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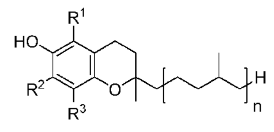
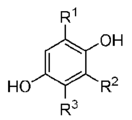
(54) **Title:** CHROMAN-6-OLS WITH AN EXTENDED LIPOPHILIC SIDE CHAIN IN POSITION 2, THEIR MANUFACTURE AND USE



(III)



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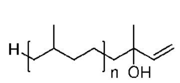

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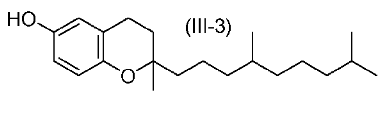

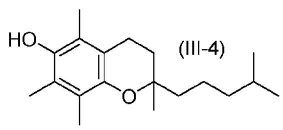

(57) **Abstract:** The present invention is directed to a process for the manufacture of a compound of formula (III), comprising the step of reacting a compound of formula (I) with a compound of formula (II) in the presence of an acid catalyst and in a mixture of two solvents, wherein n is 1 or 2, and R^1 and R^3 are independently from each other H or C_{1-5}-alkyl, and R^2 is either H or C_{1-5}-alkyl or C_{1-5}-alkyloxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H, and wherein the first of the two solvents is selected from ethylene carbonate, propylene carbonate, 1,2-butylene carbonate, gamma-butyrolactone and water, and the second of the two solvents is selected from hexane, cyclohexane, heptane, *ortho*-xylene, *meta*-xylene, *para*-xylene, mesitylene, pseudocumene, methyl *tert*-butyl ether, and toluene. The present invention is also directed to the compound of formula (III-3), as well as to the use of compounds of formula (III), especially to the use of compound of formula (III-3) and the use of compound of formula (III-4), as antioxidants, especially in feed, such as e.g. in feed for aquatic animals, in feed for terrestrial animals (especially pet food, feed for pigs and feed for poultry) and in feed for insects, and in feed ingredients, such as in fish meal, in poultry meal, in insect meal, and in PUFA-containing oils such as marine oil, microbial oil, fungal oil, algal oil and PUFA-containing plant oil The present invention is further directed towards feed and feed ingredients containing at least one compound of formula (III), especially containing a compound of formula (III-3) and/or a compound of formula (III-4).

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[Continued on next page]

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— *of inventorship (Rule 4.17(iv))*

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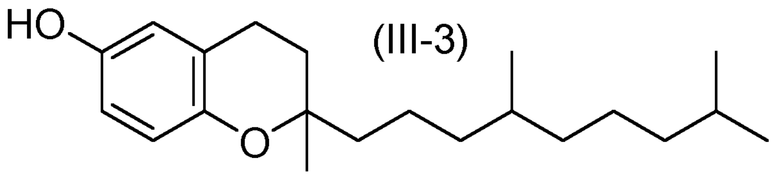
— *with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description (Rules 13bis.4(d)(i) and 48.2(a)(viii))*

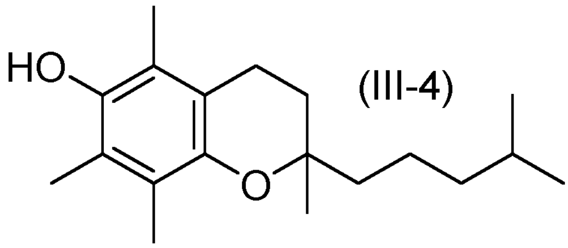
Chroman-6-ols with an extended lipophilic side chain in position 2, their manufacture and use

Summary

The present invention is directed to the compound of formula (III-3), as well as to the use of compounds of formula (III) as defined below, especially to the use of compound of formula (III-3) and the use of compound of formula (III-4), as antioxidants, especially in feed, such as e.g. in feed for aquatic animals, in feed for terrestrial animals (especially pet food, feed for pigs and feed for poultry) and in feed for insects, and in feed ingredients, such as in fish meal, in poultry meal, in insect meal, and in PUFA-containing oils such as marine oil, microbial oil, fungal oil, algal oil and PUFA-containing plant oil.



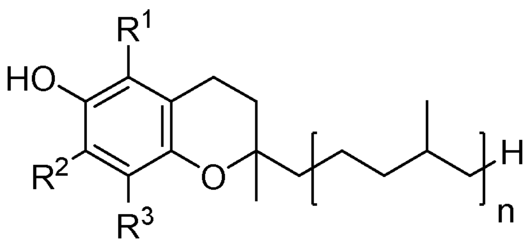
(III-3)



(III-4)

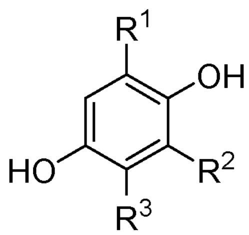
The present invention is further directed towards feed and feed ingredients containing at least one compound of formula (III) as defined below, especially containing a compound of formula (III-3) and/or a compound of formula (III-4).

The present invention is also directed to a process for the manufacture of a compound of formula (III),



(III)

comprising the step of reacting a compound of formula (I) with a compound of formula (II) in the presence of an acid catalyst and in a mixture of two solvents,



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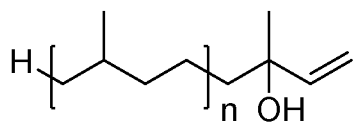


(II)

wherein n is 1 or 2, and

R^1 and R^3 are independently from each other H or C_{1-5}-alkyl, and R^2 is either H or C_{1-5}-alkyl or C_{1-5}-alkyloxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H,

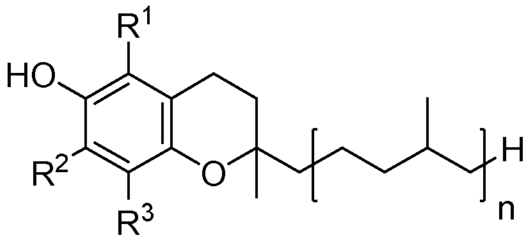
the first of the two solvents is selected from ethylene carbonate, propylene carbonate, 1,2-butylene carbonate, gamma-butyrolactone and water,

and the second of the two solvents is selected from hexane, cyclohexane, heptane, *ortho*-xylene, *meta*-xylene, *para*-xylene, mesitylene, pseudocumene, methyl *tert*-butyl ether, and toluene.

Until now there was no sustainable industrial process for the manufacture of compounds of formula (III) with a good yield based on the compound of formula (I), whereby the use of halogenated solvents is avoided. Thus, there was a need to provide such a process.

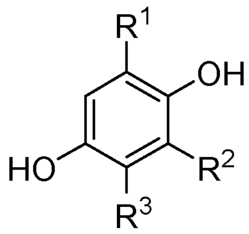
<u>**Detailed description of the invention**</u>

Thus, this need is fulfilled by the present invention, which is directed to a process for the manufacture of a compound of formula (III),



(III)

comprising the step of reacting a compound of formula (I) with a compound of formula (II) in the presence of an acid catalyst and in a mixture of two solvents,



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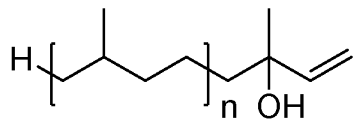
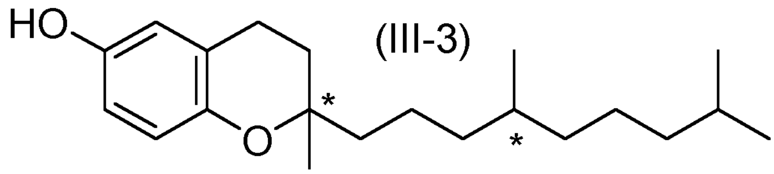


(II)

wherein n is 1 or 2, and
R^1 and R^3 are independently from each other H or C_{1-5}-alkyl, and R^2 is either H or C_{1-5}-alkyl or C_{1-5}-alkyloxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H,
the first of the two solvents is selected from ethylene carbonate, propylene carbonate, 1,2-butylene carbonate, gamma-butyrolactone and water,
and the second of the two solvents is selected from hexane, cyclohexane, heptane, *ortho*-xylene, *meta*-xylene, *para*-xylene, mesitylene, pseudocumene, methyl *tert*-butyl ether, and toluene.

The compound of formula (III-3), 2-(4,8-dimethylnonyl)-2-methylchroman-6-ol, is a novel compound and therefore also an object of the present invention.



(III-3)

The two asterisks * mark each a chiral/stereogenic center. The term "compound of formula (III-3)" encompasses all possible isomers having any configuration at said centers.

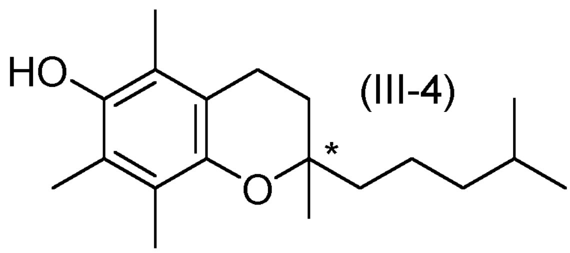
Unmodified fish meal can spontaneously combust from heat generated by oxidation of the polyunsaturated fatty acids in the fish meal. In the past, factory ships have sunk because of such fires. Strict rules regarding the safe transport of fish meal have been put in place by authorities and the International Maritime Organization (IMO). According to IMO, fishmeal must be stabilized with antioxidants to prevent spontaneous combustion during overseas transport and storage.

The shipping regulations of the United Nations for the Transport of Dangerous Goods (UN-TDG) currently only allow ethoxyquin and BHT as antioxidants to stabilize fish meal for marine transport. But authorization of ethoxyquin has now been suspended in the European Union due to safety and health concerns.

BHT must be added in higher quantities to achieve the same efficacy as ethoxyquin. Furthermore, BHT is currently under safety evaluation by ECHA and its re-registration as feed additive is pending in Europe.

Therefore, there is a need to replace ethoxyquin and BHT as an antioxidant, especially in feed comprising proteins and/or unsaturated fatty acid (derivative)s and in feed ingredients comprising proteins and/or unsaturated fatty acid (derivative)s. Such replacements are the compounds of formula (III), especially the compound of formula (III-3) as well as the compound of formula (III-4).

Thus, the compounds of formula (III), especially the compound of formula (III-3) as well as the compound of formula (III-4), are useful as antioxidants, especially in feed, such as e.g. in feed for aquatic animals, in feed for terrestrial animals (especially pet food, feed for pigs and feed for poultry) and in feed for insects, and in feed ingredients, such as in fish meal, in poultry meal, in insect meal, and in PUFA-containing oils such as marine oil, microbial oil, fungal oil, algal oil and PUFA-containing plant oil. Thus, the present invention is further directed to this use.



(III-4)

The asterisk * marks a chiral/stereogenic center. The term “compound of formula (III-4)” encompasses all possible isomers having any configuration at said center.

Furthermore, the present invention is directed towards feed and feed ingredients containing at least one compound of formula (III), especially containing a compound of formula (III-3) and/or a compound of formula (III-4).

Feed encompasses feed for aquatic animals, feed for terrestrial animals (especially pet food, feed for pigs and feed for poultry) and feed for insects. Feed ingredients encompass especially fish meal, poultry meal, insect meal, and PUFA-containing oils such as marine oil, microbial oil, fungal oil, algal oil and PUFA-containing plant oil.

“PUFA(s)” means polyunsaturated fatty acid(s) such as docosahexaenoic acid (“DHA”) and/or eicosapentaenoic acid (“EPA”) and/or docosapentaenoic acid (“DPA”) and/or oleic acid and/or stearidonic acid and/or linoleic acid and/or alpha-linolenic acid (“ALA”) and/or gamma-linolenic acid and/or arachidonic acid (“ARA”) and/or the esters of all of them, whereby the term “esters” encompasses monoglycerides, diglycerides and triglycerides as well as C_{1-6}-alkyl esters such as especially the methyl esters and the ethyl esters, whereby the triglycerides are often dominant.

DHA, EPA, ALA and stearidonic acid are omega-3 fatty acids, whereas linoleic acid, gamma-linolenic acid and ARA are omega-6 fatty acids.

The term “DPA” encompasses two isomers, the omega-3 fatty acid clupanodonic acid (7*Z*,10*Z*,13*Z*,16*Z*,19*Z*-docosapentaenoic acid) and the omega-6 fatty acid osbond acid (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-docosapentaenoic acid).

In accordance with the invention, the polyunsaturated fatty acid (PUFA) is preferably DHA and/or EPA and/or DPA and/or any ester thereof, more preferably the polyunsaturated fatty acid (PUFA) is preferably DHA and/or EPA and/or any ester thereof.

Examples of PUFA-containing oils are

- marine oil, such as preferably fish oil,
- microbial biomass containing polyunsaturated fatty acids and/or their esters (“**microbial oil**”), preferably containing high amounts of docosahexaenoic acid (“DHA”) and/or eicosapentaenoic acid (“EPA”) and/or docosapentaenoic acid (“DPA”) and/or their esters, and
- oil containing high amounts of PUFAs and/or their esters, preferably containing high amounts of docosahexaenoic acid (“DHA”) and/or eicosapentaenoic acid (“EPA”) and/or docosapentaenoic acid (“DPA”) and/or their esters, extracted from microbial biomass, such as fungae (“**fungal oil**”) or algae (“**algal oil**”), and
- plant oil with relatively high amounts of PUFAs and/or their esters, (“**PUFA-containing plant oil**”), such as e.g. canola seed oil, linseed/flaxseed oil, hempseed oil, pumpkin seed oil, evening primrose oil, borage seed oil, blackcurrent seed oil, sallow thorn/sea buckthorn oil, chia seed oil, argan oil and walnut oil.

Thus, in addition, the present invention is
(1) directed to the use of the compounds of formula (III) as antioxidants in feed, such as especially feed for aquatic animals, feed for terrestrial animals such as poultry, pigs and pets, and feed for insects; as well as

(2) directed to the use of the compounds of formula (III) as antioxidants in feed ingredients, such as especially poultry meal, fish meal, insect meal and PUFA-containing oil, and
(3) directed to feed, such as especially feed for aquatic animals, feed for terrestrial animals such as poultry, pigs and pets, and feed for insects, comprising such compounds of formula (III) and
(4) directed to feed ingredients, such as especially poultry meal, fish meal, insect meal and PUFA enriched oil, comprising such compounds of formula (III).

Thus, the present invention is directed to feed for aquatic animals comprising such compounds of formula (III) with the preferences as given above.

The present invention is also directed to feed for insects and terrestrial animals, e.g. pigs, poultry and pets, comprising such compounds of formula (III) with the preferences as given above.

Aquatic animals in the context of the present invention encompass farmed crustacea such as shrimp and carnivorous species of farmed fish such as salmons, rainbow trout, brown trout (Salmo trutta) and gilthead seabream.

Thus, the feed for aquatic animals comprising the compounds of formula (III) are especially fed to the aquatic animals as cited above.

I. Feed ingredients

Feed ingredients are broadly classified into cereal grains, protein meals, fats and oils, minerals, feed additives, and miscellaneous raw materials, such as roots and tubers.

Further antioxidants

The compounds of formula (III) can be used in combination with one or more other antioxidants as described below.

In an embodiment of the present invention the feed ingredients of the present invention additionally comprise a mixture of 2-tert-butyl-4-methoxyphenol and 3-tert-butyl-4-methoxyphenol, which is known under the name "BHA" (**b**utylated **h**ydroxy**a**nisole).

In a further embodiment of the present invention the feed ingredients of the present invention additionally comprise ascorbyl palmitate.

In another embodiment of the present invention the feed ingredients of the present invention additionally comprise BHA and ascorbyl palmitate.

Instead of ascorbyl palmitate other esters of ascorbic acid such as the esters of ascorbic acid with linear C_{12-20} alkanols, preferably the esters of ascorbic acid with linear C_{14-18} alkanols, may also be used, so that further embodiments of the present invention are directed to feed ingredients that additionally comprise esters of ascorbic acid with linear C_{12-20} alkanols, preferably esters of ascorbic acid with linear C_{14-18} alkanols, more preferably ascorbyl palmitate, whereby optionally BHA may also be present.

The feed ingredients may also comprise additionally alpha-tocopherol and/or gamma-tocopherol, whereby either an ester of ascorbic acid with a linear C_{12-20} alkanol with the preferences as given above or BHA or both may additionally be present.

The feed ingredients themselves are described in more detail below.

1. PUFA-containing oils

In the context of the present invention the term "PUFA-containing oil" encompasses

- marine oil, such as especially fish oil,
- microbial biomass containing polyunsaturated fatty acids ("PUFAs"), especially docosahexaenoic acid ("DHA") and/or eicosapentaenoic acid

("EPA") and/or docosapentaenoic acid ("DPA") and/or their esters ("**microbial oil**");

- oil containing high amounts of PUFAs, especially containing high amounts of DHA and/or EPA and/or DPA and/or their esters extracted from microbial biomass as e.g., fungi ("fungal oil") or algae ("algal oil");
- Plant oil with high amounts of PUFAs and/or their esters ("**PUFA-containing plant oil**"), such as e.g. canola seed oil, linseed/flaxseed oil, hempseed oil, pumpkin seed oil, evening primrose oil, borage seed oil, blackcurrent seed oil, sallow thorn/sea buckthorn oil, chia seed oil, argan oil and walnut oil.

The term "DHA" does not only encompass the acid but also derivatives thereof such as monoglycerides, diglycerides and triglycerides as well as C_{1-6}-alkyl esters such as the methyl and ethyl esters. The same applies for "EPA" and "DPA" and all the other PUFAs.

Fish oil and algal oil are common feed ingredients. Instead of fish oil and algal oil also the other PUFA-containing oils named above may be used as feed ingredients, i.e.:

- microbial biomass containing PUFAs ("**microbial oil**")
- oil containing high amounts of PUFAs extracted from microbial biomass, such as especially fungal oil, and
- plant oil with high amounts of PUFAs.

The above-mentioned feed ingredients may not only be used as alternative of fish oil and algal oil, but also in addition.

Examples of PUFA-containing oils that are used as feed ingredients are given below in more detail.

Marine oil

Examples of suitable marine oils include, but are not limited to, Atlantic fish oil, Pacific fish oil, or Mediterranean fish oil, or any mixture or combination thereof.

In more specific examples, a suitable fish oil can be, but is not limited to, pollack oil, bonito oil, pilchard oil, tilapia oil, tuna oil, sea bass oil, halibut oil, spearfish oil, barracuda oil, cod oil, menhaden oil, sardine oil, anchovy oil, capelin oil, herring oil, mackerel oil, salmonid oil, tuna oil, and shark oil, including any mixture or combination thereof.

Other marine oils suitable for use herein include, but are not limited to, squid oil, cuttle fish oil, octopus oil, krill oil, seal oil, whale oil, and the like, including any mixture or combination thereof.

For stabilizing marine oil an amount of at least one compound of formula (III) ranging from 10 to 500 ppm, preferably ranging from 30 to 300 ppm, more preferably ranging from 100 to 250 ppm, based on the total amount of the marine oil, is usually sufficient. The same applies for the other PUFA-containing oils such as microbial oil, algal oil, fungal oil and PUFA-containing plant oil.

A commercially available example of marine oil is the fish oil “MEG-3” (Bleached 30S TG Fish oil) from DSM Nutritional Products, LLC (US) whose specification and composition is shown in **Tables I and II** below:

Table I

ANALYSIS	SPECIFICATIONS
Colour	Max. 6 Gardner Colour
Free Fatty Acid (as % Oleic)	Max. 0.4%
p-Anisidine Value	Max. 12 (at time of release)
Peroxide Value	Max. 3 milli equivalents/kg (at time of release)
% Moisture	Max. 0.05%
Cold Test	Remains clear at 0°C for 3 hours
Cholesterol	Report Actual
TOTOX ((2 x Peroxide Value) + (*p*-Anisidine Value))	Max. 20

The peroxide value is defined as the amount of peroxide oxygen per 1 kilogram of oil. Traditionally this is expressed in units of milliequivalents or meq/kg.

Winterization is part of the processing of fish oil, and it is performed to remove solid fat in the oil. The “cold test” is performed to check if any solid fat is present and precipitated in the oil when cooled to 0°C within a specific period of time. In this fish oil (Product Code: FG30TG), any such precipitation is checked for 3 hours at 0°C.

Table II

Fatty Acid Profile	
EPA (A%)	Min. 18
EPA mg/g (as TG)	Min. 170
DHA (A%)	Min. 12
DHA mg/g (as TG)	Min. 110
EPA + DHA (A%)	Min. 30
Total Omega 3 (A%)	Min. 34

“TG” = triglyceride;
“A%” = “area %” = area percentage by GC based on 24 peak analysis (meaning the 24 highest peaks have been analyzed)

Oil containing high amounts of PUFAs, especially containing high amounts of DHA and/or EPA and/or DPA and/or their esters, extracted from microbial biomass as e.g., fungi (“fungal oil”) or algae (“algal oil”)

Algal oil

“Algal oil” is an oil containing high amounts of DHA and/or EPA and/or DPA and/or their esters extracted from algae as microbial source/biomass.

An example of algal oil is the commercially available “Algal oil containing EPA+DPA” from DSM Nutritional Products, LLC (US) whose composition is shown in the **Table III** below:

Table III

Fatty Acid Profile	

DHA + EPA content, mg/g oil	587 mg/g
DHA content, mg/g oil	401 mg/g
EPA content, mg/g oil	186 mg/g
TOTOX ((2 x Peroxide Value) + (*p*-Anisidine Value))	5
Free Fatty Acid	0.6%
Moisture	< 0.05%

A further example of a crude oil containing high amounts of DHA and/or EPA extracted from microbial sources as e.g., algae, is the oil extracted from Algae *Schizochytrium* Biomass, whose specification is given in the following **Table IV.**

Table IV

Specification	**Aqua (Base Product)**
DHA + EPA, mg/g oil	**minimal 500 mg/g**
DHA content, mg/g oil	**minimal 250 mg/g (at least 25% -> 40%)**
EPA content, mg/g oil	**minimal 100 mg/g (at least 10% -> 25%)**
Minimal ratio EPA:DHA	**1:4**
Maximal ratio EPA:DHA	**1:1**
TOTOX ((2 x Peroxide Value) + (*p*-Anisidine Value))	maximum 35
Free fatty acid	maximal 5%
Moisture	maximal 0.75%
DPA n-3 (omega-3 docosapentaenoic acid), %	< 6
Arachidonic Acid, %	< 2
Stearic, %	< 2.5
Palmitic, %	< 30
Shelf life	6 months at 25°C
Total Fat	Record
Crude Fat	> 92%

Microbial biomass containing polyunsaturated fatty acids ("PUFAs"), especially docosahexaenoic acid and/or eicosapentaenoic acid and/or docosapentaenoic acid ("DPA") and/or their esters

The biomass preferably comprises cells which produce PUFAs heterotrophically. According to the invention, the cells are preferably selected from algae, fungi, particularly yeasts, bacteria, or protists. The cells are more preferably microbial algae or fungi.

Suitable cells of oil-producing yeasts are, in particular, strains of *Yarrowia*, *Candida*, *Rhodotorula*, *Rhodosporidium*, *Cryptococcus*, *Trichosporon* and *Lipomyces*.

Oil produced by a microorganism or obtained from a microbial cell is referred to as “microbial oil”. Oil produced by algae and/or fungi is referred to as an algal and/or a fungal oil, respectively.

As used herein, a "microorganism" refers to organisms such as algae, bacteria, fungi, protist, yeast, and combinations thereof, e.g., unicellular organisms. A microorganism includes but is not limited to, golden algae (e.g., microorganisms of the kingdom *Stramenopiles*); green algae; diatoms; dinoflagellates (e.g., microorganisms of the order *Dinophyceae* including members of the genus *Crypthecodinium* such as, for example, *Crypthecodinium cohnii* or *C. cohnii*); microalgae of the order *Thraustochytriales*; yeast (*Ascomycetes* or *Basidiomycetes*); and fungi of the genera *Mucor*, *Mortierella*, including but not limited to *Mortierella alpina* and *Mortierella sect. schmuckeri*, and *Pythium*, including but not limited to *Pythium insidiosum*.

In one embodiment, the microorganisms of the kingdom *Stramenopiles* may in particular be selected from the following groups of microorganisms: *Hamatores, Proteromonads, Opalines, Developayella, Diplophrys, Labrinthulids, Thraustochytrids, Biosecids, Oomycetes, Hypochytridiomycetes, Commation, Reticulosphaera, Pelagomonas, Pelagococcus, Ollicola, Aureococcus, Parmales, Diatoms, Xanthophytes, Phaeophytes* (brown algae), *Eustigmatophytes, Raphidophytes, Synurids, Axodines* (including *Rhizochromulinales, Pedinellales, Dictyochales*), *Chrysomeridales, Sarcinochrysidales, Hydrurales, Hibberdiales, and Chromulinales.*

In one embodiment, the microorganisms are from the genus *Mortierella*, genus *Crypthecodinium*, genus *Thraustochytrium*, and mixtures thereof. In a further embodiment, the microorganisms are from *Crypthecodinium Cohnii*. In a further embodiment, the microorganisms are from *Mortierella alpina*. In a still further embodiment, the microorganisms are from *Schizochytrium sp*. In yet an even further embodiment, the microorganisms are selected from *Crypthecodinium Cohnii*, *Mortierella alpina*, *Schizochytrium sp*., and mixtures thereof.
In a still further embodiment, the microorganisms include, but are not limited to, microorganisms belonging to the genus *Mortierella*, genus *Conidiobolus*, genus *Pythium*, genus *Phytophthora*, genus *Penicillium*, genus *Cladosporium*, genus *Mucor*, genus *Fusarium*, genus *Aspergillus*, genus *Rhodotorula*, genus *Entomophthora*, genus *Echinosporangium*, and genus *Saprolegnia*.

In an even further embodiment, the microorganisms are from microalgae of the order *Thraustochytriales*, which includes, but is not limited to, the genera *Thraustochytrium* (species include *arudimentale, aureum, benthicola, globosum, kinnei, motivum, multirudimentale, pachydermum, proliferum, roseum, striatum*); the genera *Schizochytrium* (species include *aggregatum, limnaceum, mangrovei, minutum, octosporum*); the genera *Ulkenia* (species include *amoeboidea, kerguelensis, minuta, profunda, radiate, sailens, sarkariana, schizochytrops, visurgensis, yorkensis*); the genera *Aurantiacochytrium*; the genera *Oblongichytrium*; the genera *Sicyoidochytium*; the genera *Parientichytrium*; the genera *Botryochytrium*; and combinations thereof. Species described within *Ulkenia* will be considered to be members of the genus *Schizochytrium*. In another embodiment, the microorganisms are from the order *Thraustochytriales*. In yet another embodiment, the microorganisms are from *Thraustochytrium*. In still a further embodiment, the microorganisms are from *Schizochytrium sp*.

In certain embodiments, the oil can comprise a marine oil. Examples of suitable marine oils are the ones as given above.

The biomass according to the invention preferably comprises cells, and preferably consists essentially of such cells, of the taxon *Labyrinthulomycetes* (*Labyrinthulea*, net slime fungi, slime nets), in particular, those from the family of

Thraustochytriaceae. The family of the *Thraustochytriaceae* (*Thraustochytrids*) includes the genera *Althomia*, *Aplanochytrium*, *Aurantiochytrium*, *Botryochytrium*, *Elnia*, *Japonochytrium*, *Oblongichytrium*, *Parietichytrium*, *Schizochytrium*, *Sicyoidochytrium*, *Thraustochytrium*, and *Ulkenia*. The biomass particularly preferably comprises cells from the genera *Aurantiochytrium*, *Oblongichytrium*, *Schizochytrium*, or *Thraustochytrium*, more preferably from the genus *Schizochytrium*.

In accordance with the invention, the polyunsaturated fatty acid (PUFA) is preferably DHA and/or EPA and/or their esters as defined above.

The cells present in the biomass are preferably distinguished by the fact that they contain at least 20 weight-%, preferably at least 30 weight-%, in particular at least 35 weight-%, of PUFAs, in each case based on cell dry matter.

In a very preferred embodiment of the current invention, cells, in particular a *Schizochytrium* strain, is employed which produces a significant amount of EPA and DHA, simultaneously, wherein DHA is preferably produced in an amount of at least 20 weight-%, preferably in an amount of at least 30 weight-%, in particular in an amount of 30 to 50 weight-%, and EPA is produced in an amount of at least 5 weight-%, preferably in an amount of at least 10 weight-%, in particular in an amount of 10 to 20 weight-% (in relation to the total amount of lipid as contained in the cells, respectively).

Preferred species of microorganisms of the genus *Schizochytrium*, which produce EPA and DHA simultaneously in significant amounts, as mentioned before, are deposited under ATCC Accession No. PTA-10208, PTA-10209, PTA-10210, or PTA-10211, PTA-10212, PTA-10213, PTA-10214, PTA-10215.

DHA and EPA producing *Schizochytrium* strains can be obtained by consecutive mutagenesis followed by suitable selection of mutant strains which demonstrate superior EPA and DHA production and a specific EPA:DHA ratio. Any chemical or nonchemical (e.g. ultraviolet (UV) radiation) agent capable of inducing genetic change to the yeast cell can be used as the mutagen. These agents can be used alone or in combination with one another, and the chemical agents can be used neat or with a solvent.

Methods for producing the biomass, in particular, a biomass which comprises cells containing lipids, in particular PUFAs, particularly of the order *Thraustochytriales*, are described in detail in the prior art (see e.g. WO 91/07498, WO 94/08467, WO 97/37032, WO 97/36996, WO 01/54510). As a rule, the production takes place by cells being cultured in a fermenter in the presence of a carbon source and a nitrogen source, along with a number of additional substances like minerals that allow growth of the microorganisms and production of the PUFAs. In this context, biomass densities of more than 100 grams per litre and production rates of more than 0.5 gram of lipid per litre per hour may be attained. The process is preferably carried out in what is known as a fed-batch process, i.e. the carbon and nitrogen sources are fed in incrementally during the fermentation. When the desired biomass has been obtained, lipid production may be induced by various measures, for example by limiting the nitrogen source, the carbon source or the oxygen content or combinations of these.

In a preferred embodiment of the current invention, the cells are grown until they reach a biomass density of at least 80 or 100 g/l, more preferably at least 120 or 140 g/l, in particular at least 160 or 180 g/l (calculated as dry-matter content). Such processes are for example disclosed in US 7,732,170.

Preferably, the cells are fermented in a medium with low salinity, in particular, so as to avoid corrosion. This can be achieved by using chlorine-free sodium salts as the sodium source instead of sodium chloride, such as, for example, sodium sulphate, sodium carbonate, sodium hydrogen carbonate or soda ash. Preferably, chloride is used in the fermentation in amounts of less than 3 g/l, in particular, less than 500 mg/l, especially preferably less than 100 mg/l.

<u>PUFA-containing plant oils: Plant oils with relatively high amounts of PUFAs, especially with high amounts of DHA and/or EPA such as e.g., canola seed oil</u>

The plant cells may, in particular, be selected from cells of the families *Brassicaceae*, *Elaeagnaceae* and *Fabaceae*. The cells of the family *Brassicaceae* may be selected from the genus *Brassica*, in particular, from oilseed rape, turnip rape and Indian mustard; the cells of the family *Elaeagnaceae* may be selected from the genus *Elaeagnus*, in particular, from the species *Oleae europaea*; the cells of the family *Fabaceae* may be selected from the genus *Glycine*, in particular, from the species *Glycine* max.

Examples:

- Canola seed oil with a content of DHA of at least 9% by weight, of at least 12% by weight, of at least 15% by weight, or of at least 20% by weight, based on the total weight of the canola seed oil;
- Canola seed oil with a content of EPA of at least 9% by weight, of at least 12% by weight, of at least 15% by weight, or of at least 20% by weight, based on the total weight of the canola seed oil.

Examples of PUFA-containing plant oils containing high amounts of other PUFAs than EPA and/or DHA and/or DPA and/or their esters are linseed/flaxseed oil, hempseed oil, pumpkin seed oil, evening primrose oil, borage seed oil, blackcurrent seed oil, sallow thorn/sea buckthorn oil, chia seed oil, argan oil and walnut oil.

2. Other feed ingredients

Poultry meal/Chicken meal

Poultry meal is a high-protein commodity used as a feed ingredient. It is made from grinding clean, rendered parts of poultry carcasses and can contain bones, offal, undeveloped eggs, and some feathers. Poultry meal quality and composition can change from one batch to another.

Chicken meal, like poultry meal, is made of "dry, ground, rendered clean parts of the chicken carcass" according to AAFCO and may contain the same ingredients as poultry meal. Chicken meal can vary in quality from batch to batch. Chicken meal costs less than chicken muscle meat and lacks the digestibility of chicken muscle meat.

Poultry meal contains preferably not less than 50 weight-% of crude protein, not less than 5 weight-% of crude fat, not more than 5 weight-% of crude fiber, not more than 40 weight-% of ash and not more than 15 weight-% of water, each based on the total weight of the poultry meal, whereby the total amount of all ingredients sums up to 100 weight-%.

More preferably poultry meal contains from 50 to 85 weight-% of crude protein, and from 5 to 20 weight-% of crude fat, and from 1 to 5 weight-% of crude fiber, and from 5 to 40 weight-% of ash, and from 5 to 15 weight-% of water, each based on the total weight of the poultry meal, whereby the total amount of all ingredients sums up to 100 weight-%.

For stabilizing poultry meal an amount of at least one compound of formula (III) ranging from 10 to 1000 ppm, preferably ranging from 30 to 700 ppm, more preferably ranging from 100 to 500 ppm, based on the total amount of the poultry meal, is usually sufficient.

The same amounts also apply for chicken meal.

<u>**Fish meal**</u>

Fish meal contains preferably not less than 50 weight-% of crude protein, and not more than 20 weight-% of crude fat, and not more than 10 weight-% of crude fibers, and not more than 25 weight-% of ash, and not more than 15 weight-% of water, each based on the total weight of the fish meal, whereby the total amount of all ingredients sums up to 100 weight-%.

More preferably fish meal contains from 50 to 90 weight-% of crude protein and from 5 to 20 weight-% of crude fat, and from 1 to 10 weight-% of crude fibers, and from 5 to 25 weight-% of ash, and from 5 to 15 weight-% of water, each based on the total weight of the fish meal, whereby the total amount of all ingredients sums up to 100 weight-%.

For stabilizing fish meal an amount of at least one compound of formula (III) ranging from 10 to 2000 ppm, preferably ranging from 100 to 1500 ppm, more preferably ranging from 300 to 1000 ppm, based on the total amount of the fish meal, is usually sufficient.

Fish meal is a commercial product made from fish that is used primarily as a protein supplement in compound feed, especially for feeding farmed fish, crustacea, pigs and poultry, and companion animals such as cats and dogs.

A portion of the fish meal is made from the bones and offal left over from processing fish used for human consumption, while the larger percentage is manufactured from wild-caught, small marine fish. It is powder or cake obtained by drying the fish or fish trimmings, often after cooking, and then grinding it. If the fish used is a fatty fish it is first pressed to extract most of the fish oil.

The uses and need of fish meal are increasing due to the rising demand for fish, because fish has the best feed conversion rate of all farmed animals, can be produced well in developing countries and has a small size, i.e. can be slaughtered for preparing a meal, so that there is no need to store the fish. Furthermore, there are no religious constraints concerning the consumption of fish, fish is a source of high quality protein and it is easy to digest.

Fish meal is made by cooking, pressing, drying, and grinding of fish or fish waste to which no other matter has been added. It is a solid product from which most of the water is removed and some or all of the oil is removed. About four or five tons of fish are needed to manufacture one ton of dry fish meal.

Of the several ways of making fish meal from raw fish, the simplest is to let the fish dry out in the sun. This method is still used in some parts of the world where processing plants are not available, but the end-product is of poor quality in comparison with ones made by modern methods.

Currently, all industrial fish meal is usually made by the following process:

Cooking: A commercial cooker is a long, steam-jacketed cylinder through which the fish are moved by a screw conveyor. This is a critical stage in preparing the fishmeal, as incomplete cooking means the liquid from the fish cannot be pressed out satisfactorily and overcooking makes the material too soft for pressing. No drying occurs in the cooking stage.

Pressing: A perforated tube with increasing pressure is used for this process. This stage involves removing some of the oil and water from the material and the solid is known as press cake. The water content in pressing is reduced from 70% to about 50% and oil is reduced to 4%.

Drying: If the fish meal is under-dried, moulds or bacteria may grow. If it is over-dried, scorching may occur and this reduces the nutritional value of the meal.

The two main types of dryers are:
Direct: Very hot air at a temperature of about 500°C is passed over the material as it is tumbled rapidly in a cylindrical drum. This is the quicker method, but heat damage is much more likely if the process is not carefully controlled.
Indirect: A cylinder containing steam-heated discs is used, which also tumbles the meal.

Grinding: This last step in processing involves the breakdown of any lumps or particles of bone.

The fish meal has to be transported long distances by ship or other vehicles to the various locations, where it is used.

Unmodified fish meal can spontaneously combust from heat generated by oxidation of the polyunsaturated fatty acids in the fish meal. Therefore, it has to be stabilized by antioxidants. Especially advantageous for this purpose are the compounds of formula (III) of the present invention.

Insect meal

Insect meal has a high content of protein and is therefore, a valuable source of protein.

In general any insect may be manufactured to meal, but insects of special interest in the context of the present invention encompass black soldier flies (Hermetia species, commonly called BSF), mealworms (Tenebrio molitor), lesser mealworms (Alphitobius diaperinus), house cricket (Acheta domesticus, grasshoppers (Locusta migratoria), buffaloworms (Alphitobius diaperinus), cockroaches and domestic flies, whereby black soldier flies (Hermetia species, commonly called BSF), mealworms (Tenebrio molitor) and lesser mealworms (Alphitobius diaperinus) are more preferred.

For stabilizing insect meal an amount of at least one compound of formula (III) ranging from 10 to 1000 ppm, preferably ranging from 30 to 700 ppm, more preferably ranging from 100 to 500 ppm, based on the total amount of the insect meal, is usually sufficient.

<u>Preferred embodiments of the present invention</u>

The compounds of formula (III) with the preferences as given above are not only suitable for stabilizing fish meal, but also for stabilizing feed ingredients and feed. Preferences for feed ingredients and feed are given above and also apply here.

<u>II. Feed</u>

The compounds of formula (III) are not only suitable for stabilizing feed ingredients such as poultry meal, fish meal, insect meal and PUFA-containing oil, but also effective antioxidants for feed.

Feed (or ‘feedingstuff’) means any substance or product, including additives, whether processed, partially processed or unprocessed, intended to be used for oral feeding to animals.

Feed in the context of the present invention is feed for aquatic animals and for terrestrial animals, as well as feed for insects.

For stabilizing feed an amount of at least one compound of formula (III) ranging from 10 to 500 ppm, preferably ranging from 30 to 300 ppm, more preferably ranging from 100 to 250 ppm, based on the total amount of the feed, is usually sufficient.

Further antioxidants

The compounds of formula (III) can be used in combination with one or more other antioxidants as described below.

In an embodiment of the present invention the feed of the present invention additionally comprises a mixture of 2-tert-butyl-4-methoxyphenol and 3-tert-butyl-4-methoxyphenol, which is known under the name “BHA” (**b**utylated **h**ydroxy**a**nisole).

In a further embodiment of the present invention the feed of the present invention additionally comprises ascorbyl palmitate.

In another embodiment of the present invention the feed of the present invention additionally comprises BHA and ascorbyl palmitate.

Instead of ascorbyl palmitate other esters of ascorbic acid such as the esters of ascorbic acid with linear C_{12-20} alkanols, preferably the esters of ascorbic acid with linear C_{14-18} alkanols, may also be used, so that further embodiments of the present invention are directed to feed that additionally comprises esters of ascorbic acid with linear C_{12-20} alkanols, preferably esters of ascorbic acid with linear C_{14-18} alkanols, more preferably ascorbyl palmitate, whereby optionally BHA may also be present.

The feed may also comprise additionally alpha-tocopherol and/or gamma-tocopherol, whereby either an ester of ascorbic acid with a linear C_{12-20} alkanol with the preferences as given above or BHA or both may additionally be present.

The feed itself is described in more detail below.

Feed for poultry

The feed for poultry differs from region to region. In the following **Tables V and VI** typical examples for diets in Europe and Latin America are given. These diets include cereals such as wheat, rye, maize/corn, minerals such as NaCl, vegetable oils such as soya oil, amino acids and proteins.

Table V: European diet

Ingredients (%)	Starter Period (day 0-21)	Grower Period (day 22-36)
Wheat	20.00	22.50
Rye	12.00	12.00
Soybean meal	34.00	28.50
Maize	27.00	28.50
Vegetable Oil	3.10	4.20
NaCl	0.10	0.10
DL Methionine	0.24	0.24
L-Lysine	0.15	0.15
Limestone	0.85	0.85
Dicalcium Phosphate	1.50	1.90
Vitamin & Mineral mix	1.00	1.00
Coccidiostat (Avatec)	0.06	0.06
TiO_2	-	0.10
calculated Provision		
apparent metabolizable energy, MJ/kg	12.5	12.90
apparent metabolizable energy, kcal/kg	2986	3082
crude Protein, %	21.2	19.1
Methionine + Cysteine, %	0.89	0.83
Lysine, %	1.23	1.09
Calcium, %	0.83	0.91
total phosphorus, %	0.68	0.73
available phosphorus, %	0.35	0.40

Table VI: Latin American diet

Ingredients (%)	Starter	Grower
Corn	53.0	57.1

Soybean meal	38.5	34.2
Calcium	0.70	0.70
Phosphorus	2.40	2.00
$NaHCO_3$	0.23	0.24
NaCl	0.20	0.20
Methionine	0.30	0.10
Lysine	0.21	0.00
Soya Oil	3.50	4.50
Premix	1.00	1.00
Calculated provision (%)		
Crude protein	22.4	20.4
apparent metabolizable energy, (MJ/kg)	12.7	13.2
apparent metabolizable energy, (kcal/kg)	3034	3154
Total phosphorus	0.86	0.76
Calcium	1.00	0.85
Available phosphorus	0.44	0.38
d-Lysine	1.25	0.98
d-Methionine + Cysteine	0.91	0.68
d-Threonine	0.77	0.71
Na	0.18	0.18
Cl	0.20	0.19

Pet food

Pet foods are formulated to meet nutrient specifications using combinations of multiple ingredients to meet the targeted nutrient specification.

Poultry meal e.g. is an ingredient that is commonly found in Dog and Cat foods.

The nutrient specifications for a complete and balanced dog or cat food will meet or exceed the guidelines provided by AAFCO (American Association of Feed Control Officials). The ingredient composition of pet-food can include any legal feed ingredient so number of combinations are not quite infinite but close. Some examples of ingredient used in dog and cat foods can be found in **Table VII** below:

Table VII:

Ingredient Class/Ingredient	**Use rates**
1 ANIMAL MEALS	**10-35%**
Chicken	
Turkey	

Duck	
Poultry Br-Product	
Lamb	
Venison	
Beef	
Pork	
Meat & Bone	
Fish	
2 FRESH MEATS	**3-20%**
Chicken	
Turkey	
Duck	
Lamb	
Venison	
Beef	
Pork	
Fish	
3 VEGETABLE PROTEINS	**8-20%**
Soybean Meal	
Corn Gluten Meal	
Pea Protein	
Potato Protein	
Soy Protein Conc/Isolates	
4 GRAINS	**0-70%**
Corn/Maize	
Wheat	
Brown Rice/Brewers Rice	
Oatmeal/Oat Groats	
Barley	
Millet	
Milo/Sorghum	
Rye	
Corn Gluten Feed	
Wheat Middlings	
5 FIBER SOURCES	**2-8%**
Beet Pulp	
Corn Bran	
Wheat Bran	
Cellulose	
Tomato Ponace	
Potato Fiber	
Pea Fiber	
6 FATS & OILS	**1 - 15%**
Animal Fat	
Poultry Fat	
Chicken Fat	
Beef Tallow	
Sunflower Oil	
Canola Oil	

7 MICRONUTRIENTS	**0.10-1%**
Vitamins	
Minerals	
Others (e.g. Fructooligosaccharides (FOS) used as a pre-biotic)	
8 PALATANTS (FLAVORS)	**0-5%**
9 Other non-basic ingredients	
Dried Egg Product	1-15%
Fish Oil	0.5-2%
Fish Meal	1-4%
Flaxseed	1-4%
Dried Peas	5-30%
Dried Chickpeas	5-30%
Dried Lentils	5-10%
Dried Potatoes	5-20%
Dried Sweet Potatoes	5-20%
Tapioca Starch	5-15%
Potato Starch	5-15%
Pea Starch	5-15%

For stabilizing pet food an amount of at least one compound of formula (III) ranging from 10 to 500 ppm, preferably ranging from 30 to 300 ppm, more preferably ranging from 100 to 250 ppm, based on the total amount of the pet food, is usually sufficient.

<u>**Feed for fish**</u>

A typical example of feed for fish comprises the following ingredients, whereby all amounts are given in weight-%, based on the total weight of the feed for fish:

- Fish meal in an amount ranging from 5 to 15 weight-%, preferably fish meal in said amount comprising the compounds of formula (III) of the present invention;
- fish hydrolysates in an amount ranging from 0 to 5 weight-%;
- vegetable proteins in an amount ranging from 30 to 45 weight-%;
- binders, mainly starch, in an amount ranging from 9 to 12 weight-%;
- micro-ingredients such as vitamins, choline, minerals, mono calcium phosphate (“MCP”) and/or amino acids in an amount ranging from 3 to 6 weight-%;
- marine oil in an amount ranging from 5 to 10 weight-%, preferably marine oil in said amount comprising the compounds of formula (III) of the present invention;

- vegetable oil in an amount ranging from 20 to 25 weight-%, preferably vegetable oil in said amount comprising the compounds of formula (III) of the present invention;

and whereby the amount of all ingredients sum up to 100 weight-%.

For stabilizing feed for fish an amount of at least one compound of formula (III) ranging from 10 to 1000 ppm, preferably ranging from 30 to 700 ppm, more preferably ranging from 100 to 500 ppm, based on the total amount of the feed for fish, is usually sufficient.

Process for the manufacture of compounds of formula (III)

Starting material (compounds of formulae (I) and (II)) and product (compound of formula (III))

"alkyl" and "alkoxy" in the context of the present invention encompass linear alkyl and branched alkyl, and linear alkoxy and branched alkoxy, respectively.

Preferably R^1 and R^3 are independently from each other H or methyl or ethyl, and R^2 is either H or methyl or ethyl or methoxy or ethoxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H.

More preferably R^1 and R^3 are independently from each other H or methyl, and R^2 is either H or methyl or methoxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H.

The most preferred compounds used as starting materials and the most preferred compounds obtained as products by the process of the present invention are shown in **Fig. 1-3.**

Fig. 1 shows the synthesis of 2,5,7,8-tetramethyl-2-(4-methylpentyl)chroman-6-ol (compound of formula (III-1)) starting from 2,3,5-trimethyl-1,4-hydroquinone (compound of formula (I-1)) and 3,7-dimethyloct-1-en-3-ol (compound of formula (II-1)).

Fig. 2 shows the synthesis of 2-methyl-2-(4-methylpentyl)chroman-6-ol (compound of formula (III-2)) starting from 1,4-hydroquinone (compound of formula (I-2)) and 3,7-dimethyloct-1-en-3-ol (compound of formula (II-1)).

Fig. 3 shows the synthesis of 2-(4,8-dimethylnonyl)-2-methylchroman-6-ol (compound of formula (III-3)) starting from 1,4-hydroquinone (compound of formula (I-2)) and 3,7,11-trimethyldodec-1-en-3-ol (compound of formula (II-2)).

In a preferred embodiment of the present invention the molar ratio of the compound of formula (I) to the compound of formula (II) is in the range of 6.0:1 to 1.1:1, preferably in the range of 4.0:1 to 1.2:1, more preferably in the range of 3.0:1 to 1.3:1, most preferably in the range of 2.0:1 to 1.5:1.

In a further embodiment of the present invention all embodiments of the present invention with regard to the starting materials and the preferences as given above are realized.

Solvent mixture

In a preferred embodiment of the present invention the first of the two solvents is selected from ethylene carbonate, propylene carbonate, 1,2-butylene carbonate, and gamma-butyrolactone,
and the second of the two solvents is selected from hexane, cyclohexane, heptane, *ortho*-xylene, *meta*-xylene, *para*-xylene, mesitylene, pseudocumene, methyl *tert*-butyl ether, and toluene, whereby this preference is preferably combined with another preference, some other preferences or all preferences of the process according to the present invention.

In a more preferred embodiment of the present invention the first of the two solvents is ethylene carbonate or propylene carbonate, and the second of the two solvents is selected from either hexane, cyclohexane or heptane, preferably the first of the two solvents is ethylene carbonate and the second of the two solvents is heptane.

The term “hexane” encompasses n-hexane, as well as any mixture of the isomers of hexane. The same applies for heptane.

In a preferred embodiment of the present invention the volume ratio of the first solvent to the second solvent during the reaction is in the range of 1:4 to 4:1, preferably the volume ratio of the first solvent to the second solvent is in the range of 1:3 to 3:1, more preferably the volume ratio of the first solvent to the second solvent is in the range of 1:2 to 2:1.

In another embodiment of the present invention the total amount of the two solvents is in the range of 1 to 10 kg, preferably in the range of 2 to 7 kg, more preferably in the range of 2.5 to 6 kg, per kg of the compound of formula (I).

In a further embodiment of the present invention all embodiments of the present invention with regard to the solvent and the preferences as given above are realized.

Acid catalyst

Examples of suitable acid catalysts are Brønsted acids and Lewis acids and any mixture thereof.

Examples of Brønsted acids are sulfuric acid, phosphoric acid, acidic ion-exchange resins (e.g. Amberlyst 15), acidic clays (e.g. Montmorillonite K-10), zeolites (e.g. HSZ-360), hydrochloric acid, trifluoroacetic acid, trichloroacetic acid, acetic acid, formic acid, methanesulfonic acid, benzenesulfonic acid, *para*-toluenesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, bis(perfluoroalkyl-sulfonyl)methanes $(R'SO_2)(R''SO_2)CH_2$ wherein R’ and R” each signify independently from each other a perfluoroalkyl group of the formula C_nF_{2n+1} where n is an integer from 1 to 10, tris(perfluorosulfonyl)methanes $(R'SO_2)(R''SO_2)(R'''SO_2)CH$, wherein R’, R” and R’’’ each signify independently from each other a perfluoroalkyl group of the formula C_nF_{2n+1} where n is an integer from 1 to 10, and whereby at least two of R’, R” and R’’’ are identical perfluoroalkyl groups, or R’ signifies the pentafluorophenyl group ($-C_6F_5$) and R” and R’’’ each signify an identical perfluoroalkyl group of the above formula C_nF_{2n+1}, methanetrisulfonic acid, and bis(trifluormethylsulfonyl)imide, and any mixture thereof, whereby the use of single catalysts is preferred.

Examples of Lewis acids are $Al(OTf)_3$, $Sc(OTf)_3$, $Sc(NTf_2)_3$, $ScCl_3$, $Yb(OTf)_3$, $YbCl_3$, $Cu(OTf)_2$, $FeCl_2$, $Fe(OTf)_2$, $ZnCl_2$, $Zn(OTf)_2$, $Zn(NTf_2)_3$, YCl_3, $Y(OTf)_3$, $InCl_3$, $InBr_3$, $In(OTf)_3$, $In(NTf_2)_3$, $La(OTf)_3$, $Ce(OTf)_3$, $Sm(OTf)_3$, $Gd(OTf)_3$, and $Bi(OTf)_3$ in the presence or absence of 2,2-bipyridine, and any mixture thereof, whereby the use of single catalysts is preferred.

Preferably the acid catalyst is *para*-toluenesulfonic acid, sulfuric acid, methanesulfonic acid, $Al(OTf)_3$, $Sc(OTf)_3$, or $In(OTf)_3$ and any mixture thereof, more preferably the acid catalyst is *para*-toluenesulfonic acid or $Al(OTf)_3$ or any mixture thereof. Hereby the use of single catalysts is preferred.

Thus, the more preferred acid catalyst is *para*-toluenesulfonic acid, sulfuric acid, methanesulfonic acid, $Al(OTf)_3$, $Sc(OTf)_3$, or $In(OTf)_3$, and the most preferred acid catalyst is *para*-toluenesulfonic acid or $Al(OTf)_3$.

In a preferred embodiment of the present invention the amount of the acid catalyst is in the range of 0.001 to 5 mol equivalents, preferably in the range of 0.005 to 1 mol equivalents, more preferably in the range of 0.01 to 0.1 mol equivalents, relative to the amount of the compound of formula (II).

In the process according to the present invention the acid catalyst is recyclable which is a further advantage of the present invention.

In a further embodiment of the present invention all embodiments of the present invention with regard to the acid catalyst and the preferences as given above are realized.

Reaction conditions

The reaction is preferably carried out at a temperature in the range of 70 to 160°C, more preferably in the range of 80 to 130°C, most preferably in the range of 90-105°C.

The reaction is preferably carried out at a pressure in the range of 0.8 to 20 bar (absolute), more preferably at a pressure in the range of 0.8 to 10 bar (absolute), most preferably at a pressure in the range of 0.8 to 5 bar (absolute).

In a further embodiment of the present invention all embodiments of the present invention with regard to the reaction conditions and the preferences as given above are realized.

In the most preferred embodiments of the present invention all embodiments of the present invention with regard to the starting materials, the solvent, the catalyst and the reaction conditions including the preferences as given above are realized.

The invention is now further illustrated in the following non-limiting examples.

Examples

Example 1: Synthesis of 2,5,7,8-tetramethyl-2-(4-methylpentyl)chroman-6-ol (compound of formula (III-4) (see Fig. 1)

A 1.5 L 4-necked flask equipped with magnetic stirrer, oil bath, thermometer and argon supply 2,3,5-trimethyl-1,4-hydroquinone (134 g, 853 mmol, 97%, 4.0 mol equiv.), was suspended in ethylene carbonate (300 mL) and heptane (300 mL), forming a 2-phase system upon warming to 60°C. Then, 3,7-dimethyloct-1-en-3-ol (34.0 g, 213 mmol, 98%, 1.0 mol equiv.) and *para*-toluenesulfonic acid monohydrate (0.37 g, 2.13 mmol, 1 mol%) were added and the mixture was heated to reflux (85°C internal temperature). After 60 min, the reaction mixture was cooled to 50°C, diluted with water (500 mL) and the phases were separated. The lower ethylene carbonate/water phase containing precipitated trimethylhydroquinone was extracted with heptane (2x 250 mL). The combined organic phases were extracted with water (500 mL), dried over magnesium sulfate and concentrated *in vacuo* (45°C/50-20 mbar). The residue was purified by column chromatography, eluent gradient heptane/EtOAc 95:5 to 90:10 (w/w). The combined pure fractions were concentrated in vacuo (40°C/200-10 mbar) and dried under high vacuum at 40°C, furnishing 2,5,7,8-tetramethyl-2-(4-methylpentyl)chroman-6-ol **(compound of formula (III-4))** as colorless crystals (26.8 g g, 98.9% purity by quant. NMR, 91 mmol, 43% yield).

Example 2: Synthesis of 2-methyl-2-(4-methylpentyl)chroman-6-ol (see Fig. 2)

A 1500 mL 4-necked flask with magnetic stirrer, oil bath, thermometer and argon supply was charged with 1,4-hydroquinone (95.0 g, 864 mmol, 99.8%, 4.0 mol equiv.), 3,7-dimethyloct-1-en-3-ol (34.0 g, 216 mmol, 99.3 area% by GC, 1.0 mol equiv.) and dissolved in ethylene carbonate (400 mL) and heptane (300 mL), forming a 2-phase system. Then, *para*-toluenesulfonic acid monohydrate (0.38 g, 2.16 mmol, 98.5%, 1 mol%) was added and the mixture was heated to reflux. After 1 h, water (500 mL) was added to the reaction mixture and the still warm reaction phases were separated. The lower ethylene carbonate phase was extracted heptane (2x 300 mL). The combined heptane phases were dried over Na_2SO_4 and concentrated *in vacuo* (40°C/50-20 mbar). The residue was purified by column chromatography, eluent gradient heptane/EtOAc 95:5 to 85:15 (w/w). The combined pure fractions were concentrated in vacuo (40°C/200-10 mbar) and dried under high vacuum at 45°C, furnishing 2-methyl-2-(4-methylpentyl)chroman-6-ol as colorless oil (31.7 g, 97% purity by quant. NMR, 124 mmol, 58% yield).

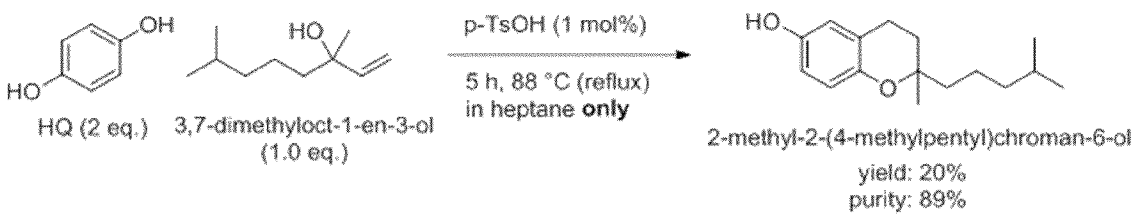
GC-HRMS: 95.4 area%. Calcd. for $C_{16}H_{24}O_2$ (M^+) 248.1776, found 248.1800.
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 0.88 (d, *J* = 6.6 Hz, 6 H), 1.12-1.23 (m, 2 H), 1.27 (s, 3 H), 1.33-1.46 (m, 2 H), 1.46-1.62 (m, 3 H), 1.64-1.89 (m, 2 H), 2.71 (t, *J* = 6.9 Hz, 2 H), 4.51 (s, 1 H, OH), 6.54-6.63 (m, 2 H), 6.66 (d, *J* = 8.9 Hz, 1 H) ppm.
^{13}C NMR (75 MHz, CHLOROFORM-d) δ 21.4 (1 C), 22.4 (1 C), 22.6 (2 C), 24.1 (1 C), 27.9 (1 C), 30.9 (1 C), 39.4 (1 C), 39.7 (1 C), 75.9 (1 C), 114.4 (1 C), 115.4 (1 C), 117.8 (1 C), 122.0 (1 C), 147.9 (1 C), 148.4 (1 C) ppm.

Example 3: Synthesis of 2-(4,8-dimethylnonyl)-2-methylchroman-6-ol (compound of formula (III-3)) (see Fig. 3)

A 200 mL 4-necked flask equipped with magnetic stirrer, oil bath, thermometer and argon supply was charged with hydroquinone (12.0 g, 109 mmol, 99.8%, 4.0 mol equiv.), 3,7,11-trimethyldodec-1-en-3-ol (6.39 g, 27.2 mmol, 96.3 area% by GC, 1.0 mol equiv.), and dissolved in ethylene carbonate (50 mL) and heptane (50 mL) forming a 2-phase system upon warming to 60°C. Then, *para*-toluenesulfonic acid monohydrate (0.10 g, 0.54 mmol, 2 mol%) was added and the mixture was heated to reflux. After 90 min, the reaction mixture was cooled to 80°C and the phases were separated. The lower ethylene carbonate phase was extracted with heptane (25 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo* (40°C/50-20 mbar). The residue was purified by column chromatography, eluent gradient heptane/EtOAc 95:5 to 85:15 (w/w). The combined pure fractions were concentrated in vacuo (40°C/200-10 mbar) and dried under high vacuum at 40 °C, furnishing 2-(4,8-dimethylnonyl)-2-methylchroman-6-ol **(compound of formula (III-3))** as light beige oil (4.95 g, 98.4% purity by quant. NMR, 15.3 mmol, 56% yield).

GC-HRMS: >99 area%. Calcd. for $C_{21}H_{34}O_2$ (M^+) 318.2559, found 318.2370.
^{1}H NMR (300 MHz, CHLOROFORM-d) δ 0.86 (d, *J* = ~6 Hz, 3 H), superimposed by 0.88 (d, *J* = 6.6 Hz, 6 H), 1.04-1.46 (m, 11 H), superimposed by 1.27 (s, 3 H), 1.46-1.67 (m, 3 H), 1.70-1.87 (m, 2 H), 2.71 (t, *J* = 6.8 Hz, 2 H), 4.54 (br s, 1 H, OH), 6.53-6.62 (m, 2 H), 6.66 (d, *J* = 8.5 Hz, 1 H) ppm.
^{13}C NMR (75 MHz, CHLOROFORM-d) δ 19.6, 21.1, 22.3, 22.6, 22.7, 24.1, 24.8, 28.0, 30.8, 30.9, 32.7, 37.3, 37.5, 39.3, 39.78, 39.82, 76.0, 114.4, 115.4, 117.8, 122.0, 147.9, 148.4 ppm.

Comparison example: reaction in one solvent only



"eq." = mol equivalents; p-TsOH = *para*-toluenesulfonic acid, h = hour.

<u>Example 4: Antioxidant activities of compound of formulae (III-3) and (III-4) in fish oil and algal oil</u>

The compounds of formulae (III-3) and (III-4) have been tested. The blank oil, i.e. oil without any antioxidant, and oil containing "MNT" have been used as benchmark. Any compound better in antioxidant activity than the blank oil indicates that it has antioxidant activity. The comparison with MNT gives an indication about the amount of the antioxidant effect, relative to the activity of MNT.

"MNT" are mixed natural tocopherols commercially available as e.g., "Tocomix 70 IP" from AOM (Buenos Aires, Argentina). Tocomix 70 IP comprises d-alpha-tocopherol, d-beta-tocopherol, d-gamma-tocopherol and d-delta-tocopherol, whereby the total amount of tocopherols is at least 70.0 weight-% and the amount of non-alpha tocopherols is at least 56.0 weight-%.

The compounds of formulae (III-3) and (III-4) were evaluated primarily for their oxidative stability by the Oil Stability Index (OSI) measurements. Two different levels of these antioxidants (0.5 and 2 mg/g) were used in 5 g of natural fish oil (Product code: FG30TG) and used in the Oxidative Stability Instrument at 80^{0}C with the air flow rate of 40 psi.

Crude algal oil (Lot# VY00010309) contained about 1.6 mg/g of MNT prior to use in these experiments whereas fish oil did not contain any antioxidants.

The compound of formula (III-4) (see **Table 2** below) and the compound of formula (III-3) (see **Table 3** below) were used at different times in the Oxidative Stability Instrument under similar operational conditions used for fish oil evaluations. MNT and the oil without any antioxidants were always used to compare. Also, the synergistic effect of only oil soluble compounds with ascorbyl palmitate was determined using the OSI values. The polymers generated at the end of the experiment were determined by LC (LC = liquid chromatography).

The solubility of the compounds used in the oxidative stability study are shown in **Table 1**.

Table 1: Solubility of compounds of formulae (III-3) and (III-4) in fish oil

Compound of formula	**Appearance**	**Amount (mg/g)**	**Solubility in fish oil**	
			Room temp.	**80ºC**
(III-4)	Off white powder	0.5	Soluble	Soluble
		2.0	Soluble	Soluble
(III-3)	Light yellow slightly viscous liquid	0.5	soluble	soluble
		2.0	soluble	soluble

Oil Stability Indices (**OSI**) for these compounds at 500 and 2000 ppm levels, in comparison with the same amounts of MNT, are shown in **Tables 2-3**.

Table 2: Oxidative stability of FG30TG fish oil with compound of formula (III-4) (SD = standard deviation)

	OSI (h)	**SD**
Blank (FG30TG)	4.55	0.1
0.5 mg/g of compound of formula (III-4)	5.75	0.1
2 mg/g of compound of formula (III-4)	6.05	0.1
0.5 mg/g of MNT	6.88	0.2
2 mg/g of MNT	7.73	0.2

Table 3: Oxidative stability of FG30TG fish oil with compound of formula (III-3) (SD = standard deviation)

	OSI (h)	SD
Blank (FG30TG)	4.73	0.4
0.5 mg/g of compound of formula (III-3)	5.48	0.1
2 mg/g of compound of formula (III-3)	5.96	0.1
0.5 mg/g of MNT	7.15	0.3
2 mg/g of MNT	8.38	0.4

The Protection Factors of the corresponding antioxidant compounds in fish oil are shown as a percentage in **Tables 4-5**.

The Protection Factors (PF) for each compound in oil were calculated in percentage as:

$$\text{PF (\%)} = \frac{100\% \text{ x (OSI of the sample with compound - OSI of the sample without compound)}}{\text{OSI of the sample without compound}}$$

Table 4: Protection Factors of compound of formula (III-4) in FG30TG fish oil

	Protection Factor (%)
0.5 mg/g of compound of formula (III-4)	26.37
2 mg/g of compound of formula (III-4)	32.97
0.5 mg/g of MNT	51.10
2 mg/g of MNT	69.78

Table 5: Protection Factors of compound of formula (III-3) in FG30TG fish oil

	Protection Factor (%)
0.5 mg/g of compound of formula (III-3)	15.42
2 mg/g of compound of formula (III-3)	25.89
0.5 mg/g of MNT	49.59
2 mg/g of MNT	77.06

Improvement of the oxidative stability of oil soluble compound of formula (III-4) when combined with AP is shown in **Table 6** whereas **Table 7** shows the same synergistic effect of compound of formula (III-3) with AP.

<u>**Table 6:**</u> Improvement of the effect of the compound of formula (III-4) in FG30TG fish oil using AP (SD = standard deviation)

	OSI (h)	**SD**
Blank (FG30TG)	4.63	0.0
2 mg/g of compound of formula (III-4)	6.30	0.4
2 mg/g of compound of formula (III-4) + 0.5 mg/g of AP	8.93	1.0
2 mg/g of MNT	8.03	0.9
2 mg/g of MNT + 0.5 mg/g of AP	15.25	1.5

<u>**Table 7:**</u> Improvement of the effect of compound of formula (III-3) in FG30TG fish oil using a synergistic compound (AP) (SD = standard deviation)

	OSI (h)	**SD**
Blank (FG30TG)	2.15	0.1
2 mg/g of compound of formula (III-3)	6.58	0.1
2 mg/g of compound of formula (III-3) + 0.5 mg/g of AP	7.03	1.5
2 mg/g of MNT	7.58	0.3
2 mg/g of MNT + 0.5 mg/g of AP	16.25	4.0

Improvements of the Protection Factors of these oil soluble compounds with AP in fish oil are shown in **Tables 8** and **9**.

<u>**Table 8:**</u> Improvement of the Protection Factors of compound of formula (III-4) with AP in FG30TG fish oil

	Protection Factor (%)
2 mg/g of compound of formula (III-4)	36.1
2 mg/g of compound of formula (III-4) + 0.5 mg/g of AP	92.8
2 mg/g of MNT	73.3
2 mg/g of MNT + 0.5 mg/g of AP	229.4

Table 9: Improvement of the Protection Factor of compound of formula (III-3) with AP in FG30TG fish oil

	Protection Factor (%)
2 mg/g of compound of formula (III-3)	145
2 mg/g of compound of formula (III-3) + 0.5mg/g of AP	130
2 mg/g of MNT	60
2 mg/g of MNT + 0.5mg/g of AP	194

Polymers generated at the end of the stabilization experiment of fish oil with compound of formula (III-4) and AP are shown in **Table 10.**

Table 10: Reduction of polymers in FG30TG oil with a compound (AP) synergistic to compound of formula (III-4) (SD = standard deviation)

	Polymers(%)	**SD**
Blank (FG30TG)	43.97	3.7
2 mg/g of compound of formula (III-4)	40.34	2.0
2 mg/g of compound of formula (III-4) + 0.5mg/g of AP	31.06	3.2
2 mg/g of MNT	33.87	1.1
2 mg/g of MNT + 0.5 mg/g of AP	12.72	2.6

Tables 11, 12 and **13** show the PV (peroxide value), *p*-AV (*p*-anisidine value) and CD (conjugated dienoic acid %) of the fish oil samples stabilized with compounds of formulae (III-3) and (III-4), respectively.

Table 11: Variation of PV (peroxide value) with compounds of formulae (III-3) and (III-4) in FG30TG

	Initial	**4 days**	**6 days**	**8 days**	**11 days**	**13 days**	**17 days**
Blank (FG30TG)	0.9	1.6	2.2	2.7	5.6	7.8	11.9
2 mg/g of MNT	0.9	1.1	1.2	1.4	1.7	1.5	2.1
2 mg/g of compound of formula (III-4)	0.9	2.9	7.3	8.8	11.2	15	19.2
2 mg/g of compound of formula (III-3)	0.9	1.6	1.8	3.1	3.7	8.7	11.5

<u>**Table 12:**</u> Variation of *p*-AV (*p*-anisidine value) with compounds of formulae (III-3) and (III-4) in FG30TG

	Initial	**4 days**	**6 days**	**8 days**	**11 days**	**13 days**	**17 days**
Blank (FG30TG)	9.9	9.8	9.9	10.5	10.9	11.2	11.9
2 mg/g of MNT	9.9	10.3	9.9	10.1	10	9.8	10
2 mg/g of compound of formula (III-4)	9.9	10.5	9.9	10.3	10.5	10.5	11
2 mg/g of compound of formula (III-3)	9.9	10.3	9.8	10	10.4	10.6	11

<u>**Table 13:**</u> Variation of CD (**c**onjugated **d**ienoic acid in %) with compounds of formulae (III-3) and (III-4) in FG30TG

	Initial	**4 days**	**6 days**	**8 days**	**11 days**	**13 days**	**15 days**
Blank(FG30TG)	0.7	0.7	0.6	0.7	0.7	0.8	0.7
2 mg/g of MNT	0.7	0.7	0.6	0.7	0.7	0.7	0.7
2 mg/g of compound of formula (III-4)	0.7	0.7	0.7	0.8	0.9	0.8	0.8
2 mg/g of compound of formula (III-3)	0.7	0.6	0.6	0.2	0.7	0.7	0.8

<u>**Results:**</u>

Compounds of formulae (III-3) and (III-4) showed very similar pattern of OSI in fish oil. The compound of formula (III-4) had clearly lower OSI values than those of MNT in algal oil and seems to have possible prooxidant effect at higher levels (2 mg/g). The antioxidant effect of compounds of formulae (III-3) and (III-4) can be improved by combination with ascorbyl palmitate (“AP”) (**Tables 6-7**). Protection Factors of the compounds of formulae (III-3) and (III-4), including MNT, in fish oil could be improved by the addition of AP (**Tables 8-9**) indicating the possibility of combining AP with compounds of formulae (III-3) and (III-4) to improve the oxidative stability of matrices containing high amounts of unsaturated fatty acids such as marine oil.

A combination of complex, polymeric compounds generated at the end of the oxidation cascade of unsaturated fatty acids indicate the levels of overall oxidation of the matrix. The generation of such polymers in fish oil containing these novel antioxidant compounds could be reduced considerably when AP was added as a synergistic compound (**Table 10**).

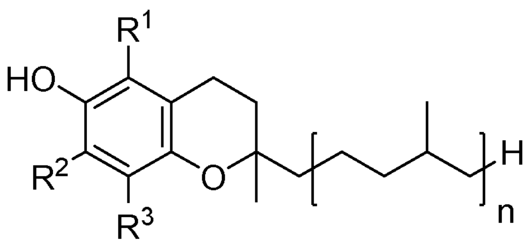
For the storage stability study oil soluble compounds were used in fish oil at 2 mg/g level only. Compared to the same level of MNT, all compounds showed much higher PVs than those of MNT (**Table 11**). There was no considerable variation in *p*-AV and CD (**Tables 12-13**) during the storage.

All compounds showed antioxidant properties in fish oil at different levels.

The oxidative stability of fish oil with compound of formula (III-4) is comparable to the antioxidative effect of MNT.

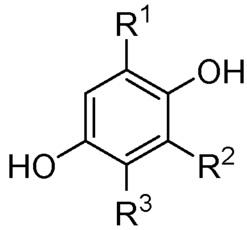
Claims

1. A process for the manufacture of a compound of formula (III),

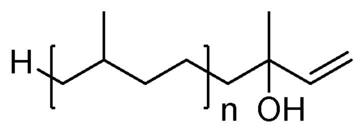


(III)

comprising the step of reacting a compound of formula (I) with a compound of formula (II) in the presence of an acid catalyst and in a mixture of two solvents,



(I)



(II)

wherein n is 1 or 2, and
R^1 and R^3 are independently from each other H or C_{1-5}-alkyl, and R^2 is either H or C_{1-5}-alkyl or C_{1-5}-alkyloxy, with the proviso that at least one of R^1, R^2 and R^3 is H, and wherein
the first of the two solvents is selected from ethylene carbonate, propylene carbonate, 1,2-butylene carbonate, gamma-butyrolactone and water,
and the second of the two solvents is selected from hexane, cyclohexane, heptane, *ortho*-xylene, *meta*-xylene, *para*-xylene, mesitylene, pseudocumene, methyl *tert*-butyl ether, and toluene.

2. The process according to claim 1, wherein R^1 and R^3 are independently from each other H or methyl or ethyl, and R^2 is either H or methyl or ethyl or methoxy or ethoxy, with the proviso that at least one of R^1, R^2 and R^3 is H.

3. The process according to claim 1, wherein R^1 and R^3 are independently from each other H or methyl, and R^2 is either H or methyl or methoxy, with the proviso that at least one of R^1, R^2 and R^3 is H.

4. The process according to any one or more of the preceding claims, wherein the first of the two solvents is ethylene carbonate or propylene carbonate, and the second of the two solvents is selected from either hexane, cyclohexane or heptane, preferably wherein the first of the two solvents is ethylene carbonate and the second of the two solvents is heptane.

5. The process according to any one or more of the preceding claims, wherein the volume ratio of the first solvent to the second solvent during the reaction is in the range of 1:4 to 4:1, preferably wherein the volume ratio of the first solvent to the second solvent is in the range of 1:3 to 3:1 most preferably wherein the volume ratio of the first solvent to the second solvent is in the range of 1:2 to 2:1.

6. The process according to any one or more of the preceding claims, wherein the total amount of the two solvents is in the range of 1 to 10 kg, preferably in the range of 2 to 7 kg, more preferably in the range of 2.5 to 6 kg, per kg of the compound of formula (I).

7. The process according to any one or more of the preceding claims, wherein the acid catalyst is selected from Brønsted acids, Lewis acids and any mixtures thereof.

8. The process according to claim 7, wherein the acid catalyst is a Brønsted acid, and whereby the Brønsted acid is selected from sulfuric acid, phosphoric acid, acidic ion-exchange resins, acidic clays, zeolites, hydrochloric acid, trifluoroacetic acid, trichloroacetic acid, acetic acid, formic acid, methanesulfonic acid, benzenesulfonic acid, *para*-toluenesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, bis(perfluoroalkylsulfonyl)-methanes $(R'SO_2)(R''SO_2)CH_2$ wherein R' and R" each signify independently from

each other a perfluoroalkyl group of the formula C_nF_{2n+1} where n is an integer from 1 to 10, tris(perfluorosulfonyl)methanes $(R'SO_2)(R''SO_2)(R'''SO_2)CH$, wherein R', R" and R''' each signify independently from each other a perfluoroalkyl group of the formula C_nF_{2n+1} where n is an integer from 1 to 10, and whereby at least two of R', R" and R''' are identical perfluoroalkyl groups, or R' signifies the pentafluorophenyl group ($-C_6F_5$) and R" and R''' each signify an identical perfluoroalkyl group of the above formula C_nF_{2n+1}, methanetrisulfonic acid, and bis(trifluormethylsulfonyl)imide.

9. The process according to claim 7, wherein the acid catalyst is a Lewis acid, and whereby the Lewis acid is selected from $Al(OTf)_3$, $Sc(OTf)_3$, $Sc(NTf_2)_3$, $ScCl_3$, $Yb(OTf)_3$, $YbCl_3$, $Cu(OTf)_2$, $FeCl_2$, $Fe(OTf)_2$, $ZnCl_2$, $Zn(OTf)_2$, $Zn(NTf_2)_3$, YCl_3, $Y(OTf)_3$, $InCl_3$, $InBr_3$, $In(OTf)_3$, $In(NTf_2)_3$, $La(OTf)_3$, $Ce(OTf)_3$, $Sm(OTf)_3$, $Gd(OTf)_3$ and $Bi(OTf)_3$ in the presence or absence of 2,2-bipyridine.

10. The process according to any one or more of the claims 1 to 6, wherein the acid catalyst is *para*-toluenesulfonic acid, sulfuric acid, methanesulfonic acid, $Al(OTf)_3$, $Sc(OTf)_3$, or $In(OTf)_3$, most preferably wherein the acid catalyst is *para*-toluenesulfonic acid or $Al(OTf)_3$.

11. The process according to any one or more of the preceding claims, wherein the amount of the acid catalyst is in the range of 0.001 to 5 mol equivalents, preferably in the range of 0.005 to 1 mol equivalents, more preferably in the range of 0.01 to 0.1 mol equivalents, relative to the amount of the compound of formula (II).

12. The process according to any one or more of the preceding claims, wherein the molar ratio of the compound of formula (I) to the compound of formula (II) is in the range of 6.0:1 to 1.1:1, preferably in the range of 4.0:1 to 1.2:1, even more preferably in the range of 3.0:1 to 1.3:1, most preferably in the range of 2.0:1 to 1.5:1.

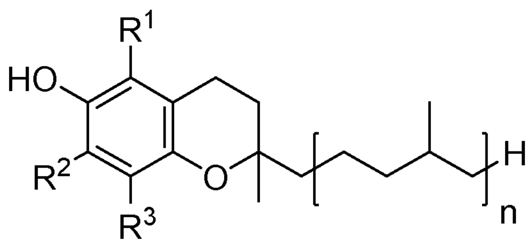
13. The process according to any one or more of the preceding claims, wherein the reaction is carried out at a temperature in the range of 70 to 160°C, preferably in the range of 80 to 130°C, most preferably in the range of 90-105°C.

14. The process according to any one or more of the preceding claims, wherein the reaction is carried out at a pressure in the range of 0.8 to 20 bar (absolute), preferably at a pressure in the range of 0.8 to 10 bar (absolute), most preferably at a pressure in the range of 0.8 to 5 bar (absolute).

15. The process according to any one or more of the preceding claims, wherein the acid catalyst is recyclable.

16. 2-(4,8-dimethylnonyl)-2-methyl-chroman-6-ol.

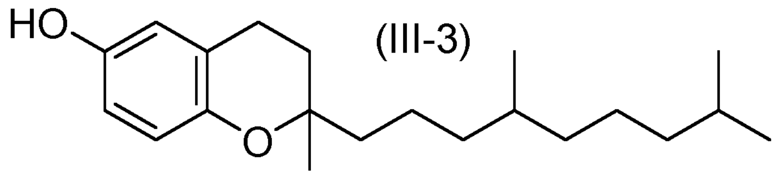
17. Use of the compounds of formula (III) as antioxidants,

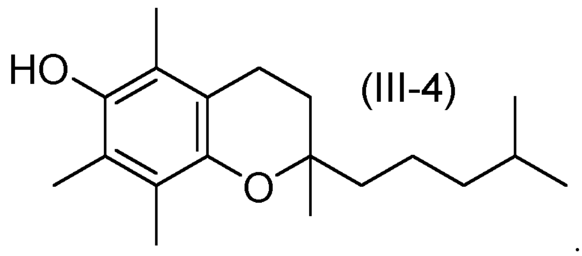


(III)

wherein n is 1 or 2, and
R^1 and R^3 are independently from each other H or C_{1-5}-alkyl, and
R^2 is either H or C_{1-5}-alkyl or C_{1-5}-alkyloxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H.

18. The use according to claim 17, wherein the compound of formula (III) is the compound of formula (III-3) and/or the compound of formula (III-4).





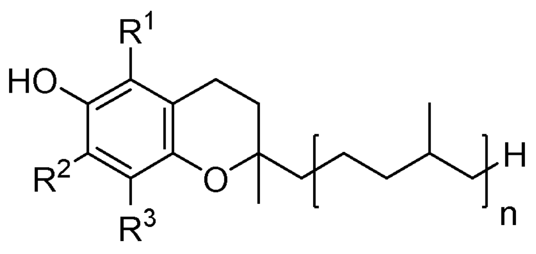
19. The use according to claim 17 and/or 18, wherein the compounds of formula (III) are used as antioxidants in feed or feed ingredients.

20. The use according to claim 19, wherein the feed is feed for aquatic animals, feed for terrestrial animals and feed for insects.

21. The use according to claim 19, wherein the feed ingredients are selected from fish meal, poultry meal, insect meal, and PUFA-containing oils.

22. The use according to claim 21, wherein the PUFA-containing oil is selected from marine oil, microbial oil, fungal oil, algal oil and PUFA-containing plant oil.

23. Feed for aquatic animals, feed for terrestrial animals and feed for insects containing at least one compound of formula (III),



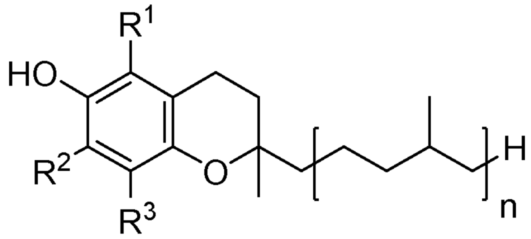
(III)

wherein n is 1 or 2, and

R^1 and R^3 are independently from each other H or C_{1-5}-alkyl, and

R^2 is either H or C_{1-5}-alkyl or C_{1-5}-alkyloxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H.

24. Feed ingredients containing at least one compound of formula (III),



(III)

wherein n is 1 or 2, and

R^1 and R^3 are independently from each other H or C_{1-5}-alkyl, and

R^2 is either H or C_{1-5}-alkyl or C_{1-5}-alkyloxy, preferably with the proviso that at least one of R^1, R^2 and R^3 is H.

Fig. 1

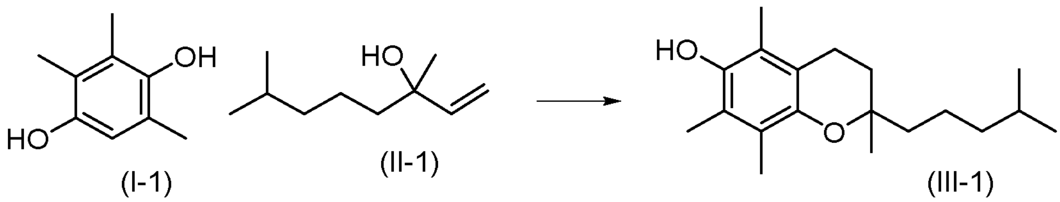


Fig. 2

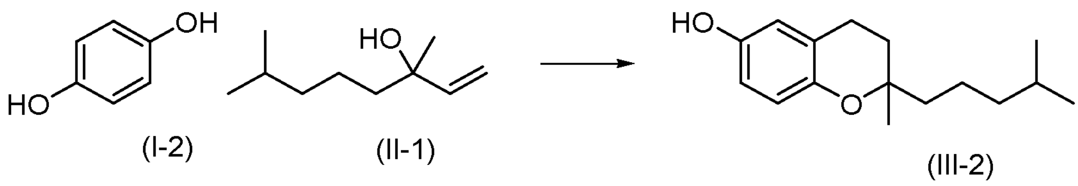
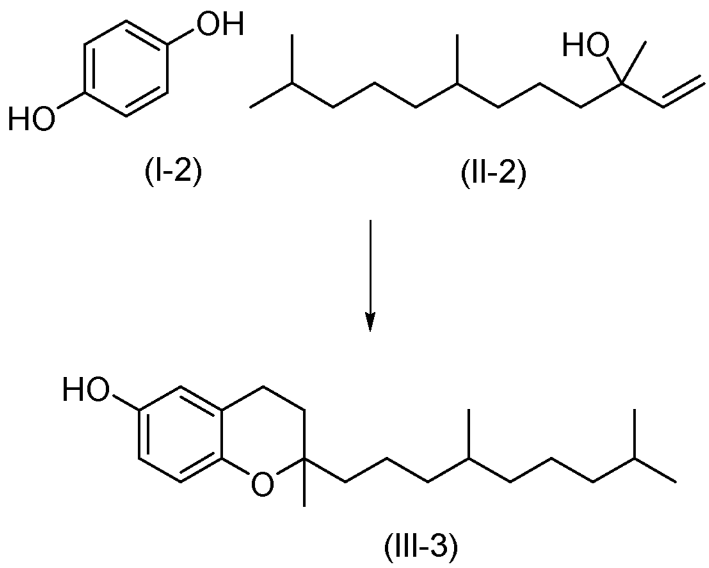


Fig. 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/058071

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/72 A23L13/10 A23L17/10
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 A23L

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TOSHIE FUJISHIMA ET AL: "Synthesis of Vitamin E Analogues: Possible Active Forms of Vitamin E", ARCHIV DER PHARMAZIE, vol. 329, no. 1, January 1996 (1996-01), pages 27-34, XP055026652, ISSN: 0365-6233, DOI: 10.1002/ardp.19963290106	17
Y	abstract page 27; figure 1 page 28; figure 2; compounds 4a-4d * chart 1 *; page 28 page 29; figure 3 page 30; table 1 * experimental part *; page 31 -----	1-16, 18-24

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2019	03/07/2019

Name and mailing address of the ISA/	Authorized officer
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	WO 2004/046127 A1 (DSM IP ASSETS BV [NL]; BONRATH WERNER [DE] ET AL.) 3 June 2004 (2004-06-03) abstract pages 2-3 page 4, line 30 - page 5, line 4 page 5, lines 14-24 example 1 claims 1-10 -----	1-15 16-24
X Y	JP S60 94976 A (SUMITOMO CHEMICAL CO) 28 May 1985 (1985-05-28) abstract pages 742-743 table 1 claims 1-3 -----	17-19,24 16,20-23
X Y	KENJI TERASHIMA ET AL: "Powerful antioxidative agents based on garcinoic acid from Garcinia kola", BIOORGANIC & MEDICINAL CHEMISTRY : A TETRAHEDRON PUBLICATION FOR THE RAPID DISSEMINATION OF FULL ORIGINAL RESEARCH PAPERS AND CRITICAL REVIEWS ON BIOMOLECULAR CHEMISTRY, MEDICINAL CHEMISTRY AND RELATED DISCIPLINES, ELSEVIER, NL, vol. 10, no. 5, May 2002 (2002-05), pages 1619-1625, XP002688697, ISSN: 0968-0896, DOI: 10.1016/S0968-0896(01)00428-X abstract * scheme 1 *; page 1620; compounds 4, 11a-11c page 1621; table 2 * experimental part *; page 1623 - page 1625 -----	17 16,18-24
X Y	EP 0 732 329 A1 (SHUDO KOICHI [JP]) 18 September 1996 (1996-09-18) abstract page 4, lines 9-14 examples 1-36 pages 14-15; table 1 pages 16-17; tables 2, 3 claims 1-8 -----	17,19,24 16,18, 20-23

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	CLÁUDIA AFONSO ET AL: "Tocopherols in Seafood and Aquaculture Products", CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION, vol. 56, no. 1, 11 October 2013 (2013-10-11), pages 128-140, XP055598887, USA ISSN: 1040-8398, DOI: 10.1080/10408398.2012.694920 abstract page 129; figure 1 pages 129-133 pages 134-136	18-24 1-17

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/058071

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