, most preferred hexane or heptane.

It is preferred that said reaction is performed in another embodiment the presence of a solvent which is an organic carbonate, preferably a carbonate of the the formula (X)



(X)

wherein Y^1 and Y^2 represent independently from each other either H or a methyl or ethyl group.

Preferably the organic carbonate is ethylene carbonate or propylene carbonate. It is also possible that mixtures of different carbonate of the formula (X) are used, particularly as binary or ternary mixture of ethylene carbonate and/or propylene carbonate and/or butylene carbonate, most preferably as a binary mixture of ethylene carbonate and propylene carbonate. It is preferred that the ratio of ethylene carbonate to propylene carbonate is between 20:80 to 80:20, particularly 25:75 to 75:25.

Preferably, the solvent of the formula is a carbonate solvent as commercialized by Huntsman under the trademark Jeffsol®, particularly the blends of ethylene carbonate with propylene carbonate Jeffsol® EC-75, Jeffsol® EC-50 and Jeffsol® EC-25.

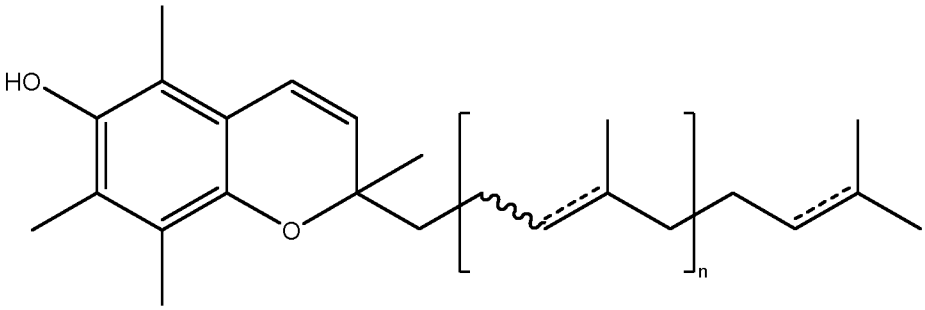
In a further, even more preferred, embodiment said reaction is performed in the presence of a two-phase solvent mixture comprising at least one hydrocarbon and at least one organic carbonate. Said hydrocarbon is preferably toluene, or a C_{5-10} alkane, most preferred hexane or heptane. Said organic carbonate is preferably a carbonate of the formula (X). Also in this embodiment the organic carbonate used can be a mixture of different carbonates of the formula (X), particularly as binary or ternary mixture of ethylene carbonate and/or propylene carbonate and/or butylene carbonate, most preferably as a binary mixture of ethylene carbonate and propylene carbonate. If mixtures of ethylene carbonate and propylene carbonate are used together with the hydrocarbon, it is preferred that the ratio of ethylene carbonate to propylene carbonate is between 20:80 to 80:20, particularly 25:75 to 75:25.

Most preferably, the reaction is performed in a two-phase solvent mixture of hexane and/or heptane with ethylene carbonate and/or propylene carbonate.

It is preferred that all bonds having dotted lines in formula (I) and (IIIa) and (IIIb) represent carbon-carbon double bonds.

The compound of the formula (I) can be oxidized to the compound of the formula (V) and cyclized to the compound of formula (VI).

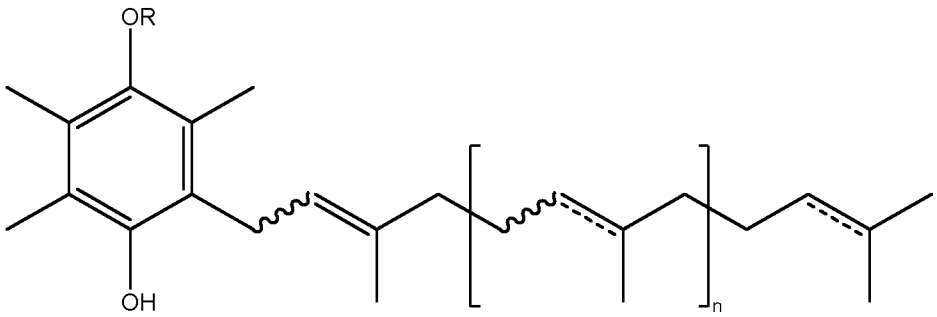
Hence, in a further aspect, the present invention relates to a process of manufacturing the compound of the formula (VI)



(VI)

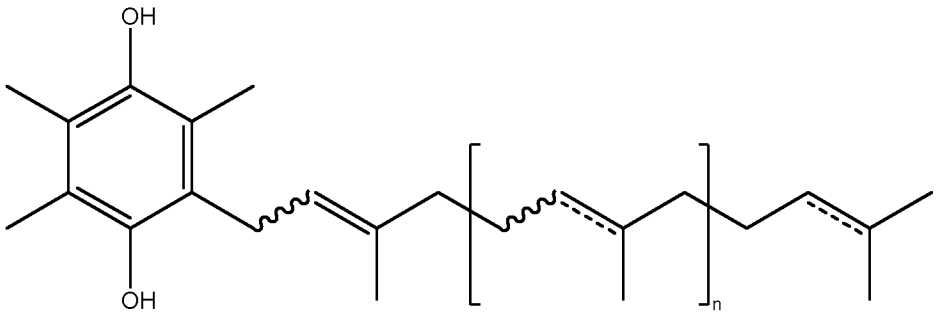
comprising the steps

a) manufacturing a compound of the formula (I) by a process as described above in great detail,



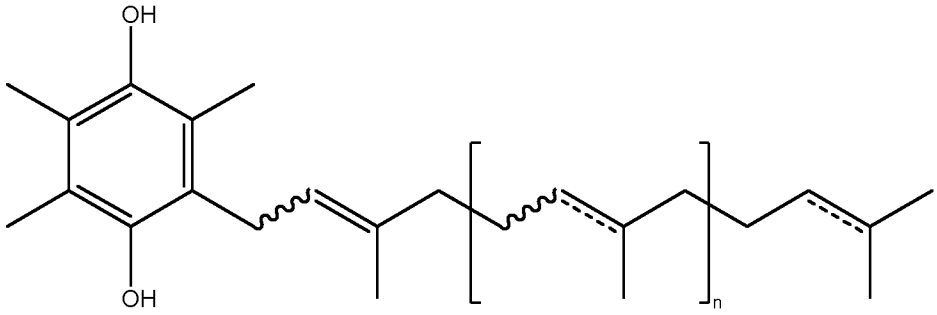
(I)

b) deprotecting the compound of the formula (I) to (I') in case of R in the formula (I) is a phenol protecting group

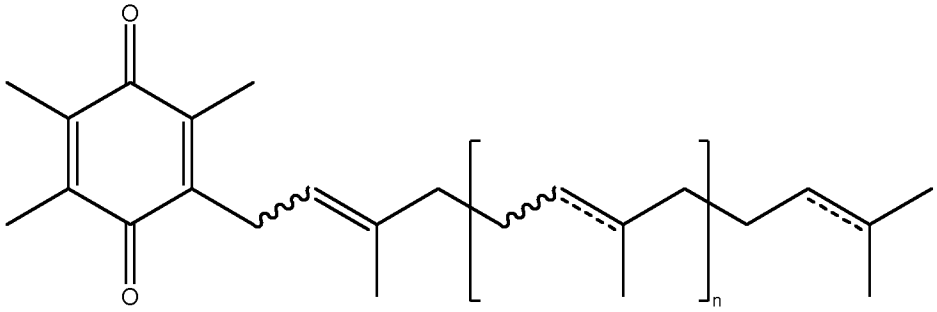


(I')

c) oxidizing compound of the formula

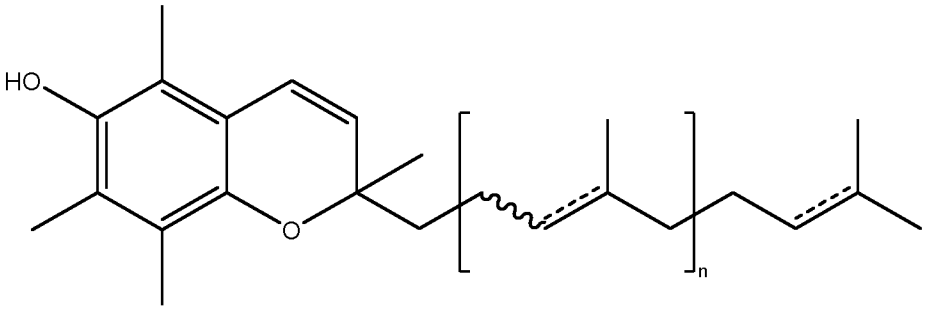


to the compound of the formula (V)



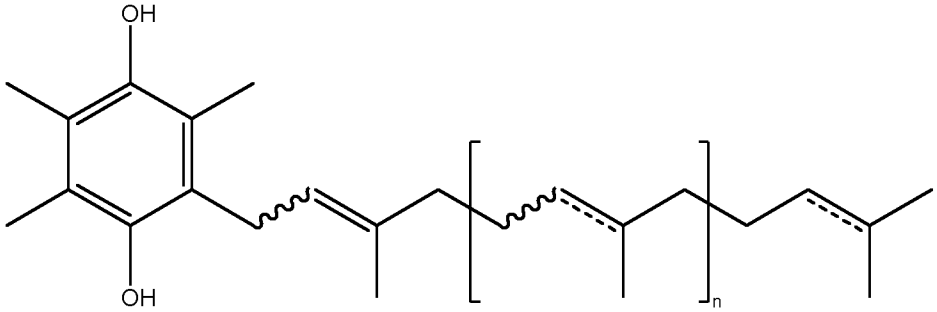
(V)

d) cyclization of compound of the formula (V) to the compound of the formula (VI) in the presence of a basic catalyst



(VI).

When the compound of the formula (I) has phenolic groups in a protected form, i.e. R = R', the respective protection group needs to be removed by a deprotection reaction in a step b) to yield the respective deprotected compound of the formula (I')



(I').

The conditions for said deprotection reaction in step b) depend on the kind of phenol protecting group and are known to the person skilled in the art. For

example, esters can be easily deprotected under the influence of an acid or a base or acetals can be easily deprotected under the influence of acids.

Esters, such as acetate, are particularly cleaved to yield the respective unprotected phenol by lithium aluminum hydride.

The oxidation in step c) can be performed by the use of a suitable oxidizing agent, preferably with silver oxide in the presence of an acid, particularly acetic acid, or with oxygen or air in methanol.

In step d), the compound of the formula (V) is cyclized to the compound of the formula (VI) in the presence of a basic catalyst.

Said basic catalyst is preferably either an organic amine, preferably an organic tertiary amine, or a metal hydroxide or carbonate, particularly an organic tertiary amine or an alkali metal hydroxide.

It has been shown that the conjugated acids of said basic catalysts having a pK_a of between 8.6 and 15.7, particularly of between 9 and 15.7, measured in water, are particularly suitable. This means that the basic catalyst has preferably a pK_b of between 5.4 and 0, particularly of between 5 and 0.

A few, non-limiting, examples of pk_a of the corresponding acids for:

Base	pka[1]
1,5-diazabicyclo[4.3.0]non-5-ene (=DBN)	13.42[3]
1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU)	12[2],13.28[3]
1-azabicyclo[2.2.2]octane (=quinuclidine)	11[2], 10.95[3]
4-(dimethylamino)pyridine (=DMAP)	9.2[2], 9.7[3]
sparteine	9.45[2]
1,4-diazabicyclo[2.2.2]octane (=DABCO)	8.8[2], 8.82[3]
NaOH	15.7[2]
Na_2CO_3	10.4[3]
morpholine[4]	*8.36*[2]*, 8.49*[3]
triethanolamine[4]	*7.76*[3]
pyridine[4]	*5.23*[2]*, 5.23*[3]

1 pka of the corresponding conjugated acid

2 H. Ripin; D. A. Evans (2002). "pK_a's of Nitrogen Acids"

https://organicchemistrydata.org/hansreich/resources/pka/pka_data/evans_pKa_table.pdf

[3] https://www.aatbio.com/data-sets/pka-and-pkb-reference-table

[4] basic catalysts which are less preferred (pk_a < 8.6)

In one embodiment the basic catalyst is an organic amine, particularly selected from the group consisting of 4-dimethylaminopyridine (=DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (=DBN), 1,4-diazabicyclo[2.2.2]octane (=DABCO), 1-azabicyclo[2.2.2]octane (=quinuclidine) and sparteine, preferably from the group consisting of 4-dimethylaminopyridine (=DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (=DBU) and 1-azabicyclo[2.2.2]-octane (=quinuclidine).

In another embodiment the basic catalyst is preferably a hydroxide or a carbonate, preferably a hydroxide, of an alkali metal or an earth alkali metal, particularly an alkali metal hydroxide. In this embodiment, most preferably, the basic catalyst is NaOH or KOH.

It is preferred that the ring closing step is performed in a hydrocarbon solvent, particularly in toluene.

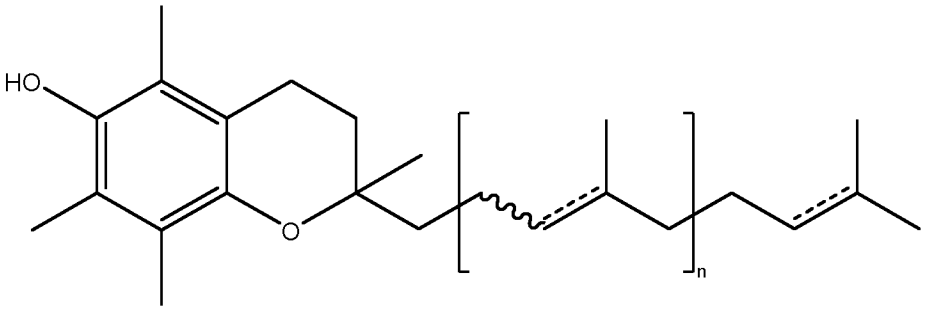
In case a hydrocarbon solvent is used, the solvent is preferably used in such an amount that the solution with the compound of the formula (V) is between 0.05 and 5 molar, more preferred between 0.1 and 1 molar, in respect to the compound of the formula (V).

In case of water being present, it is preferred that the ring closure reaction is performed in a two-phase system, i.e. water phase and organic phase, particularly with a water and organic solvent phase

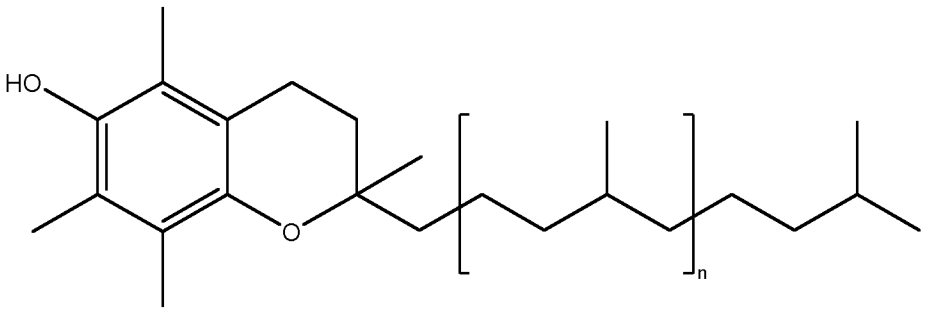
It is preferred that the basic catalyst is present in catalytical amounts, i.e. the basic catalyst is not present in stoichiometric amounts relative to the compound of the formula (V), but in significantly lower amounts, i.e. the molar ratio of the basic catalyst to the compound of the formula (V) is preferably 1:1'000 to 1:5, particularly 1:100 to 1:10.

The ring closing step is typically performed under stirring preferably at a temperature of between 40 and 200°C, preferably between 90 and 150°C, more preferably at the reflux temperature of the organic solvent when an organic solvent is used, and/or at a pressure of between 1 bara and 10 bara. It is further preferred that this reaction is performed under inert atmosphere, preferably under nitrogen.

The compound of the formula (VI) can be hydrogenated by means of a hydrogenation agent either compound of the formula (VIIII) (partial hydrogenation) or (IX) (complete hydrogenation)

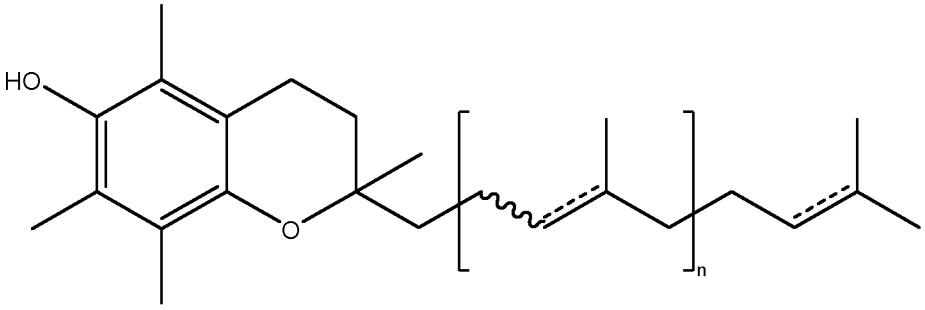


(VIII)



(IX).

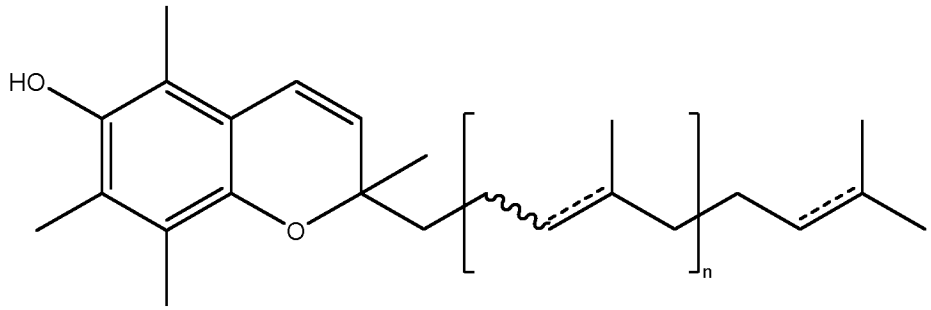
Hence, in a further aspect the present invention relates to a process of manufacturing a compound of the formula (VIII)



(VIII)

comprising the steps

i) manufacturing the compound of the formula (VI) by a process as described above in great detail



(VI)

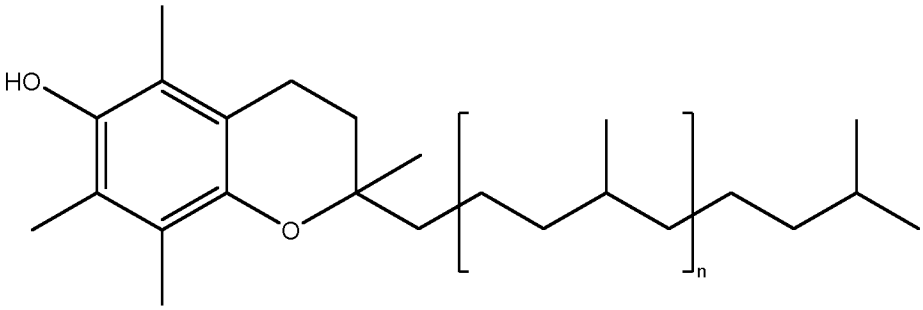
ii) partially hydrogenating the compound of the formula (VI) by means of a hydrogenating agent suitable for partial hydrogenation to yield the compound of the formula (VIII).

In the partial hydrogenation of step ii) only the carbon-carbon double bond in the ring is hydrogenated whereas the olefinic carbon-carbon double bonds are not hydrogenated ("partial hydrogenation"), so that the hydrogenation leads to the compound of the formula (VIII).

The hydrogenating agent used in step ii) is a hydrogenating agent which only hydrogenates the carbon-carbon double bond of the ring in formula (VIII). Particularly suitable as hydrogenating agent is sodium / ethanol such as described by Schudel, Mayer, Isler, *Helv. Chim. Acta* 46, 2517-2526 (1963), particularly in the last paragraph on page 2524.

This process particularly leads to α-tocotrienol, which has three double bonds in the side chain.α-Tocotrienol is an important compound in natural vitamin E.

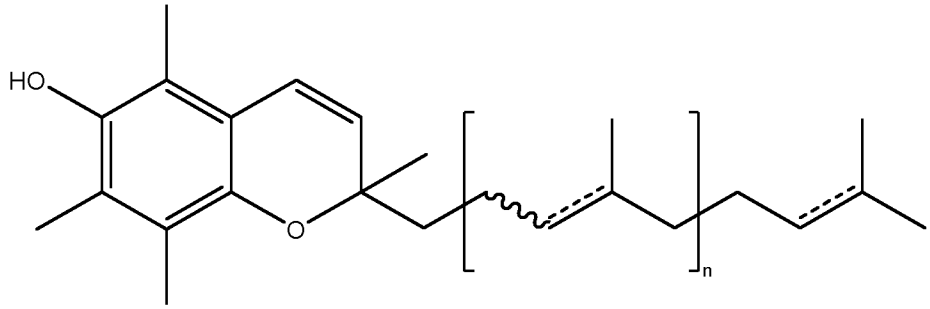
Hence, in a further aspect the present invention relates to a process of manufacturing a compound of the formula (IX)



(IX)

comprising the steps

i) manufacturing the compound of the formula (VI) by a process as described above in great detail



(VI)

ii') hydrogenating the compound of the formula (VI) by means of a hydrogenating agent to yield the compound of the formula (IX).

The hydrogenating agent used in step ii') is a hydrogenating agent which hydrogenates all olefinic carbon-carbon double bond of the ring in formula (VI). Particularly suitable as hydrogenating agent is hydrogen in the presence of a transition metal from the groups 7, 8, 9 or 10, particularly selected form the group consisting of Pd, Pt, Rh, Ru, Mn, Fe, Co, and Ni, more preferably Pd.

The heterogenous transition metal catalyst is preferably a heterogenous supported transition metal catalyst.

Such hydrogenation is disclosed for example by Kabbe and Heitzer, Synthesis **1978**, *12*, 888-889.

In this embodiment, the transition metal is supported on a carrier, i.e. palladium is attached to/or deposited on a carrier. The carrier is a solid material.

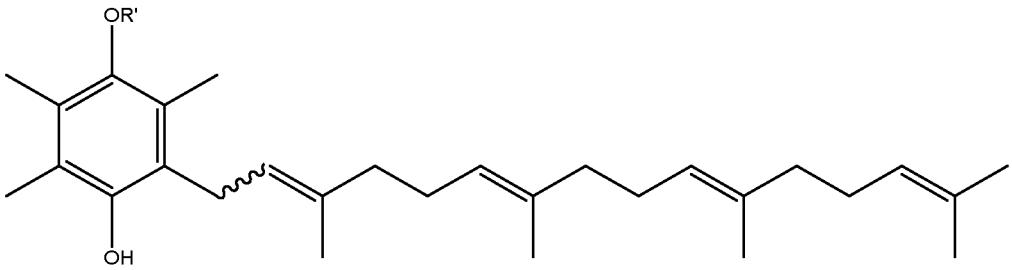
Preferably said carrier is carbon or an inorganic carrier. Preferred inorganic carriers are oxides or carbonates. Preferred oxides are oxides of Si, Al, Ce, Ti or Zr, particularly of Al or Si. Particularly preferred are silicon dioxide, alumina and titanium dioxide and ceria.

In case the support is Ce, the preferred oxide is CeO_2. Preferably, the oxide of Al is Al_2O_3 and AlO(OH). Particularly preferred is Al_2O_3.

It is preferred to perform the hydrogenation under pressure, particularly under a hydrogen pressure of 2 to 20 bar. It is further preferred to perform the hydrogenation at a temperature between 0°C and 100°C.

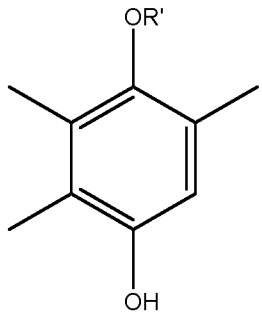
This process particularly leads to α-tocopherol, which has a completely saturated side chain. α-Tocopherol is an important compound in natural vitamin E.

The compound of the formula (I-A) is new. Hence, in a further aspect, the invention relates to a compound of the formula (I-A)

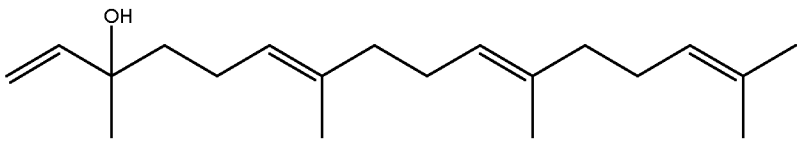


(I-A).

As already pointed out R' represents a phenol protecting group and the wavy line represents a carbon-carbon bond which is linked to the carbon-carbon double bond which is either in the *Z*- or in the *E*-configuration. The protecting group has been discussed in great detail above. In this embodiment, the protecting group R' is preferably an acetyl group.



It has been shown that an *E/Z* mixture is prepared from



and in the presence of according to the process discussed above in great detail.

The *E/Z* mixture can be separated by chromatography, if needed.

As this invention demonstrates, the compound of the formula (I) is a very suitable agent for the synthesis of compound of the formula (V'), (VI') and (VIII') respectively (IX')

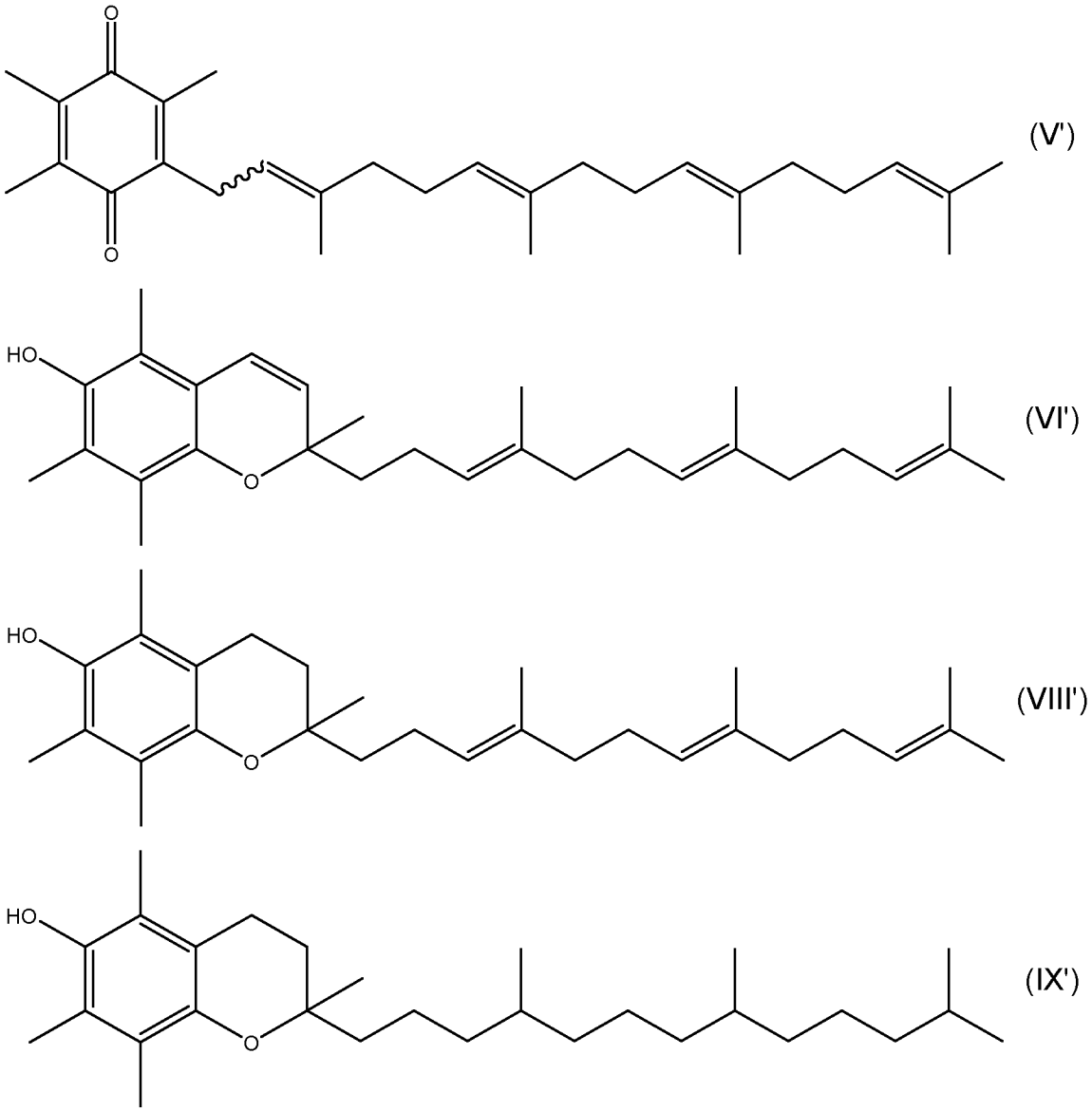


Figure 1 shows schematically the processes discussed above in great detail, particularly, highlighted by the box, the process of manufacturing the compound of the formula (I) comprising a step of reacting a compound of the formula (II) with a compound of the formula (IIIa) or (IIIb) in the presence of an acidic catalyst ("*cat*") being either $Gd(OTf)_3$ or $Tm(OTf)_3$ or $Al(OTf)_3$ or $Y(OTf)_3$ or $Fe(OTf)_2$ or camphorsulfonic acid or $BiCl_3$.

Examples

The present invention is further illustrated by the following experiments.

Experimental series 1

Geranyllinalool (12.51 g (43 mmol)), 65 ml of a mixture ethylene carbonate/heptane (1.17/1 g/g) and 9.91 g (65mmol) of 2,3,6-trimethylhydro-quinone (TMHQ) have been added under stirring in the presence of the catalyst indicated in table 1 to yield 2,3,5-trimethyl-6-((*2E,6E,10E*)-3,7,11,15-tetramethyl-hexadeca-2,6,10,14-tetraen-1-yl)benzene-1,4-diol in conversion and yield as indicated in table 1.

Example	Catalyst	Catalyst [eq]	Conversion [%]	Yield [%]
1	Camphorsulfonic acid[1]	0.00025	100	32
2	Camphorsulfonic acid	0.0002	100	30
3	$Gd(OTf)_3$	0.0000625	100	45
4	$Tm(OTf)_3$	0.0001250	100	42

Table 1. Different acidic catalysts for condensation of TMHQ and geranyllinalool.
[1]in all experiments of this document (+)-camphorsulfonic acid is used.

Experimental series 2

Geranylgeraniol (3.45 g (12 mmol)), 15 ml of a mixture ethylene carbonate/heptane (1.17/1 g/g) and 2.29 g (15 mmol) of 2,3,6-trimethylhydro-quinone (TMHQ) have been added under stirring in the presence of the catalyst indicated in table 2 to yield 2,3,5-trimethyl-6-((*2E,6E,10E*)-3,7,11,15-tetramethyl-hexadeca-2,6,10,14-tetraen-1-yl)benzene-1,4-diol in conversion and yield as indicated in table 2.

Example	Catalyst	Catalyst [eq]	Conversion [%]	Yield [%]
5	Camphorsulfonic acid	0.0005	100	23.1
6	$Al(OTf)_3$	0.0002	100	38.6
Ref.1	$LiN(Tf)_2$*	0.1	39	5.0
Ref.2	Cu/Zn / HCOOH**	2.3	100	0

Table 2. Different acidic catalysts for condensation of TMHQ and geranylgeraniol.

* $LiN(Tf)_2$ = Lithium bis((trifluoromethyl)sulfonyl)amide.

** Cu/Zn / HCOOH: Cu and Zn in formic acid (M. Kajiwara et al., *Heterocyles*, Vol. 14, No 12, 1995-1198, 1980).

Experimental series 3

Geranylgeraniol (3.42 g (12 mmol)), 15 ml of a mixture ethylene carbonate/heptane (1.17/1 g/g) and 2.91 g (15 mmol) of 2,3,6-trimethylhydro-quinone-1-acetate have been added under stirring in the presence of the catalyst indicated in table 3 to yield 4-hydroxy-2,3,6-trimethyl-5-((2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)phenyl acetate in conversion and yield as indicated in table 3.

Example	Catalyst	Catalyst [eq]	Conversion [%]	Yield [%]
7	Camphorsulfonic acid	0.001	100	20
8	Camphorsulfonic acid	0.0005	100	25
9	Camphorsulfonic acid	0.00025	100	35
10	Camphorsulfonic acid	0.000125	100	32

Table 3. Condensation of TMHQ-1 acetate and geranylgeraniol.

Experimental series 4

Geranyllinalool (12.51 g (43 mmol)), 65 ml of a mixture ethylene carbonate/heptane (1.17/1 g/g) and 16.54 g (65mmol) of 2,3,6-trimethylhydro-quinone-1-benzoate have been added under stirring in the presence of the catalyst indicated in table 4 to yield 4-hydroxy-2,3,6-trimethyl-5-((2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)phenyl benzoate in conversion and yield as indicated in table 4.

Example	Catalyst	Catalyst [eq]	Conversion [%]	Yield [%]	Selectivity [%]
11	$Al(OTf)_3$	0.0002	>99	20	20
12	Camphorsulfonic acid	0.0002	89	24	27
Ref.3	$Bi(OTf)_3$	0.0002	99	13	13

Table 4. Different acidic catalysts for condensation of TMHQ-1 benzoate and geranylgeraniol.

Experimental series 5

A solution of 2.19 g (11.3 mmol) of 2,3,6-trimethylhydroquinone-1-acetate and the amount of the catalyst indicated in table 5 in a mixture of 5.95 g of ethylene carbonate and 7.5 ml of n-heptane (ethylene carbonate/n-heptane 1.17/1 g/g) was heated to reflux under stirring. 2.2 g (7.5 mmol) of (all-*E*)-geranyllinalool were added. After removal of ethylene carbonate phase by extraction with heptane, 4-hydroxy-2,3,6-trimethyl-5-((6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl)phenyl acetate has been obtained in the yield as indicated in table 5.

Example	Catalyst	Catalyst [mol-%]	Yield[3] [%]	Yield E[1] [%]	Yield Z[2] [%]
13	$Gd(OTf)_3$	1.0	31.8	29.0	2.8
14	$Fe(OTf)_2$	0.4	31.3	28.5	2.8

Table 5. Different acidic catalysts for condensation of TMHQ-1 acetate and (all-*E*)- geranyllinalool.
[1]Yield in the E-isomer [2]Yield in the Z-isomer [3]Yield Total yield (E+Z) determined by GC using internal standard.

Experimental series 6

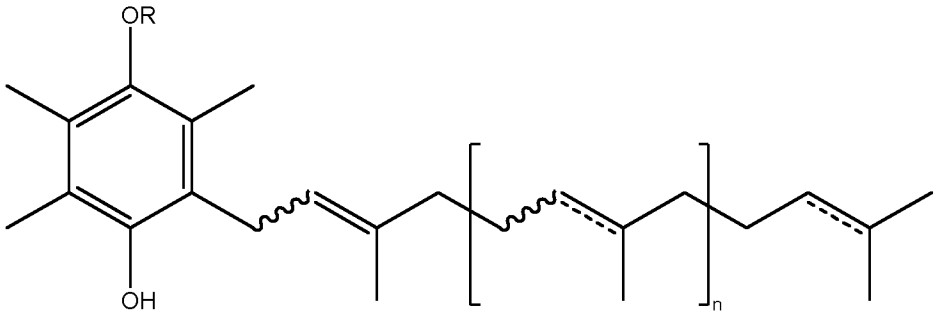
A solution of 2.19 g (11.3 mmol) of 2,3,6-trimethylhydroquinone-1-acetate and the amount of the catalyst indicated in table 6 in a mixture of 5.95 g of ethylene carbonate and 7.5 ml of n-heptane (ethylene carbonate/n-heptane 1.17/1 g/g) was heated to reflux under stirring. 1.69 g (7.5 mmol) of (all-*E*)-farnesol or *E*-nerolidol were added. After removal of ethylene carbonate phase by extraction with heptane, 4-hydroxy-2,3,6-trimethyl-5-((6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)phenyl acetate has been obtained in the yield as indicated in table 6.

Example	Alcohol	Catalyst	Catalyst [mol-%]	Yield[1] [%]
15	*E*-nerolidol	$Gd(OTf)_3$	1.0	34.7
16	*E*-nerolidol	$Fe(OTf)_2$	0.4	25.9
17	(all *E*)-farnesol	$Gd(OTf)_3$	1.0	36.0
18	(all *E*)-farnesol	$Fe(OTf)_2$	0.4	34.2

Table 6. Different acidic catalysts for condensation of TMHQ-1 acetate and *E*-nerolidol and (all *E*)-farnesol. [1]determined by GC using internal standard

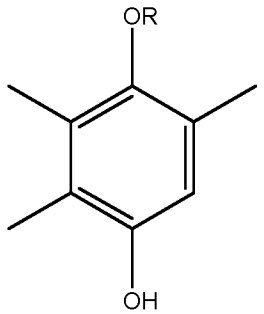
Claims

1. A process of manufacturing the compound of the formula (I)

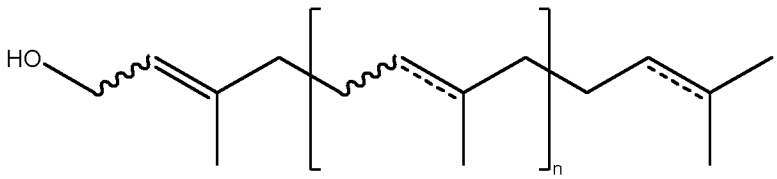


(I)

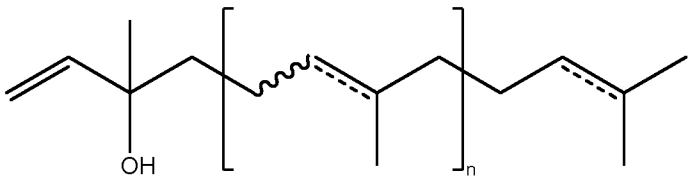
comprising a step of reacting a compound of the formula (II) with a compound of the formula (IIIa) or (IIIb)



(II)



(IIIa)



(IIIb)

in the presence of an acidic catalyst being

either

$Gd(OTf)_3$ or $Tm(OTf)_3$ or $Al(OTf)_3$ or $Y(OTf)_3$ or $Fe(OTf)_2$

or

camphorsulfonic acid;

or

$BiCl_3$;

wherein

n = 0 or 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12;

R represents hydrogen or R' which is a phenol protecting group;

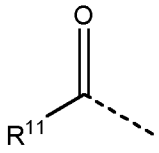
OTf represents trifluoromethanesulfonate;

and

any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond, with the proviso that at least one of the bonds having dotted lines represents a carbon-carbon double bond;

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the *Z*- or in the *E*-configuration.

2. The process according to claim 1, characterized in that R' is a phenol protecting group of the formula



wherein R^{11} is a C_{1-15}-alkyl or a fluorinated C_{1-15}-alkyl or a C_{1-15}-cycloalkyl or a C_{7-15}-aralkyl group, preferably a methyl or a benzyl group.

3. The process according to claim 1 or 2, characterized in that n=0 or 1 or 2, preferably 2.

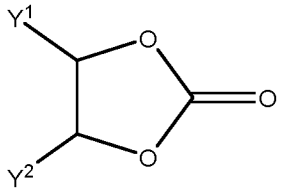
4. The process according to any of the preceding claims characterized in that all bonds having dotted lines in formula (I) and (IIIa) and (IIIb) represent carbon-carbon double bonds.

5. The process according to any of the preceding claims characterized in that the molar ratio of the compound of formula (II) to the compound of formula (IIIa) or (IIIb) is in the range of between 3 and 1, preferably between 2.5 and 1.1, more preferably between 2.0 and 1.2.

6. The process according to any of the preceding claims characterized in that the molar ratio of the compound of the formula (II) to the acidic catalyst is 0.001 mol% to 1 mol%.

7. The process according to any of the preceding claims, characterized in that the reaction is performed in the presence of a solvent which is a hydrocarbon, preferably toluene, or a C_{5-10} alkane, most preferred hexane or heptane.

8. The process according to any of the preceding claims, characterized in that the reaction is performed in the presence of a solvent which is an organic carbonate, preferably a carbonate of the the formula (X)



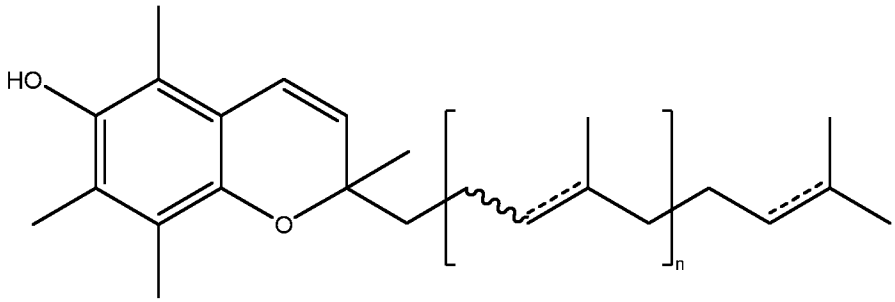
(X)

wherein Y^1 and Y^2 represent independently from each other either H or a methyl or ethyl group.

9. The process according to any of the preceding claims, characterized that the reaction is performed in the presence of a two-phase solvent mixture comprising at least one hydrocarbon and at least one organic carbonate.

10. The process according to any of the preceding claims, characterized that the reaction is performed at a temperature of between 20°C and 160°C.

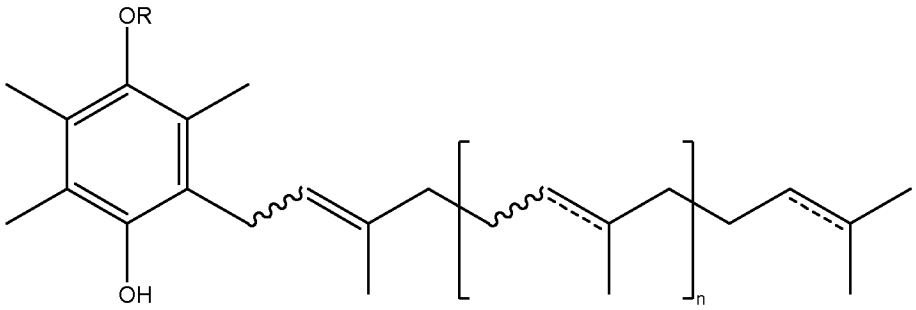
11. A process of manufacturing the compound of the formula (VI)



(VI)

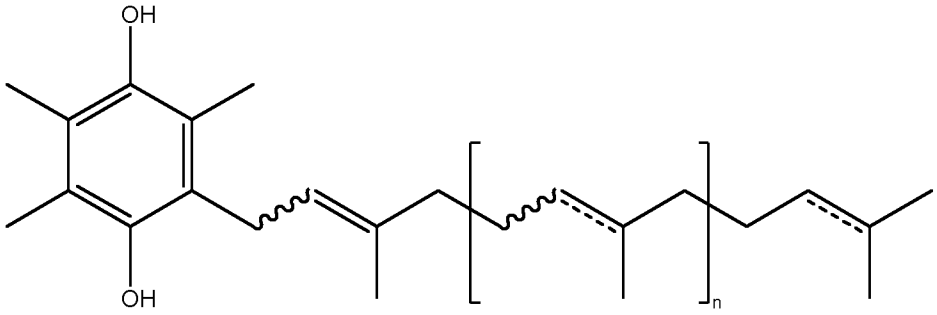
comprising the steps

a) manufacturing a compound of the formula (I) by a process according to any of the preceding claims 1 to 10,



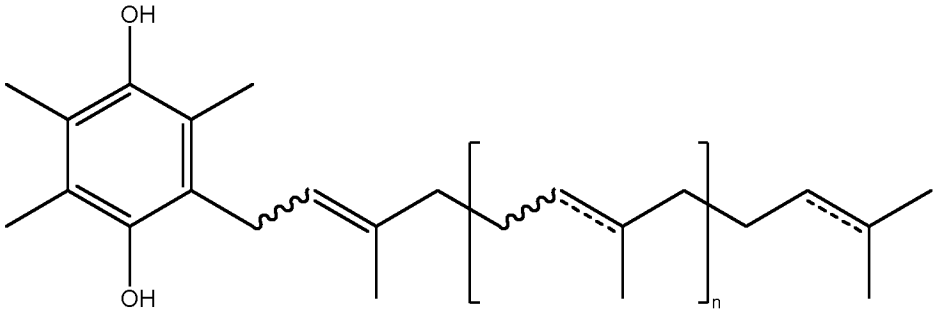
(I)

b) deprotecting the compound of the formula (I) to (I') in case of R in the formula (I) is a phenol protecting group

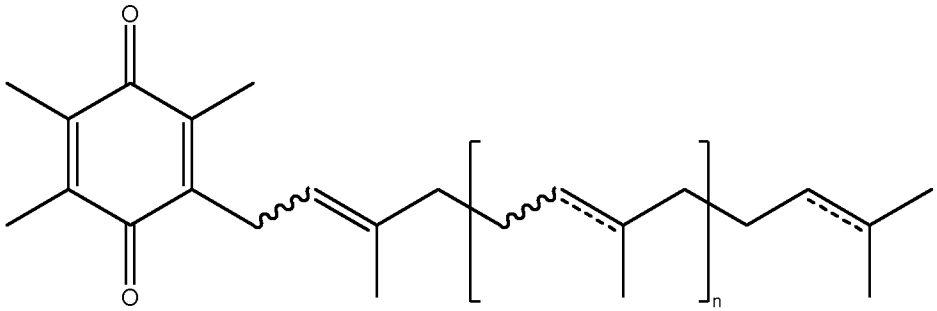


(I')

c) oxidizing compound of the formula

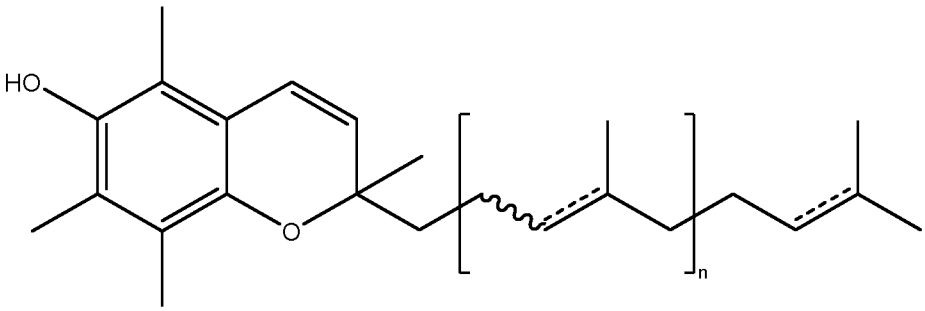


to the compound of the formula (V)



(V)

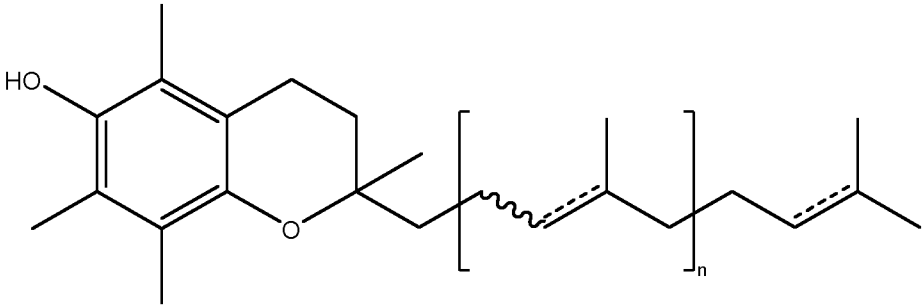
d) cyclization of compound of the formula (V) to the compound of the formula (VI) in the presence of a basic catalyst



(VI)

12. The process according to claim 11 characterized in that the basic catalyst in step d) is present in an molar ratio to the compound of the formula (V) of between 1:1'000 to 1:5, particularly 1:100 to 1:10.

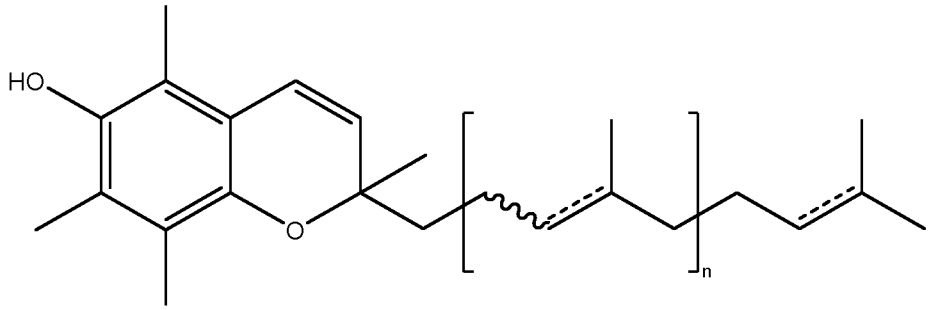
13. The process of manufacturing a compound of the formula (VIII)



(VIII)

comprising the steps

i) manufacturing the compound of the formula (VI) by a process according to claim 11 or 12



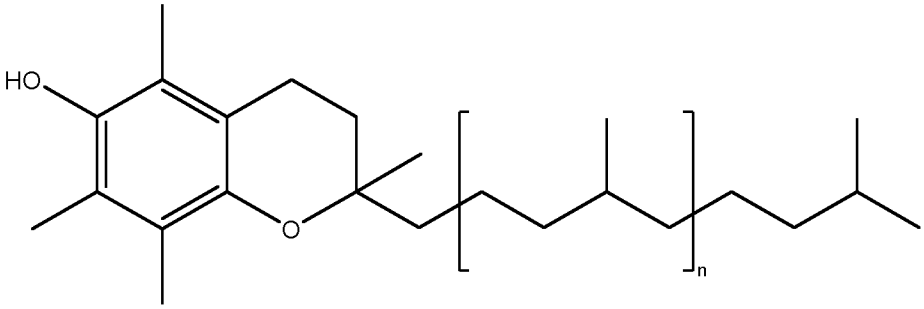
(VI)

wherein any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the Z or in the E-configuration;

ii) partially hydrogenating the compound of the formula (VI) by means of a hydrogenating agent suitable for partial hydrogenation to yield the compound of the formula (VIII).

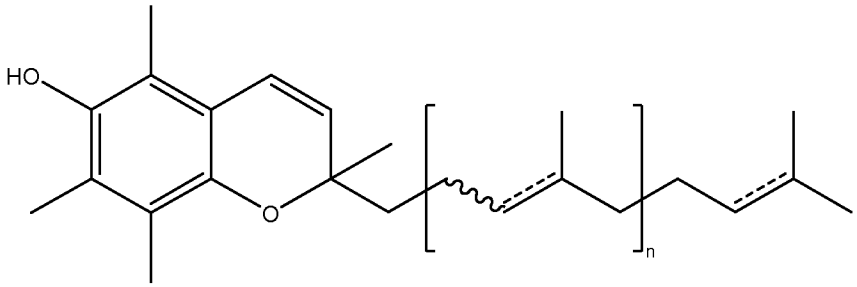
14. The process of manufacturing a compound of the formula (IX)



(IX)

comprising the steps

i) manufacturing the compound of the formula (VI) by a process according to claim 11 or 12



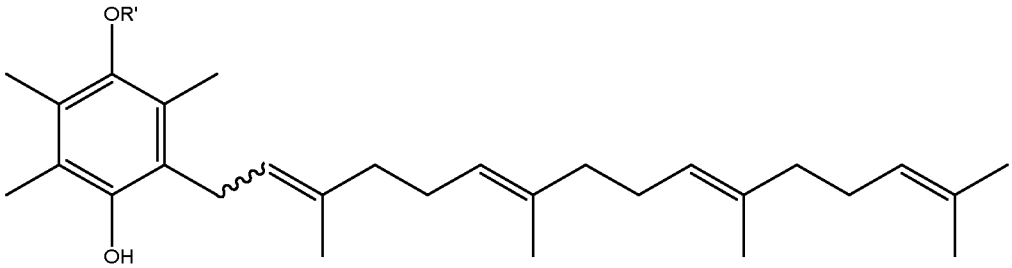
(VI)

wherein any bond having dotted line (------) represents independently from each other either a carbon-carbon single bond or a carbon-carbon double bond; and

any wavy line represents independently from each other a carbon-carbon bond and which when linked to the carbon-carbon double bond is either in the Z or in the E-configuration;

ii') hydrogenating the compound of the formula (VI) by means of a hydrogenating agent to yield the compound of the formula (IX).

15. The compound of formula (I-A)



(I-A)

wherein R' represents a phenol protecting group

and the wavy line represents a carbon-carbon bond linked to the carbon-carbon double bond which is either in the Z or in the E-configuration.

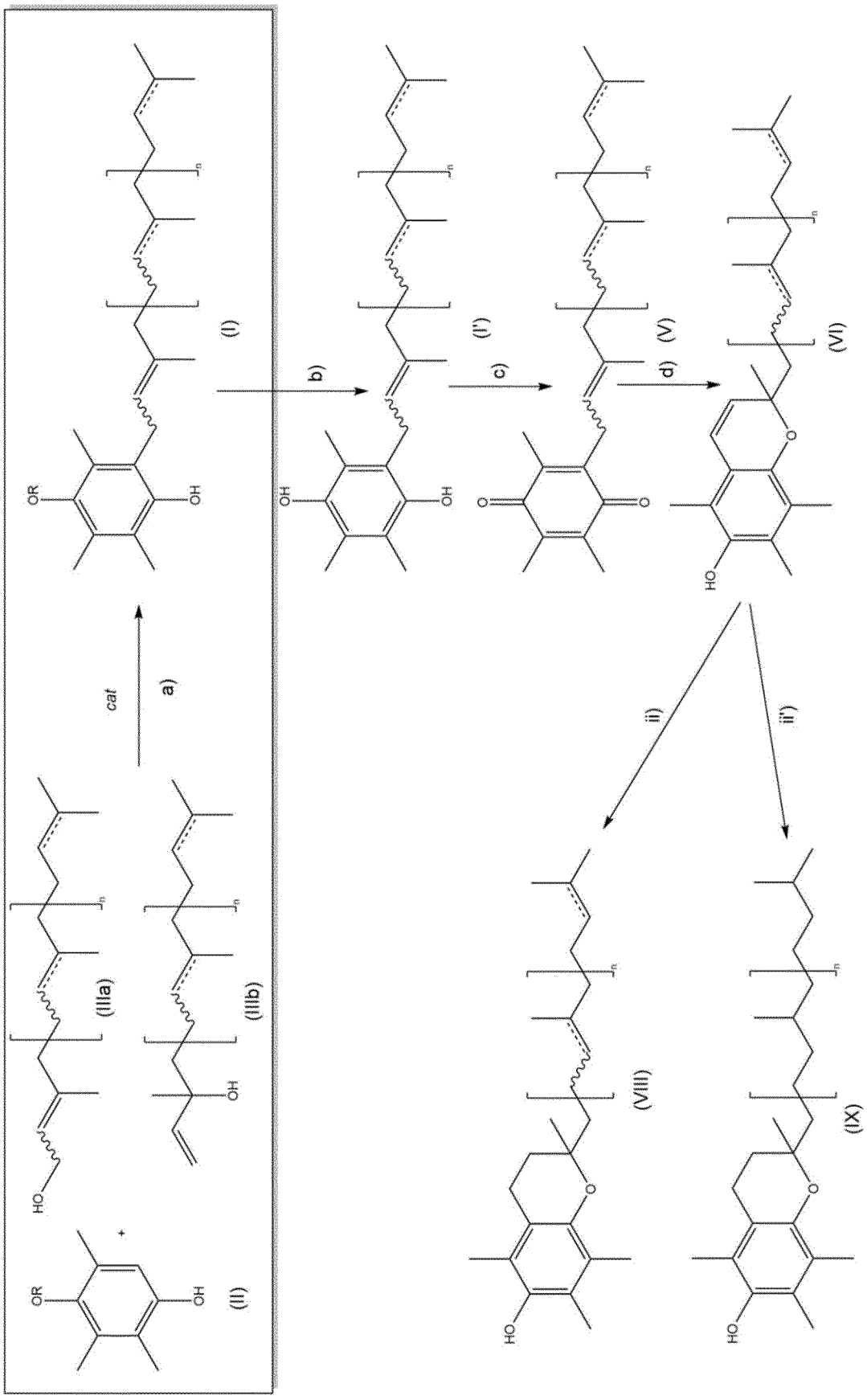


Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/061093

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/72 C07C67/293 C07C69/16
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/063182 A1 (DSM IP ASSETS BV [NL]; BONRATH WERNER [DE] ET AL.) 29 July 2004 (2004-07-29) cited in the application the whole document	1-15
X	WO 2004/046126 A1 (DSM IP ASSETS BV [NL]; BONRATH WERNER [DE] ET AL.) 3 June 2004 (2004-06-03) cited in the application examples scheme on page 2	1-15

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 2022	15/07/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Panday, Narendra

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CANDU N ET AL: "FriedelCrafts alkylations on nanoscopic inorganic fluorides", APPLIED CATALYSIS A: GENERAL, ELSEVIER, AMSTERDAM, NL, vol. 391, no. 1, 4 August 2010 (2010-08-04), pages 169-174, XP028360567, ISSN: 0926-860X, DOI: 10.1016/J.APCATA.2010.08.004 [retrieved on 2010-08-11]	15
A	scheme 1, reaction of 1 with 4	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/061093

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