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Field of the invention

The present invention is in the field of aromatic molecules, their manufacturing method and use.

More particularly, the present invention provides a synthesis method of dairy-lactone and various precursors for their use for their organoleptic properties in the food industry, pharmaceutics, cosmetics and perfumeries.

Prior Art

Known from the prior art is a synthesis method of the dairy-lactone by fermentation.

The patent EP0578388 describes a fermentation method for preparing 10-hydroxy-C18-carboxylic acid derivatives and compositions comprising them and compositions comprising derivatives of gamma-dodecalactone (including dairy-lactone) for their uses for their organoleptic properties in particular to increase or correct perfumes or fragrances aromas, perfumed articles, food products, chewing gum, toothpaste, hair products, tobacco. Gamma-lactones are useful as food flavors (Eric Frerot and al, "Easy access to active aroma unsaturated (gamma)-lactones by addition of modified titanium homoenolate to aldehydes," Journal of agricultural and food chemistry, 2011).

Also known from the prior art is the dairy-lactone and its enantiomers (Andreas Habel and al, "Efficient and flexible synthesis of chiral (gamma)- and (delta)-lactones" (Organic and biomolecular chemistry, 2008; Mr. Mark Midland and al, "the synthesis of naturally occurring 4-alkyl and -4-alkenyl-(gamma)-lactones using asymmetryc reducing agent -3-pinanyl-9-borabicyclo(3.3.1)nonane", Tetrahedron letters, 1980).

Finally, also known from the prior art are synthesis methods of different intermediates that can be involved in the synthesis of lactones (P.Haverkamp Begemann et al, "the synthesis of lactones Part III: (delta)-enollactones and lactones with exocyclic double bonds ", Recueil des travaux chimiques des Pays-Bas (Reports of the chemical industry in the Netherlands), 1967; E.I. Heiba and al, "oxidation by metal salts. X. One step synthesis of (gamma)-lactones from olefins”, Journal of the American chemical society 1974; Stuart JG et al, "Cobalt-mediated alkylation of siloxy furans", Heterocycles: an international journal for reviews and communications in heterocyclic chemistry, Japan institute of heterocyclic chemistry, 1991).

Drawbacks of the prior art

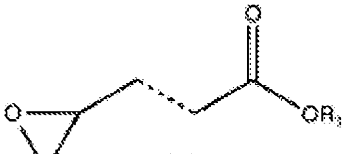
The method of patent EP0578388 provides by fermentation a racemic mixture of dairy-lactone. The dairy-lactone obtained by fermentation requires the successive use of several fermentation species, which is a particularly important obstacle to the industrialization of the method.

The fermentation results in the production of a racemic mixture of dairy-lactone. However, it is well known that two enantiomers of the same chemical formula can have radically different properties.

Solutions provided by the invention

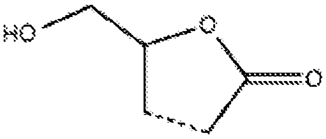
To remedy these drawbacks, the present invention provides in its most general sense a method for preparing a precursor of a single isomer of dairy-lactone comprising a preparation step for a glycidyl ester followed by an epoxide opening step.

The glycidyl ester has the formula (V) below, wherein R_1 is an alkyl group, in particular a CH_3 or C_2H_5 group and wherein the dotted line represents a single or double carbon-carbon bond (of Z or E configuration):



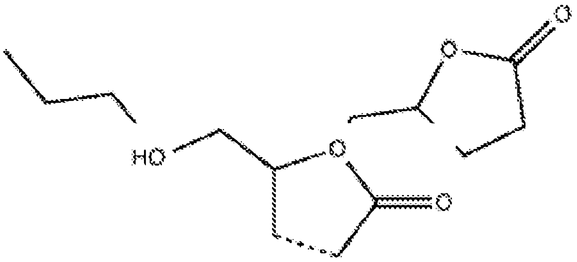
(V)

The glycidyl ester is prepared from a lactone of formula (III) below only of R or S conformation, wherein the dotted line represents a single or double carbon-carbon bond, so that said glycidyl ester and said precursor are in pure isomeric form of only R or S conformation, and the dairy-lactone is a pure isomer of only R or S corresponding form.



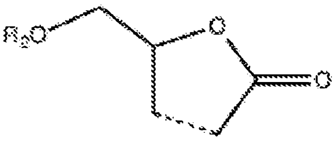
(III)

Unlike the method of the prior art, the method of the present invention allows to obtain pure enantiomers of each of the precursors of dairy-lactone and also a pure enantiomer of dairy-lactone. The method according to the invention preferably allows synthesizing the (Z)-dairy-lactone, of the formula $C_{12}H_{20}0_2$ and of developed formula (VIII) bellow.



The method according to the invention allows to obtain quickly and at minimum cost a pure solution of dairy- lactone. Preferably a pure solution of Z-dairy-lactone is obtained by the method according to the invention.

The synthesis step of a glycidyl ester consists in the opening of the lactone and the concerted elimination of an activated alcohol from a molecule of formula (IV) below, wherein R_2 is chosen from the tosyl (Ts) or mesyl (Ms) groups and wherein the dotted line represents a single or double carbon-carbon bond.



(IV)

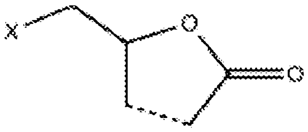
This molecule of formula (IV) is for example (S)-(5-oxotetrahydrofuran-2-yl)methyl-4-methylbenzenesulfonate in the case in which R_2 is a tosyl group, and in which the carbon-carbon bond represented by line dotted is a single bond; or (S)-(5-oxotetrahydrofuran-2-yl)-methyl methanesulfonate in the case in which R_2 is a mesyl group, and in which the carbon-carbon bond represented by the dotted line is a single bond.

The molecule of formula (IV) is obtained by activation of the alcohol by sulfonation of a molecule of formula (III) below wherein the dotted line represents a single or double carbon-carbon bond:

(III)

Sulfonation enables to activate the alcohol in order to replace it later. This sulfonation is carried out by tosylation, by mesylation.

Another alternative for the synthesis step of a glycidyl ester consist in the opening of the lactone and concerted elimination of a halide of a molecule of formula (IV-bis) below, wherein X is selected from Br, Cl or I, and wherein the dotted line is a single or double carbon-carbon bond.



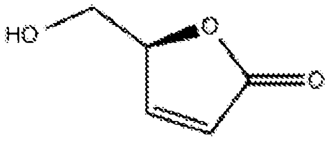
(IV-bis)

The molecule of formula (IV-bis) is obtained by the substitution by a halogen of the alcohol of a molecule of formula (III) wherein the dotted line represents a single or double carbon-carbon bond.

In one embodiment, the molecule of formula (IV) is obtained by activation of the alcohol by sulfonating a lactone.

Alternatively, said molecule of formula (III) in which the dotted line represents a single carbon-carbon bond is obtained by hydrogenating a α,β-unsaturated lactone.

The α,β-unsaturated lactone is preferably a lactone of formula (II) below:

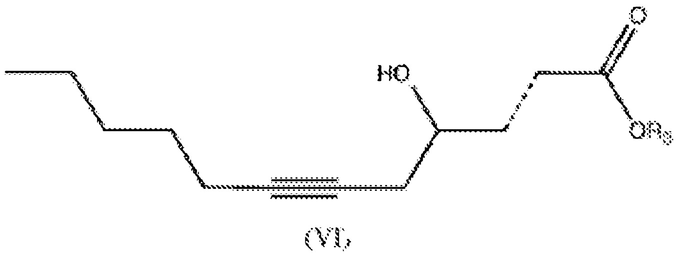


(Π)

This lactone is preferably the (S)-furanone (HFO) obtained by modifying the levoglucogenone from the transformation of the cellulose according to the method described in the patent application FR1453957 whose content is incorporated by reference.

Alternatively, the molecule of formula (III) in which the dotted line represents a single carbon-carbon bond is obtained by oxidation of the dihydrolevoglucosenone in the presence of a peracid, for example the peracetic acid or the MCPBA, followed by an acid or basic hydrolysis of the resulting product mixture, for example in the presence of an acid resin. This dihydrolevoglucosenone is obtained by hydrogenation of a levoglucosenone.

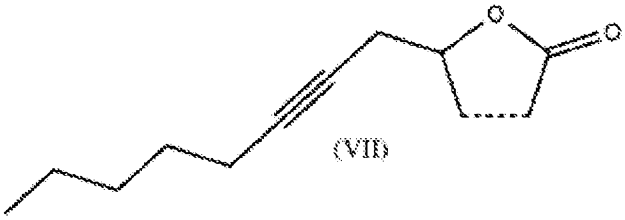
Advantageously, the method for preparing a precursor of at least one isomer of dairy-lactone further comprises a step of lactonization of a molecule of formula (VI) below, wherein R_3 is preferably an alkyl group, for example a CH_3 or C_2H_5 group, and wherein the dotted line represents a single or double carbon-carbon bond.



(VI)

This compound of formula (VI) is obtained by epoxide opening of a glycidyl ester of formula (V) described above.

Lactonization of the molecule of formula (VI) can be achieved in acidic or basic medium. Preferably, it is carried out by acid hydrolysis. This lactonization provides a molecule of formula (VII) in which the dotted line represents a single or double carbon-carbon bond.



(VII)

The molecule of formula (VII) in which the dotted line represents a single carbon-carbon bond is for example (*S*)-5-(oct-2yn-1-yl)-dihydrofuran-2(3*H*)-one. The molecule of formula (VII) in which the dotted line represents a double carbon-carbon bond is for example (*R*)-5-(oct-2-yn-1-yl)-furan-2(5H)-one.

The preparing method for a precursor of at least one isomer of dairy-lactone further comprises a step of syn-hydrogenation of a molecule of formula (VII).

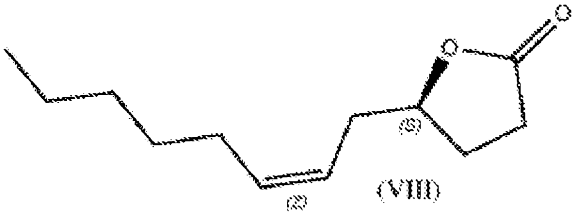
This syn-hydrogenation of the molecule of formula (VII) leads to the synthesis of the end product, the dairy-lactone having particularly advantageous organoleptic properties. It is understood that all the above steps lead to the synthesis of a single isomer of dairy-lactone.

According to one alternative, the synthesis of dairy-lactone from the molecule of the formula (VII) having a double bond in the ring involves a syn-hydrogenation allowing, in a single step, the reduction of the alkyne to alkene of Z configuration and the unsaturation of the lactone, α,β-unsaturated.

Alternatively, the form E enantiomer of dairy-lactone is obtained by hydrogenation.

According to one embodiment, the method of preparation of a single isomer of dairy-lactone comprises the previously listed steps.

The dairy-lactone obtained is a pure enantiomer of all possible conformations. The isomer of dairy-lactone obtained by the method is pure and of Z-R, Z-S, E-R or E-S form. Preferably, the dairy-lactone obtained is the Z-dairy-lactone. Even more preferably, the dairy-lactone obtained by the method is (Z,S)-dairy-lactone of formula (VIII) below:



(VIII)

This (Z,S)-dairy-lactone of formula (VIII) has particularly interesting organoleptic properties for use as a flavor and/or aroma in the food industry, pharmaceutics, cosmetics and perfumeries...

In one aspect, the invention relates to a glycidyl ester of formula (V) described above, wherein R_2 is an alkyl group to synthesize a pure isomer of precursor of dairy-lactone and/or a pure isomer of dairy-lactone.

According to yet another aspect, the invention relates to the use of a pure isomer of dairy-lactone as food flavoring. Preferably, the invention relates to the use a pure isomer of dairy-lactone obtained by the method of the present invention as a food flavoring. According to one embodiment, the invention relates to the use of a pure enantiomer of (Z, S)-dairy-lactone as a food flavoring.

In another aspect, the invention relates to the use of a pure isomer of dairy-lactone as odorant molecule to flavor a food product. According to one embodiment, the invention relates to the use of a pure enantiomer of (Z,S)-dairy-lactone as odorant molecule to flavor a food product.

In another aspect, the invention relates to the use of a pure isomer of dairy-lactone as odorant molecule to flavor a cosmetic product. According to one embodiment, the invention relates to the use of a pure enantiomer of (Z,S)-dairy-lactone as odorant molecule to flavor a cosmetic product.

Advantageously, the invention relates to a bakery product comprising a pure isomer of dairy-lactone to give a "buttered" note to said bakery product. In a particular embodiment, the bakery product has a pure enantiomer of (Z,S)-dairy-lactone to give a "buttered" note to said bakery product.

Advantageously, the bakery product contains 5 to 10 ppm of (Z,S)-dairy-lactone.

Advantageously, the invention relates to a product based on vegetable milk or animal milk substitute with a pure isomer of dairy-lactone to give a "milky" note to said product. In a particular embodiment, the product based on vegetable milk or animal milk substitute comprises a pure isomer of (Z,S)-dairy-lactone to give a "milky" note to said product.

Description

The invention will be better understood in light of an non-limiting example of embodiment.

Figure 1 shows a diagram of the various steps of the synthesis method of at least one precursor of an isomer of (Z,S)-dairy-lactone and an isomer of (Z,S)-dairy-lactone from the lactone (II).

Figure 2 shows a diagram of the enzymatic synthesis of precursors of the dairy-lactone, (S)-furanone (molecule II) and of 4-hydroxymethylbutyrolactone (molecule III) and is described in examples 1 and 2.

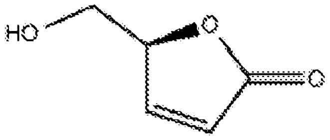
Figure 3 represents an alternative synthesis route of 4-hydroxymethylbutyrolactone (molecule III) by chemical synthesis and is described in example 2bis.

Figure 4 shows an alternative synthesis route of at least one precursor of an isomer of (Z,S)-dairy-lactone and an isomer of the (Z,S)-dairy-lactone.

Example 1 Synthesis of (S)-furanone (HFO) of formula (II) from a specific ketone, levoglucosenone

Any of the methods described in the patent application FR1453957 whose content is incorporated by reference may be used.

(S)-furanone or (S)-4-hydroxymethylbutenolide has the formula (II) below:



(II)

4-hydroxymethylbutenolide of formula (II) is prepared from levoglucosenone (LGO), which is obtained by use of biomass, according to the particular implementation of the "one-pot" method.

Oxidation

In a reactor, an aqueous solution of hydrogen peroxide H_2O_2 at 30% (2.57 mmol, 0.26 mL, 1.2 eq. relative to the LGO) is added in one portion to a LGO suspension (270 mg, 2.14 mmol) and CAL-B lipase (Novozym® 435, 75 mg, 315 U/nmol LGO) in ethyl acetate (3 mL) with stirring at room temperature in a planar agitation incubator. For this example, as for all the examples described below, 1 g of Novozym® 435 corresponds to 9000 units of CAL-B lipase (activity measured after residence of the enzyme in ethyl acetate). The reaction mixture is stirred at 40 C° for 4h then evaporated to dryness.

Acid hydrolysis

Concentrated hydrochloric acid (5 mmol, 0.4 mL) is added to a solution of this crude mixture in methanol (5 mL) at room temperature. The reaction mixture is heated under stirring for 8 to 16 hours, so as to convert the formate to the corresponding alcohol. The reaction mixture is evaporated to dryness with a silica gel. The crude product is purified by chromatography on silica gel (elution with 75-100% ethyl acetate in cyclohexane) to obtain pure (S)-4-hydroxymethylbutenolide of formula (II) (175 mg, 72%).

^{1}H NMR ($CDCl_3$): d 7.53 (dd, J = 1.5 and 5.7 Hz, 1 H), 6.2 (dd, J = 1.5 and 5.7 Hz, 1 H), 5.17 (m, 1 H), 4.0 (d, J = 3.6 and 12.0 Hz, 1 H), 3.80 (dd, J = 3.6 and 12.0 Hz, 1 H)
^{13}C NMR ($CDCl_3$): d 173.5 (s), 154.0 (d), 122.8 (d), 84.3 (d), 62.2 (t)

Alternatively, after of the LGO treatment step with the lipase, the latter is separated from the reaction medium before the dry evaporation step of the medium. The acid hydrolysis is then carried out as described above. Pure 4-hydroxymethylbutenolide is also obtained, with the same yield of 72%.

In other variants of the method, the acid hydrolysis step is carried out directly on the reaction medium obtained after the oxidation step, without having priorly performed an evaporation to dryness step. Whether or not the lipase is removed from the reaction medium by filtration, in such embodiments, the reaction yield is similar to that obtained for the implementation mode described above in detail, that is about 72%.

Example 2: Synthesis of 4-hydroxymethylbutyrolactone of formula (III) from (S)-furanone of formula (II)

(S)-4-hydroxymethylbutenolide or (S)-furanone of formula (II) obtained in Example 1 is subjected to catalytic hydrogenation, in the following manner.

Pd/C (10% p/p, 250 mg) is added to a 4-hydroxymethylbutenolide solution (1.4 g, 12.3 mmol) in ethyl acetate (15 mL) at room temperature. The stirring suspension is degassed 3 times under nitrogen/vacuum. A hydrogen atmosphere at room temperature then hydrogenates the suspension for 4 hours. The crude mixture is filtered through a celite buffer and the filtrate is concentrated to dryness with a silica gel. The crude product is purified by chromatography on silica gel (elution with a gradient from 75 to 100% ethyl acetate in cyclohexane) to give a pure (S)-4-hydroxymethylbutyrolactone of formula (III) (1.19 g, 82%).

^1H NMR ($CDCl_3$): d 4.64 (m, 1 H), 3.92 (dd, J = 2.7 and 12.6 Hz, 1 H), 3.66 (dd, J = 4,5 and 12.6 Hz, 1 H), 2,72-2,49 (m, 3 H), 2.35 to 2.09 (m, 2 H)

^{13}C NMR ($CDCl_3$): d 177.7 (s), 80.8 (d), 64.1 (t), 28,7 (t), 23.1 (t)

This synthetic route allows to obtain, with high yields the (S)-4-hydroxymethylbutyrolactone of formula (III) and S form, whose structure is confirmed by proton and carbon NMR, and polarimetry (optical rotation).

Example 2bis: Synthesis of (S)-4-hydroxymethylbutyrolactone of formula (III) from dihydrolevoglucosenone

This example is an alternative to Example 1 and 2 above and is presented in Figure 3.

(*S*) (+)-5-(Hydroxymethyl)dihydrofuran-2(3*H*)-one (III).

To a dihydrolevoglucosenone solution (5.0 g, 39 mmol) in water (30 mL) is added 32% peracetic acid (13 g, 55 mmol) over a period of 30 minutes while maintaining the mixture temperature between 25 and 35°C. The mixture is stirred at this temperature for 8 hours, then is neutralized by pouring it on the iron dust (1.0 g) and by stirring until no peroxides (iodine test paper, 5 minutes) and then for a additional 16 hour period. The mixture is then filtered through celite and concentrated under reduced pressure to give an oil-solid mixture. The latter is then suspended in ethyl acetate (50 mL) and filtered to remove the iron salts, which are then washed with ethyl acetate. The organic phases are then combined and concentrated under reduced pressure to provide a colorless oil (4.23 g, 80%, mixture of lactone III, its formate and its acetate). This oil is then taken up in ethanol (40 mL) and is then added IRP-69 (H+) (600 mg), and the mixture is refluxed for 1 hour before being cooled to ambient temperature. The ethanol is evaporated under reduced pressure and the residue is re-dissolved in dichloromethane (10 mL) and stirred for 16 hours. The mixture is then filtered and concentrated under reduced pressure to give (S)-4-hydroxymethylbutyrolactone as a colorless oil (75%).

Example 3: Synthesis of (S)-(5-oxotetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate of formula (IVa) from 4-hydroxymethylbutyrolactone of formula (III)

Tosyl chloride (1.55 g, 8.1 mmol) is added in one portion to a solution constituted by a mixture of 4-hydroxymethylbutyrolactone (0.9 g, 7.7 mmol) in DCM (5 mL) /pyridine (1.5 mL) at room temperature under nitrogen. The reaction mixture is stirred at room temperature for 4 hours. DCM (20 mL) is added and the reaction mixture is rinsed with a solution of HCl 3M, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to obtain a dry product. This crude product is then triturated with diethyl ether (15 mL). The generated white precipitate is recovered by filtration and dried to obtain a pure product of (S)-(5-oxotetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate formula (IVa) (1.3 g, 62%) which is then used as is, without further purification for the following synthesis.

^{1}H NMR (500 MHz): 7.8 ppm (2H, d); 7.4 ppm (2H, d); 4.7 ppm (1H, m); 4.2 ppm (2H, m); 2.6 ppm (2H, m); 2.5 ppm (3H, s); 2.4 ppm (1H, m); 2.1 ppm (1H, m)

Example 4: Synthesis of (S)-5-(iodomethyl)dihydrofuran-2(3H)-one (IV-bis-a)

Triphenylphosphine (524 mg, 2 mmol) is added to a 4-hydroxymethylbutyrolactone solution (116 mg, 1 mmol), iodine (508 mg, 2 mmol) and imidazole (136 mg, 2 mmol) in acetonitrile (10 mL) at 0°C. The mixture is then refluxed overnight before being cooled to room temperature and then extracted with ether (3 x 20 mL). The organic phases are then combined, washed with water (20 mL), brine (20 mL) then dried over anhydrous magnesium sulfate. After filtration and concentration under reduced pressure, the crude product is purified by flash chromatography (3:1 hexane:ethyl acetate) on silica gel to give, after combination and evaporation of the pure fractions, the product of formula (IV-bis-a) as a colorless oil (160 mg, 71%).

Example 5: Synthesis of Glycidyl ester of formula (Va) from the (S)-(5-oxotetrahydrofuran-2-yl) methyl 4-methylbenzenesulfonate of formula (IVa)

Sodium methoxide (0.7 g, 13 mmol) is added in one portion to a mixture of (S)-(5-oxotetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate of formula (IVa) tosylated (3 g, 11 mmol) in methanol (20 mL) at 0°C under nitrogen. The reaction mixture is stirred at room temperature for one hour. Ethyl acetate (100 mL) is added and the reaction mixture is quenched with a saturated aqueous solution of ammonium chloride (50 mL). The phases are separated and the aqueous phase is again extracted with ethyl acetate. The combined organic phases are washed with brine then dried over anhydrous magnesium sulfate, filtered and concentrated by drying to obtain an glycidyl ester epoxide (0.9 g, 63%) as an oil. This crude product is used as is to synthesize the following desired product.

^{1}H NMR (500 MHz): 3.7 ppm (3H, s); 3.0 ppm (1H, m); 2.78 ppm (1H, t) ppm 2.52 (1H, dd); 2.48 ppm (2H, t) 2.0 ppm (H, m) 1.8 ppm (1H, m)

Example 6: Synthesis of Glycidyl ester of formula (Va) from the (S)-5-(iodomethyl)dihydrofuran-2(3H)-one (IV-bis-a)

Sodium methoxide (0.7 g, 13 mmol) is added in one portion to a mixture of (S)-5-(iodomethyl)dihydrofuran-2(3H)-one (IV-bis-a) (2.5 g, 11 mmol) in methanol (20 mL) at 0°C under nitrogen. The reaction mixture is stirred at room temperature for one hour. Ethyl acetate (100 mL) is added and the reaction mixture is quenched with a saturated aqueous solution of ammonium chloride (50 mL). The phases are separated and the aqueous phase is again extracted with ethyl acetate. The combined organic phases are washed with brine then dried over anhydrous magnesium sulfate, filtered and concentrated by drying to obtain an epoxide glycidyl

ester (0.9 g, 63%) as an oil. This crude product is used as is to synthesize the following desired product.
^{1}H NMR (500 MHz): 3.7 ppm (3H, s); 3.0 ppm (1H, m); 2.78 ppm (1H, t) 2.52 ppm (1H, dd); 2.48 ppm (2H, t) 2.0 ppm (1H, m) 1.8 ppm (1H, m)

Example 7: Synthesis of methyl (S)-4-hydroxyundec-5-ynoate of formula (Via) from glycidyl ester of formula (Va)

N-BuLi (2.5 mol/L in hexane, 3 mL, 8.3 mmol) is added to a mixture of hept-1-yne (750 mg, 7.8 mmol) in dry THF (10 mL) at -78°C under nitrogen. The reaction mixture is mixed at the same temperature for 20 min. BF_3Et_2O (1 mL, 8.3 mmol) is then added at -78°C. The reaction is continued at the same temperature for 20 min before incorporating the previously obtained pure glycidyl ester epoxide (1 g, 7.7 mmol). The reaction is continued for 2 h at -78°C. The reaction mixture, back to -10°C, is then quenched with a saturated aqueous solution of ammonium chloride (10 mL) and extracted with ethyl acetate (3x30 mL).

The combined organic phases are washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated by drying. The crude product (absorbed on celite) is purified by flash chromatography (5 to 30% of EtOAc with cyclohexane as eluent) on silica gel to give, after combination and evaporation of the pure fractions, the PRODUCT 6 (700 mg, 40 %) as a colorless oil.

Example 8: Synthesis of (S)-5-(oct-2-yn-1-yl)dihydrofuran-2(3H)-one of formula (VIIa) from methyl (S)-4-hydroxyundec-5-ynoate of formula (VIa)

A mixture of methyl (S)-4-hydroxyundec-5-ynoate of formula (VIa) (600 mg, 2.6 mmol) in 5 mL of an aqueous solution of 80% acetic acid is heated with stirring at 50°C for 18 hours. Ethyl acetate (20 mL) is added and the reaction mixture is rinsed with sodium bicarbonate-saturated aqueous solution, brine, then dried over anhydrous magnesium sulfate, filtered and then concentrated by drying. The crude product (absorbed on celite) is purified by flash chromatography (5 to 30% of EtOAc with cyclohexane as eluent) on silica gel to give, after combination and evaporation of the pure fractions, a lactone called (S)-5-(oct-2-yn-1-yl)dihydrofuran-2(3H)-one of formula (VIIa) (275 mg, 53%) as a colorless oil.

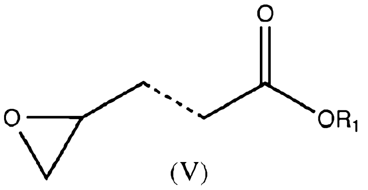
Example 9: Synthesis of (Z,S)-dairy-lactone from (S)-5-(oct-2-yn-1-yl)dihydrofuran-2(3H)-one of formula (VIIa)

A mixture of (S)-5-(oct-2-yn-1-yl)dihydrofuran-2(3H)-one of formula (VIIa) (270 mg, 1.39 mmol) in 10 mL of ethyl acetate is hydrogenated in a stream of dihydrogen stirred with Lindlar catalyst (50 mg) at room temperature for 6 hours. The reaction mixture is filtered through a celite filter and concentrated by drying to obtain the pure (Z)-dairy-lactone (270 mg, 90%) as a colorless oil. The obtained dairy-lactone is of the Z-S form.

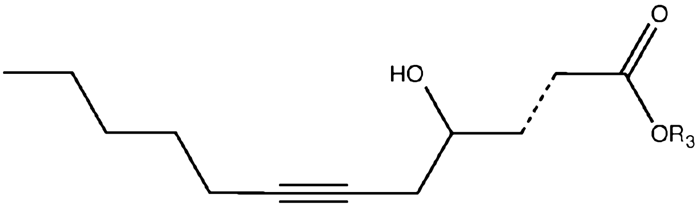
^{1}H NMR (500 MHz): 5.6 ppm (1H, m); 5.35 ppm (1H, m); 2.55 ppm (3H, m); 2.4 ppm (1H, m); 2.3 ppm (1H, m); 2.05 ppm (2H, m); 1.9 ppm (1H, m); 1.2-1.4 ppm (7H, m), 0.9 ppm (3H, t)

Patentkrav

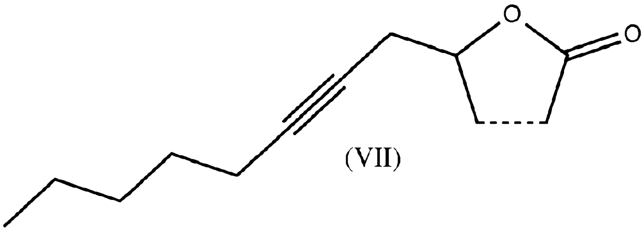
1. Fremgangsmåde til fremstilling af en prækursor af en enkelt isomer af dairy-lacton, med formelen (VI) eller (VII), hvor R_1 og R_3 er alkylgrupper, og hvor de punkterede linjer står for en enkelt eller dobbelt carbon-carbon-forbindelse, omfattende et trin med fremstilling af en glycidyl-ester med formelen (V) i ren isomerisk form kun i R- eller S-konformation, efterfulgt af et epoxid-åbningstrin, hvor prækurserne repræsenteres med de følgende formler:



(V)

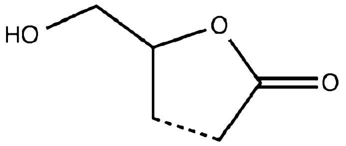


(VI)



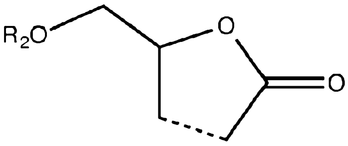
(VII)

2. Fremgangsmåde ifølge krav 1, hvor glycidyl-esteren fremstilles ud fra en lacton med formelen (III) kun i R- eller S-konformation, hvor den punkterede linje står for en enkelt eller dobbelt carbon-carbon-forbindelse, således at glycidyl-esteren og prækursoren er i ren isomerisk form kun i R- eller S-konformation, og at dairy-lactonen er en tilsvarende ren isomerisk R- eller S-form.



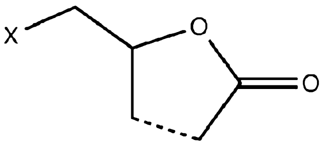
(III)

3. Fremgangsmåde ifølge mindst ét af de foregående krav, **kendetegnet ved, at** trinnet med syntese af en glycidyl-ester består i åbningen af lactonen og koncerteret eliminering af en aktiveret alkohol af et molekyle med formelen (IV), hvor R_2 er udvalgt blandt tosyl- eller mesyl-grupperne, og hvor den punkterede linje står for en enkelt eller dobbelt carbon-carbon-forbindelse.



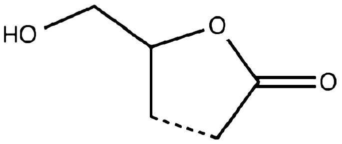
(IV)

4. Fremgangsmåde ifølge mindst ét af kravene 1 eller 2, **kendetegnet ved, at** trinnet med syntese af en glycidyl-ester består i åbningen af lactonen og koncerteret eliminering af en halogenid af et molekyle med formelen (IV-Bis), hvor X er udvalgt blandt Br, Cl eller I og hvor den punkterede linje står for en enkelt eller dobbelt carbon-carbon-forbindelse, hvor molekylet med formelen (IV-Bis) opnås med substitutionen med en halogen af alkoholen af en lacton med formelen (III).



(IV-Bis)

5. Fremgangsmåde ifølge et af kravene 3 eller 4, **kendetegnet ved, at** molekylet med formelen (IV) opnås med aktivering af alkoholen af et molekyle med formelen (III), hvor den punkterede linje står for en enkelt eller dobbelt carbon-carbon-forbindelse.

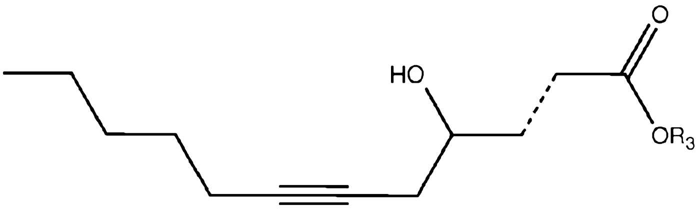


(III)

6. Fremgangsmåde ifølge krav 5, **kendetegnet ved, at** molekylet med formelen (III), hvor den punkterede linje står for en enkelt carbon-carbon-forbindelse, opnås med hydrogenering af en α,β-mættet lacton.

7. Fremgangsmåde ifølge krav 5, **kendetegnet ved, at** molekylet med formelen (III) opnås med oxidering af en dihydrolevoglucosenon i tilstedeværelse af en peracid, efterfulgt af en hydrolyse, hvor dihydrolevoglucosenonen opnås med hydrogenering af en levoglucosenon.

8. Fremgangsmåde til fremstilling af en prækursor med formelen (VII) af en enkelt isomer af dairy-lacton ifølge mindst ét af de foregående krav, **kendetegnet ved, at** den desuden omfatter et trin med lactonisering af et molekyle med formelen (VI), hvor R_3 er en alkyl-gruppe, og hvor den punkterede linje står for en enkelt eller dobbelt carbon-carbon-forbindelse til at opnå et molekyle med formelen (VII).



(VI)

9. Fremgangsmåde til fremstilling af en enkelt isomer af dairy-lacton, der omfatter de følgende trin:

- fremstilling af en glycidyl-ester med formelen (V) i ren isomerisk form kun i R- eller S-konformation, efterfulgt af et epoxid-åbningstrin, der fører til forbindelsen (VI)
- lactonisering af et molekyle med formelen (VI), hvor R_3 er en alkyl-gruppe, og hvor den punkterede linje står for en enkelt eller dobbelt carbon-carbon-forbindelse til at opnå et molekyle med formelen (VII)
- syn-hydrogenering af molekylet med formelen (VII)

10. Fremgangsmåde til fremstilling af en enkelt isomer af dairy-lacton ifølge krav 9, **kendetegnet ved, at** den opnåede isomer af dairy-lacton er ren og i Z-R-, Z-S-, E-R- eller E-S-form.

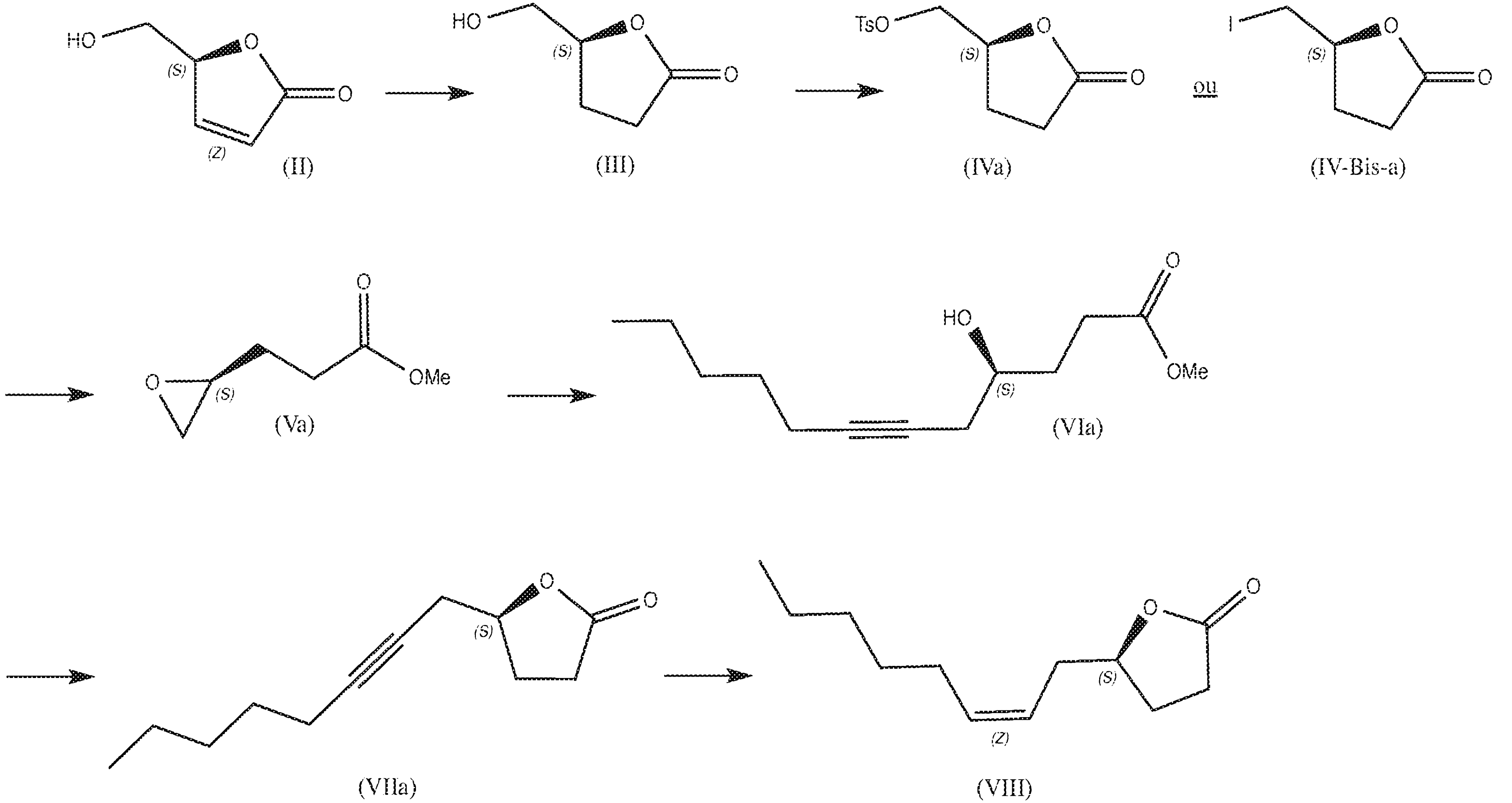

HO
(S)
(Z)
(II)
HO
(S)
(III)
TsO
(S)
(IVa)
ou
I
(S)
(IV-Bis-a)
OMe
(S)
(Va)
HO
(S)
OMe
(VIa)
(S)
(VIIa)
(S)
(Z)
(VIII)

Fig. 1

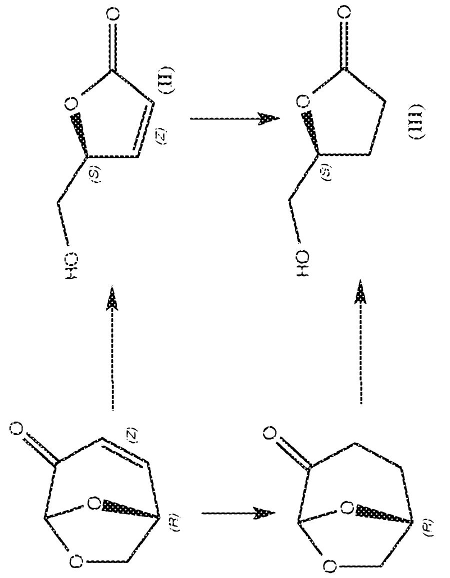

(R)
(Z)
HO
(S)
(Z)
(II)
(III)

Fig. 2

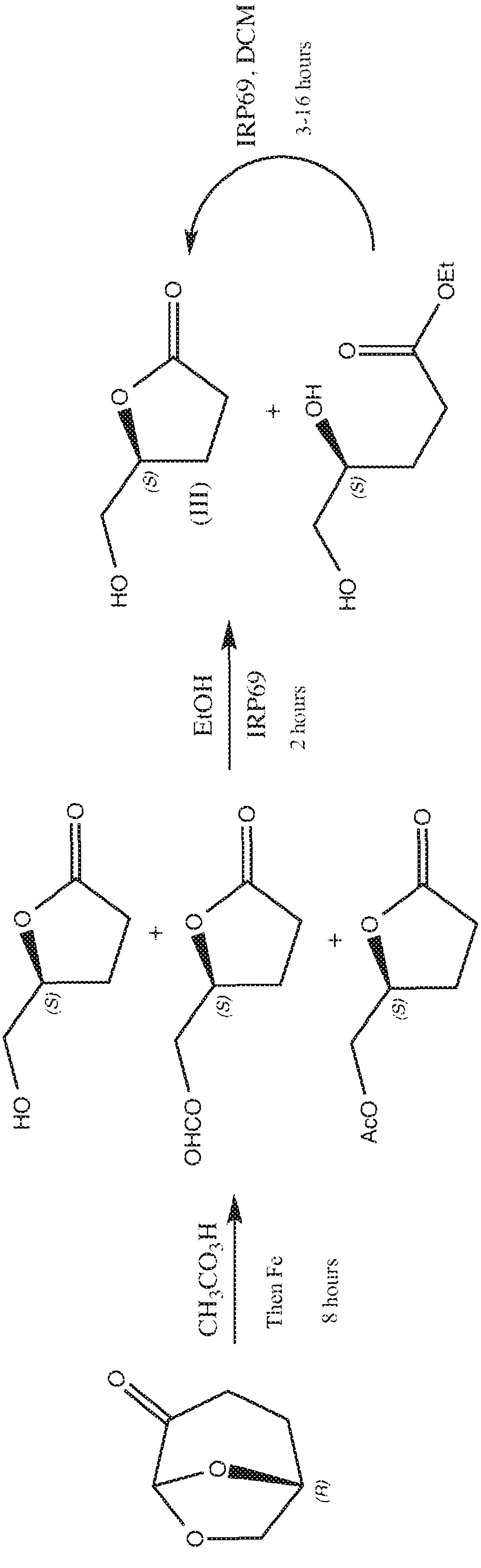
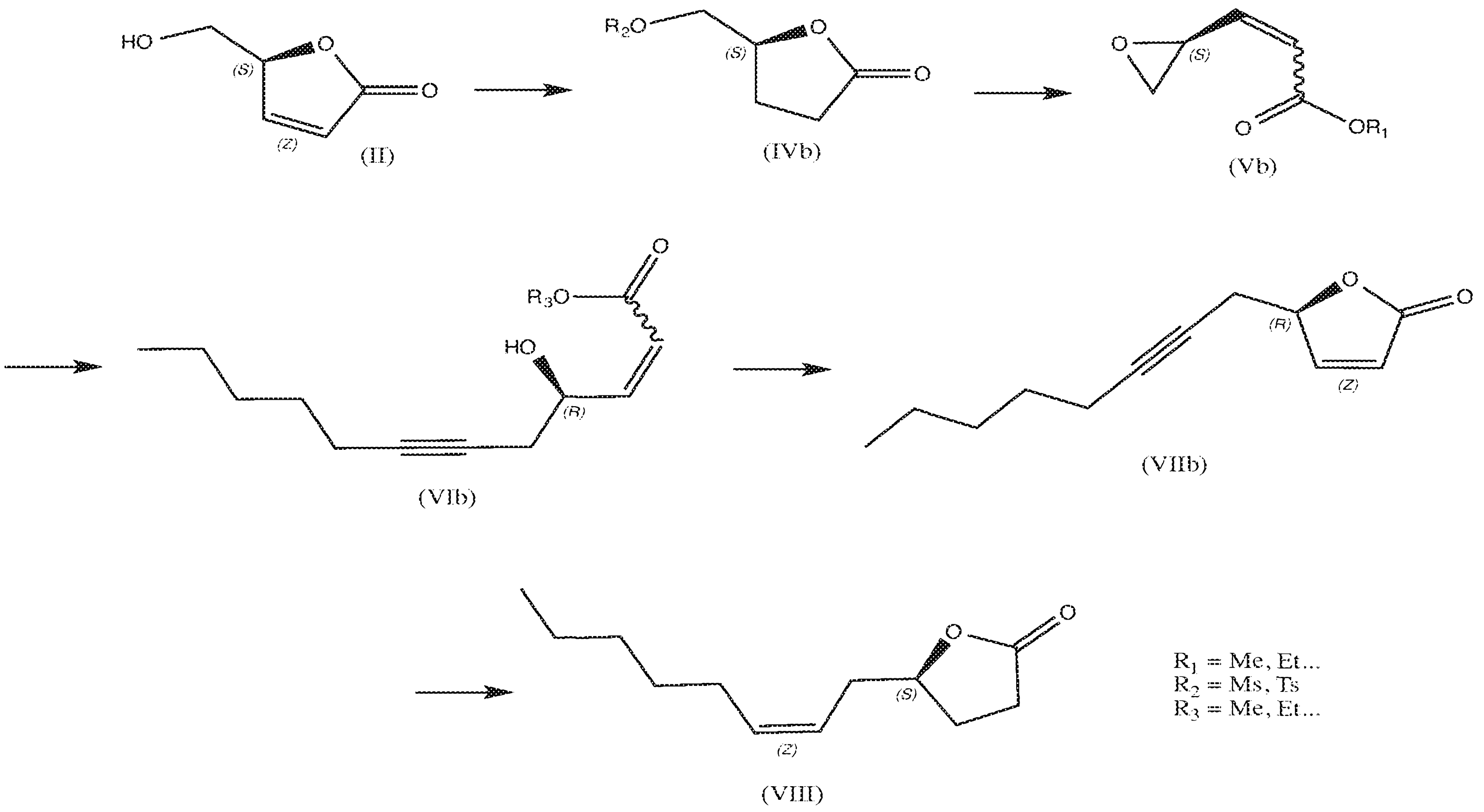

(R)
CH$_3$CO$_3$H
Then Fe
8 hours
HO
OHCO
AcO
(S)
EtOH
IRP69
2 hours
(III)
OH
OEt
IRP69, DCM
3-16 hours

Fig. 3



R_1 = Me, Et...
R_2 = Ms, Ts
R_3 = Me, Et...

Fig. 4