(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2022 (29.12.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/268786 A1

(51) International Patent Classification:
C07C 67/32 (2006.01) *C07C 31/20* (2006.01)
C07C 29/147 (2006.01) *C07C 69/738* (2006.01)

(21) International Application Number:
PCT/EP2022/066838

(22) International Filing Date:
21 June 2022 (21.06.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
21181248.2 23 June 2021 (23.06.2021) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

WO 2022/268786 A1

(54) Title: PRODUCTION PROCESS FOR 1,2-ALKANEDIOLS AND COMPOSITIONS CONTAINING 1,2-ALKANEDIOLS

(57) Abstract: The current invention relates to a process for the production of 1,2-alkanediols comprising the steps of: providing a dialkyl oxalate (component A); providing an ester or an aldehyde (component B), which is characterised by having at least one hydrogen atom bound to the second (alpha-)carbon atom; reaction of the dialkyl oxalate (component A) with an ester or aldehyde (component B) in the presence of a base (component C), thereby forming at least one new carbon-carbon bond and obtaining an intermediate; conversion of the obtained intermediate to an alpha-keto carboxylic acid, an alpha-keto ester or a mixture thereof; optionally, esterification of the obtained alpha-keto carboxylic acid; reduction of the alpha-keto carboxylic acid or its ester to the corresponding 1,2-alkanediol; and optionally, purification of the obtained 1,2-alkanediol and/or any of the intermediates formed during the prior steps.

PRODUCTION PROCESS FOR 1,2-ALKANEDIOLS AND COMPOSITIONS CONTAINING 1,2-ALKANEDIOLS

The invention relates to a process for the preparation of 1,2-alkanediols with carbon chains between 4 and 30 atoms and intermediates thereof. The process provides alpha-keto carboxylic acids and/or esters thereof in a first step and converts them into 1,2-alkanediols in a second step.

BACKGROUND OF THE INVENTION

1,2-Alkanediols are commonly used as solvents, humectants, conditioners, rheology modifiers and antimicrobial components. They are applied as additives in compositions utilized in various industries, including personal care, cleaning, and medical applications. The most commonly used 1,2-alkanediols contain a straight chain of 3 to 12 carbon atoms. Well-known examples include 1,2-propanediol (propylene glycol), 1,2-butanediol, 1,2-pentanediol (pentylene glycol), 1,2-hexanediol, 1,2-heptanediol, 1,2-octanediol (caprylyl glycol), 1,2-decanediol (decylene glycol) and 1,2-dodecanediol (lauryl glycol). Longer chain 1,2-alkanediols comprise, for example, 1,2-tetradecanediol (myristyl glycol), 1,2-octacosanediol (octacosanyl glycol) and mixtures such as C14-C18 glycol, C18-C30 glycol and C20-C30 glycol.

The most common synthetic route for producing such 1,2-alkanediols involves the oxidation of 1-alkenes with hydrogen peroxide as a reagent in combination with a carboxylic acid such as formic acid or acetic acid (see for example **D1**: US7385092 B2).

The resulting 1,2-epoxyalkanes are reacted with water to give the 1,2-alkanediols, together with the corresponding formate or acetate esters. The obtained mixture of products is further contacted with a suitable base, such as aqueous sodium hydroxide, to convert the alkanediol esters to the free 1,2-alkanediol. Each step of this most common production process for 1,2-alkanediols has several drawbacks:

The 1-alkenes used as feedstocks for 1,2-alkanediols are mostly of petrochemical origin. They are mainly produced by ZIEGLER-oligomerization of ethylene, which is obtained by steam cracking of hydrocarbons. During cracking, large hydrocarbons are heated with steam to 750-950 °C, converting them to short-chain hydrocarbons and introducing unsaturation. Ethylene is separated from the resulting complex mixture of products by repeated compression and distillation. The whole process of

steam reforming requires large amounts of energy, which is costly and leads to the emission of significant amounts of carbon dioxide. Furthermore, steam reforming commonly uses fossil carbon sources as feedstock, such as coal, crude oil, or natural gas. These materials are classified as non-renewable and therefore considered unsustainable, which can be seen as a disadvantage. A common side reaction during the oligomerization of ethylene to alkenes is the formation of branched alkenes. Such vinylidenes are undesired impurities. Their oxidation leads to branched alkanediols, which are particularly difficult to separate from straight-chain 1,2-alkanediols. Finally, the 1-alkenes used as precursors are volatile and flammable components that are hazardous to the environment. Their application contradicts the green chemistry principle of preferably using safe and environmentally friendly chemicals.

The subsequent oxidation of 1-alkenes to 1,2-alkanediols requires stoichiometric amounts of hydrogen peroxide and a carboxylic acid, which together form a peroxyacid in situ. The use of concentrated hydrogen peroxide in combination with carboxylic acid leads to potentially hazardous reaction mixtures. The oxidation reaction itself is exothermic and therefore needs to be controlled by active cooling. This consumes additional energy, which causes costs and may lead to emission of greenhouse gases. Finally, the harsh conditions during the oxidation reaction may result in over-oxidation of the 1,2-alkanediols. Trace-amounts of potentially formed oxo-components like ketones, aldehydes or carboxylic acid can cause undesired effects such as skin or eye irritation or a strong and unpleasant odour. The product isolation by means of aqueous workup creates significant amounts of waste streams. Their disposal further increases the production costs and enlarges the environmental footprint of the process.

Considering the ongoing climate change and the resulting global action plans for achieving a sustainable and circular economy, low-temperature processes starting from natural and/or renewable ("sustainable") raw materials are preferred over high temperature processes or those using petrochemical feedstocks. Sustainable processes based on "green chemistry" can be expected to have a positive impact on society and a lower negative impact on the environment. The term "green chemistry" also refers to lower energy consumption and more selective synthesis routes, making such processes more commercially attractive compared to conventional production processes.

Natural and renewable materials are derived from a bio-sourced and/or non-petroleum-derived feedstock, which is produced by methods including, but not limited to, agricultural activities, fermentation of biomass, or the fixation of carbon dioxide from the air by means of technical measures such as the Fischer-Tropsch process. Such "renewable," "natural," or "bio" feedstocks therefore contain only modern carbon recently assimilated by a living organism or fixated from the surrounding atmosphere by a green chemical process. They stay in contrast to petrochemical or other fossil feedstock containing "old" carbon.

Therefore, the term "sustainable" refers to materials that come from such renewable sources and are not derived from petrochemical or other fossil sources of carbon. The traditional method for testing the concentration of modern carbon in a product is the determination of the content of carbon-14, a radioactive isotope of carbon that is not present in fossil carbon. Alternatives to radiocarbon analyses are quantification of carbon-14 by accelerated mass spectrometry (AMS), as well as detailed analyses of stable isotopes or stable nuclides using mass spectroscopy, thereby evaluating the ratios of, for example, carbon-12/carbon-13 and/or hydrogen-1/hydrogen-2.

One possible route for the production of biobased 1,2-alkanediols is the replacement of fossil carbon-based 1-alkenes by those obtained from renewable feedstocks (**D2**: US10882803 B2). One commonly known route for obtaining bio-based 1-alkenes is the dehydration of biobased primary alcohols (**D3**: US8912373 B2). The resulting bio-based 1-alkenes can be used as substitutes for petrochemical 1-alkenes. However, the dehydration of primary alcohols has several disadvantages: First, it requires heating to temperatures beyond 200 °C, which is quite energy intensive. Secondly, bio-based fatty alcohols such as 1-hexanol, 1-octanol, 1-decanol or 1-dodecanol are typically obtained from palm kernel oil or coconut oil. These vegetable oils are in high demand, and their production often leads to deforestation and destruction of ecosystems such as tropical rainforest. Finally, the dehydration of primary fatty alcohols is not completely selective for the primary 1-alkene. Instead, mixtures of different isomeric alkenes (1-alkene, 2-alkene, 3-alkene, ...) are formed. The reason for this is the rearrangement and migration of the double bond along the carbon chain during the dehydration process of the primary alcohols. Such isomeric alkenes lead to undesired impurities in the further course of the synthesis (2,3-alkanediol, 3,4-alkanediol, ...). Such impurities reduce the yield and make the purification of the 1,2-alkanediol more difficult. They can also reduce its antimicrobial performance. In conclusion, even if the 1-alkenes are produced from renewable raw

materials, the aforementioned disadvantages of the commonly used production process for 1,2-alkanediols remain.

Considering the high energy consumption and significant amounts of waste generated by the commonly used synthesis route, more efficient and sustainable alternative processes for the production of 1,2-alkanediols are highly desirable.

BRIEF SUMMARY OF THE INVENTION

The present invention and embodiments thereof serve to provide a solution to one or more of above-mentioned disadvantages.

In a first aspect, the invention relates to a process according to claim 1. Disclosed herein is a novel process for obtaining 1,2-alkanediols having carbon chains of about 4 to about 30 atoms. The process involves the reaction of oxalic acid esters (component A) with aldehydes and/or esters of carboxylic acids (component B) to alpha-keto carboxylic acids and/or esters thereof. The reaction takes place in the presence of a base (component C). Subsequent reduction, preferably by catalytic hydrogenation, leads to the formation of 1,2-alkanediols. This process is shown in a simplified form in Fig. 1.

The following problems are solved or at least improved:

- The disclosed novel process is safer than the state of the art because it does not use 1-alkenes as intermediates, which are hazardous chemicals that require high temperatures during manufacture.
- The disclosed process also avoids the use of concentrated solutions of hydrogen peroxide or peroxyacid, the handling of which can pose a risk of explosion or other exothermic runaway reactions that are difficult or energy-intensive to control.
- Unlike the usual oxidation route, the final step of the disclosed novel process involves a chemical reduction, which reduces the concentration of unwanted oxo-impurities that can impact the quality and safety of the 1,2-alkanediols. The favourable impurity profile of the 1,2-alkanediols obtained from this process enables their application in areas where high purity and low odour are crucial, for example in cosmetics and personal care products.

- The feedstock used for the disclosed novel production process is preferably bio-based and renewable, which enables sustainable production and avoids non-renewable petrochemicals.
- The feedstock for the disclosed process is preferably derived from resources other than palm and coconut oil, thereby addressing the need for sustainable alternatives.

Further embodiments disclosed herein are:

- A **method of providing antimicrobial activity** to a composition by incorporating an antimicrobial system into the composition that contains a 1,2-alkanediol obtained by the disclosed process.
- **1,2-Alkanediols** obtainable by the process according to the first aspect of the invention.
- The **use of 1,2-alkanediols** obtained by the disclosed process **as antimicrobial ingredients** in compositions.
- **Products containing 1,2-alkanediols** obtained by the disclosed process, characterised by passing a microbial challenge test according to the norm ISO 11930.
- **Antimicrobial systems**, containing one or more 1,2-alkanediols obtained by the disclosed process.
- A **method of creating self-preserving compositions** by incorporating 1,2-alkanediols obtained by the disclosed process.

DESCRIPTION OF FIGURES

The following description of the figures of specific embodiments of the invention is merely exemplary in nature and is not intended to limit the present teachings, their application or uses. Throughout the drawings, corresponding reference numerals indicate like or corresponding parts and features.

Figure 1 shows a schematic representation of a reaction scheme according to an embodiment of the present invention.

Figure 2 shows a schematic representation of a reaction scheme including possible reaction intermediates according to an embodiment of the present invention.

Figure 3 shows a schematic representation of a reaction scheme according to an embodiment of the present invention.

Figure 4 shows a schematic representation of a reaction scheme including possible reaction intermediates according to an embodiment of the present invention.

Figure 5 shows a schematic representation of organometallic catalysts according to an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined, all terms used in disclosing the invention, including technical and scientific terms, have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. By means of further guidance, term definitions are included to better appreciate the teaching of the present invention.

As used herein, the following terms have the following meanings:

"A", "an", and "the" as used herein refers to both singular and plural referents unless the context clearly dictates otherwise. By way of example, "a compartment" refers to one or more than one compartment.

"Comprise", "comprising", and "comprises" and "comprised of" as used herein are synonymous with "include", "including", "includes" or "contain", "containing", "contains" and are inclusive or open-ended terms that specifies the presence of what follows e.g. component and do not exclude or preclude the presence of additional, non-recited components, features, element, members, steps, known in the art or disclosed therein.

Furthermore, the terms first, second, third and the like in the description and in the claims, are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order, unless specified. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described or illustrated herein.

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within that range, as well as the recited endpoints.

The expression "% by weight", "weight percent", "%wt" or "wt%", here and throughout the description unless otherwise defined, refers to the relative weight of the respective component based on the overall weight of the formulation.

Whereas the terms "one or more" or "at least one", such as one or more or at least one member(s) of a group of members, is clear per se, by means of further exemplification, the term encompasses inter alia a reference to any one of said members, or to any two or more of said members, such as, e.g., any ≥3, ≥4, ≥5, ≥6 or ≥7 etc. of said members, and up to all said members.

Unless otherwise defined, all terms used in disclosing the invention, including technical and scientific terms, have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. By means of further guidance, definitions for the terms used in the description are included to better appreciate the teaching of the present invention. The terms or definitions used herein are provided solely to aid in the understanding of the invention.

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular features, structures or characteristics may be combined in any suitable manner, as would be apparent to a person skilled in the art from this disclosure, in one or more embodiments. Furthermore, while some embodiments described herein include some but not other features included in other embodiments, combinations of features of different embodiments are meant to be within the scope of the invention, and form different embodiments, as would be understood by those in the art. For example, in the following claims, any of the claimed embodiments can be used in any combination.

As used herein, the terms "in a single reaction step", "in a single reaction" or "in a single synthesis step" refer to one or several reactions which take place in a single reactor. Preferably the reaction occurs simultaneously and does not require a

substantial change in reaction conditions. If the reaction is carried out in a continuous manner, preferably the feed rate of reactants is substantially constant. If the reaction is carried out in a batch operation, preferably the feed rate is such that if several reactions occur, they can occur simultaneously rather than subsequently.

In a first aspect, the invention relates to a process for the production of 1,2-alkanediols comprising the following steps:

1) Providing a dialkyl oxalate (component A).
2) Providing an ester or an aldehyde (component B), which is characterised by having at least one hydrogen atom bound to the second (alpha-)carbon atom.
3) Reaction of the dialkyl oxalate (component A) with an ester or aldehyde (component B) in the presence of a base (component C), thereby forming at least one new carbon-carbon bond and obtaining intermediate A and/or intermediate B.
4) Conversion of the obtained intermediate to an alpha-keto carboxylic acid, an alpha-keto ester or a mixture thereof,
5) Optionally, esterification of obtained alpha-keto carboxylic acid.
6) Reduction of the alpha-keto carboxylic acid or its ester to the corresponding 1,2-alkanediol.
7) Optionally, purification of the obtained 1,2-alkanediol and/or any of the intermediates formed during the prior steps 1-6, by means of distillation, recrystallisation or similar refining steps.

Wherever practical, several of the above steps 1-7 can be combined into one technical step. This minimizes the effort involved in isolating intermediate products or using additional production equipment. The reaction sequence of the process is summarized in Fig. 2.

In a first step, a dialkyl oxalate is provided. Preferably, the alkyl groups of the dialkyl oxalate are independently selected from lower alkyl groups having from 1 to 8 carbon atoms. More preferably the alkyl groups of the dialkyl oxalate are independently selected from lower alkyl groups having from 1 to 6 carbon atoms, even more preferably the alkyl groups of the dialkyl oxalate are independently selected from lower alkyl groups having from 1 to 4 carbon atoms. The two alkyl groups may be straight or branched. The two alkyl groups may be identical or different. Preferably, the dialkyl oxalate is selected from diethyl oxalate, dimethyl oxalate, di-n-propyl oxalate, di-n-butyl oxalate, methyl ethyl oxalate, methyl n-

propyl oxalate, methyl n-butyl oxalate or a mixture thereof. Particularly preferably, diethyl oxalate or di-n-butyl oxalate is provided.

The dialkyl oxalate can be either used as isolated substance, or it can be generated in situ as part of the production process, by an esterification reaction of oxalic acid with the corresponding alcohol. The esterification is typically mediated by an acidic or alkaline catalyst. The catalyst may be either heterogeneous or homogeneous, i.e., the catalyst may be either soluble in the reaction mixture or a portion thereof, or it may be an insoluble liquid or solid. The esterification reaction may take place in the presence or absence of a solvent, at temperatures ranging from 0 to 250 °C and at pressures ranging from 0.01 mbar to 100 bar. Preferably, the reaction takes place at the boiling point of the solvent or alcohol used and/or at the boiling point of azeotropic mixtures formed in the reaction mixture.

The esterification of oxalic acid with ethanol offers the advantage of abundant availability of this alcohol from bio-based and sustainable sources. The low molecular weight of ethanol provides a high yield per volume, which is advantageous in terms of productivity. In addition, diethyl oxalate is liquid at ambient temperature, which simplifies handling on an industrial scale.

The esterification of oxalic acid with n-butanol offers the advantage of easy removal of the water formed during esterification by azeotropic distillation. Since n-butanol forms a heterogeneous azeotrope with water, no additional solvent is required for the reaction. This simplifies recycling, which is why processes based on n-butanol can be regarded as particularly economical and environmentally friendly. In addition, dibutyl oxalate is liquid at room temperature. The lipophilic nature of butanol and dibutyl oxalate facilitates rapid phase separation during aqueous workup. It also allows esterification under phase transfer conditions, optionally in the absence of an additional solvent.

In order to increase the yield of the dialkyl oxalate, the water contained in the oxalic acid and/or formed during the esterification reaction is preferably removed from the ester. It may be removed, for example, by azeotropic distillation, whereby either a heterogeneous or a homogeneous low-boiling mixture ("azeotropic mixture" or "azeotrope") of water and organic component is removed from the reaction mixture. The removal can be realized, for example, by distillation. In a preferred embodiment, the solvent is returned to the reaction mixture after the water has been removed,

using suitable technologies such as phase separation or adsorption or combinations thereof. In a further embodiment, the reaction mixture or distilled solvent is contacted with an absorbent capable of absorbing the water contained in the solvent or reaction mixture.

In another embodiment, the esterification takes place under phase transfer conditions in the presence of an organic solvent. The solvent should be capable of at least partially dissolving the dialkyl oxalate formed, while exhibiting limited miscibility with water. Thus, the ester formed is taken up by the solvent and is therefore protected from a hydrolysis reaction with the water present in the reaction mixture. The use of phase transfer reaction conditions and the removal of water by azeotropic distillation or adsorption can also be combined. In a further embodiment, the alcohol used as reaction partner also serves as the organic solvent.

In another embodiment, the dialkyl oxalate is synthesized via a transesterification reaction.

The oxalic acid used as starting material is preferably produced by oxidation of carbohydrates such as sugar or cellulose with nitric acid. The nitrogen oxides produced as a by-product are preferably recycled, making the production process sustainable and environmentally friendly.

In a second step, a carboxylic acid ester and/or an aldehyde is provided, characterised by having at least one hydrogen atom bound to the second (alpha-) carbon atom. The ester or aldehyde is preferably of bio-based origin. An exemplary list of commercially available biobased feedstocks is provided below, without this listing being construed as a limitation:

- Propanoic acid (propionic acid), butanoic acid (butyric acid), pentanoic acid (valeric acid) and hexanoic acid (caproic acid) are obtained by fermentation of sugar (AFYREN process).
- Heptanal and undecanoic acid are obtained from the ricinoleic acid esters contained in castor oil, following a thermal treatment (ARKEMA process). Heptanoic acid (enanthic acid) is accessible by oxidation of heptanal.
- Nonanoic acid (pelargonic acid) can be obtained by oxidative cleavage of oleic acid derived from vegetable oil.
- Hexanoic acid (caproic acid), octanoic acid (caprylic acid), decanoic acid (capric acid), dodecanoic acid (lauric acid), myristic acid (C14), myristoleic

acid (C14:1), palmitic acid (C16), stearic acid (C18), oleic acid (C18:1), palmitoleic acid (C18:1), linoleic acid (C18:2), linolenic acid (C18:3), arachidic acid (C20), arachidonic acid (C20:4), behenic acid (C22), erucic acid (C22:1), lignoceric acid (C24), cerotic acid (C26), montanic acid (C28) and melissic acid (C30) are examples of carboxylic acids commonly found in vegetable oils and natural waxes.

The carboxylic acids are esterified with an alcohol prior to condensation with dialkyl oxalate. Preferably, the carboxylic acids are reacted with a mono-, di- or trihydric alcohol having from 1 to 8 carbon atoms. In a preferred embodiment, the carboxylic acids are converted to their methyl-, ethyl, n-propyl or n-butyl esters by reaction with the corresponding alcohols. In a most preferred embodiment, the carboxylic acids are converted to their ethyl or butyl esters by reaction with bio-based ethanol or bio-based butanol.

The esterification of the carboxylic acid with ethanol offers the advantage of abundant availability of this alcohol from bio-based and sustainable sources. The low molecular weight of ethanol provides a high yield per volume, which is advantageous in terms of productivity. In addition, ethyl esters of fatty acids are typically liquid at ambient temperature, which simplifies handling on an industrial scale.

The esterification of the carboxylic acid with n-butanol offers the advantage of easy removal of the water formed during esterification by azeotropic distillation. Since n-butanol forms a heterogeneous azeotrope with water, no additional solvent is required for the reaction. This simplifies recycling, which is why processes based on n-butanol can be regarded as particularly economical and environmentally friendly. In addition, butyl esters of fatty acids are typically liquid at room temperature. The lipophilic nature of butanol and butyl esters facilitates rapid phase separation during aqueous workup. It also allows esterification under phase transfer conditions, optionally in the absence of an additional solvent.

The carboxylic acid esters can either be provided separately, or they can be synthesized in one step together with a dialkyl oxalate. The second option offers the advantage that only one esterification step is necessary. Similar reaction conditions can be employed as outlined above for the production of dialkyl oxalates (step 1).

In a third step, at least one dialkyl oxalate (component A) reacts with at least one carboxylic acid ester and/or at least one aldehyde (component B), thereby forming

a new carbon-carbon bond between the second carbon (alpha-carbon) of the ester or the first carbon of the aldehyde and one of the carbon atoms of the oxalate. The reaction is mediated by a base (component C) that is characterised by being sufficiently strong to subtract a C-H-acidic proton. Preferably the base is an alkali or earth alkali alkoxide of a lower alcohol, such as methanol, ethanol, 1-propanol, 2-propanol, n-butanol, sec-butanol, tert-butanol or other isomers thereof. Most preferably, the alkoxide is selected from sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, or potassium tert-butoxide. The alkoxide can be either used in its pure form as a dry solid, or as a solution in the corresponding alcohol. Alternatively, the alkoxide can be formed in situ, for example by addition of a metal, a metal hydride or a metal amide to the alcohol.

The reaction can be carried out without additional solvent or in the presence of a suitable solvent. Polar/hydrophilic as well as non-polar/hydrophobic solvents can be used. In a further embodiment, the at least one alcohol formed during the reaction is removed from the reaction mixture by distillation.

In the case of a reaction between an ester and a dialkyl oxalate, an alpha-oxaloester is presumably formed (intermediate **A**). This reaction mechanism is shown in Fig. 3.

In the case of a reaction between an aldehyde and a dialkyl oxalate, two molecules of the aldehyde first react with another to form an aldol addition product (intermediate C). This intermediate reacts further with the dialkyl oxalate, leading to the formation of a cyclic intermediate containing a 5-membered ring (intermediate **B**). In the course of this second reaction, a formic acid ester is released as a leaving group. This reaction mechanism is shown in Fig. 4.

In another embodiment, the formic acid ester is removed from the reaction mixture by means of a distillation.

In a further embodiment, the reaction mixture is cooled below the boiling point of the formic acid ester, in order to avoid evaporation of the potentially flammable and low boiling ester during the reaction.

To carry out the condensation reaction, the at least two reactants (component A and component B) can be added to the base (component C) either separately or

simultaneously. Alternatively, the base can be added to one of the two reactants or to both reactants. Preferably, the dialkyl oxalate is charged first, followed by addition of the base and finally dosage of the ester or aldehyde.

The condensation reaction can be carried out at temperatures of between -80°C and +150°C, preferably between -20°C and +100 °C, most preferably between 0°C and 50°C. The dosage of either of the three reactants, i.e., the base, the dialkyl oxalate and the ester or aldehyde can be adjusted to keep exothermic reactions under control.

The base (component C) and the aldehyde and/or ester (component B) can be used in molar ratios of between 1:10 and 10:1. Preferably, the base is used in a molar excess. More preferably, the base is used in a molar ratio of at least 1.3:1, more preferably at least 1.5:1, more preferably at least 1.6:1, more preferably at least 1.7:1, more preferably at least 1.8:1, more preferably at least 1.9:1, more preferably at least 2:1, with respect to the aldehyde or ester. More preferably, the base is used in a molar ratio of at least 1.5:1, more preferably at least 1.6:1, more preferably at least 1.7:1, more preferably at least 1.8:1, more preferably at least 1.9:1, more preferably at least 2:1, with respect to the sum of aldehyde and ester. More preferably, the base is used in a molar ratio of at most 10:1, more preferably at most 8:1, more preferably at most 7:1, more preferably at most 6:1, more preferably at most 5:1, more preferably at most 4:1, more preferably at most 3:1, more preferably at most 2.5:1, with respect to the aldehyde or ester, more preferably with respect to the sum of aldehyde and ester. Most preferably, the base is used in a molar ratio of about 2:1 or more with respect to the aldehyde or ester, more preferably with respect to the sum of aldehyde and ester. The inventors found a molar excess of 2:1 of base to aldehyde and / or ester is desirable to maximize the conversion. Increasing the molar excess past 2:1 of the sum of aldehyde and ester has limited effects on conversion as complete or near complete conversion is already obtained.

The dialkyl oxalate can be used in a molar ratio of between 1:100 – 100:1 with regard to the ester or aldehyde. Preferably, the dialkyl oxalate is used in a molar excess compared to the ester or aldehyde. Most preferably, the dialkyl oxalate is used in a 1.1-fold to 10-fold molar excess compared to the ester or the aldehyde.
The intermediates A and/or B are either isolated, or they are directly converted to the corresponding alpha-keto acids and/or alpha-keto ester in the following step 4.

Preferably, the intermediates A and/or B are not isolated, but are transferred to the corresponding alpha-keto ester without prior extensive purification. Particularly preferably, excess amounts of dialkyl oxalate(s) are removed from the product mixture. These can be reused in the production of a subsequent batch, thus reducing the costs and the amount of resources required. A preferred method for removing the excess dialkyl oxalate(s) is vacuum distillation.

In a fourth step, the intermediates A and/or B are converted to the corresponding alpha-keto carboxylic acids and/or alpha-keto esters by reaction under acidic or under alkaline conditions. Alpha-ketoacids are described in prior art as being somehow instable with a tendency to condense with themselves under strong acidic or basic conditions, following the aldol-like pathway. However, the formation of alpha-ketoacids usually involves the treatment of a precursor with strong alkali or strong acid. It can therefore be concluded that alpha-ketoacids are sufficiently stable under such conditions, providing the reaction conditions such as reaction time and temperature are kept under control.

Alpha-oxaloesters (intermediate A) are preferably converted to alpha-keto carboxylic acids under acidic conditions. In the course of the conversion, ester bonds get hydrolysed and carbon dioxide is released as a leaving group of a decarboxylation reaction.

The applied acids can be any Brønsted or Lewis acids that are sufficiently strong to mediate the desired reaction. The acids can be either soluble in at least one compartment of the reaction mixture (homogenous), or they can be insoluble solids (heterogenous). Suitable acids comprise, for example, mineral acids such as hydrochloric acid, sulphuric acid, or phosphoric acid, as well as heteropoly acids such as molybdic, tungstic, or silicic acid. Other suitable acids comprise soluble organic acids such as para-toluene sulphonic acid, methane sulphonic acid or trifluoro methane sulphonic acid. Insoluble or heterogenous acids may comprise, for example, polyacryl or polystyrene or fluorinated resins that are available under trade names such as Amberlite®, Amberlyst®, DOWEX®, Purolite® or Nafion®. Heterogenous acids may further comprise acidic minerals such as, for example, Zeolite or other silicates or aluminosilicates. The acid is preferably used in a molar excess with respect to the intermediate A.

In a further embodiment of the invention, the alpha-oxalo ester (intermediate A) is reacted only with hot water at temperatures of at least 150°C, preferably between 150°C and 250°C. The hot water is used as reagent and solvent which is able to generate sufficiently acidic conditions for the thermal decarboxylation of the intermediates, particularly the alpha-oxalo ester (intermediate A). This variant typically leads to the direct formation of alpha-keto esters as the major product. It therefore avoids the isolation of the free alpha-keto carboxylic acid and its further conversion to the alpha-keto ester. In a further preferred embodiment, the pH of the intermediate and hot water mixture lies between 3 and 10, preferably between 4 and 9, more preferably between 5 and 8, more preferably between 6 and 8, most preferably about 7. The low acidity of hot water also typically avoids side-reactions of the Aldol type. Before the reaction with hot water, the alpha-oxalo ester (intermediate A) is preferably purified by aqueous extraction in order to remove basic and/or alkaline impurities.

In another embodiment, the alpha-oxaloester (intermediate A) is first hydrolysed under alkaline conditions. Any base capable of generating a sufficiently high pH can be used for this purpose. The at least one base can either be soluble in at least one compartment of the reaction mixture (homogeneous), or it can be an insoluble solid (heterogeneous). Suitable bases include alkali metal hydroxides or alkaline earth metal hydroxides. Insoluble or heterogeneous bases can consist, for example, of polyacrylic or polystyrene resins available under trade names such as Amberlite®, Amberlyst®, DOWEX® or Purolite®. The resulting carboxylate salt is then neutralized with an acid and subjected to a decarboxylation reaction under acidic conditions as described above. The alcohol released during the alkaline hydrolysis is preferably removed from the reaction mixture to avoid conversion of the alcohol to an alkene by elimination of water under strongly acidic conditions. The removal may be carried out, for example, by distillation or extraction or phase separation. In a further embodiment, the removed alcohol is recycled or reused. In a preferred embodiment, the isolated alcohol is reacted with the alpha-keto acid obtained in step 4.

The cyclic intermediate B is preferably converted to the corresponding alpha-keto carboxylic acid under alkaline conditions. Any base can be used that is able to create a sufficiently high pH-value. The at least one base can be either soluble in at least one compartment of the reaction mixture (homogenous), or it can be an insoluble solid (heterogenous). Suitable bases comprise, for example, alkali or earth alkali

hydroxides. Insoluble or heterogenous bases may comprise, for example, polyacrylic or polystyrene resins that are available under trade names such as Amberlite®, Amberlyst®, DOWEX® or Purolite®.

The conversion of intermediate A and/or intermediate B to an alpha-keto carboxylic acid may take place in the presence or absence of a solvent and/or a phase transfer catalyst, at temperatures ranging from 0 to 250 °C and at pressures ranging from 0.01 mbar to 100 bar. Preferably, the reaction takes place at temperatures of not more than 150°C, most preferably not more than 100°C.

The obtained alpha-keto carboxylic acid is either directly subjected to a reduction reaction (step 6), or it is optionally converted to an ester (step 5) before being subjected to a reduction reaction.

In an optional fifth step, the obtained alpha-keto carboxylic acid is esterified by reaction with an alcohol. Preferably, the ester is formed by reaction with a lower alcohol containing between 1 and 8 carbon atoms. Most preferably, methyl or ethyl or n-propyl or n-butyl esters are formed.

The esterification of the alpha-keto carboxylic acid with ethanol offers the advantage of abundant availability of this alcohol from bio-based and sustainable sources. The low molecular weight of ethanol provides a high yield per volume, which is advantageous in terms of productivity. In addition, ethyl esters of alpha-keto carboxylic acids are typically liquid at ambient temperature, which simplifies handling on an industrial scale.

The esterification of alpha-keto carboxylic acids with n-butanol offers the advantage of easy removal of the water formed during esterification by azeotropic distillation. Since n-butanol forms a heterogeneous azeotrope with water, no additional solvent is needed for the reaction. This simplifies recycling, which is why processes based on n-butanol can be regarded as particularly economical and environmentally friendly. Moreover, butyl esters of alpha-keto carboxylic acids are typically liquid at room temperature. The lipophilic nature of butanol and butyl esters facilitates rapid phase separation during aqueous workup. It also allows esterification under phase transfer conditions, optionally in the absence of an additional solvent.

In a further embodiment, the esterification reaction (step 5) is combined with the formation of the alpha-keto carboxylic acid (step 4). Suitable reaction conditions comprise, for example, the use a lipophilic solvent or co-solvent that is characterised by having a low or limited solubility in water. Such lipophilic solvents allow the formation of esters of alpha-keto carboxylic acids under phase-transfer condition, where the ester is taken up by the solvent. This limits the contact of the ester with water and thereby protects the ester bond from hydrolysis. Suitable solvents are, for example, selected from alkanes such as hexane, heptane or cyclohexane, ethers such as tert-butyl methyl ether (MTBE), 2-methyltetrahydrofuran or dialkyl ethers, and aromatic solvents such as toluene or xylene. In another embodiment, a lipophilic alcohol, such as 1-butanol, is used as solvent and reactant.

Alternatively, the esterification can be catalysed by a suitable enzyme. Typical enzymes include esterases such as Candida antarctica lipase B (CALB). The enzyme can be used in its free form, or it can be immobilised on a solid support.

The formed ester is either isolated by common techniques or used in the following step 6 without further purification.

In a sixth step, the alpha-keto carboxylic acid and/or alpha-keto carboxylic acid ester is converted to a 1,2-alkanediol by reducing the keto-function to a secondary alcohol and the carboxylic acid and/or ester to a primary alcohol.

The reduction can be carried out either in one step, or in several consecutive steps. For example, the carbonyl group of the keto-function can be first reduced to form a secondary alcohol, and the remaining carboxylic acid or ester function can be reduced in second step to a primary alcohol. The alpha-hydroxy acid or alpha-hydroxyester can be isolated and/or purified before further conversion to the 1,2-alkanediol. Preferably, the alpha-hydroxy carboxylic acid and/or alpha-hydroxy carboxylic acid ester is not isolated prior to reduction to the 1,2-alkanediol.

In one embodiment, the carbonyl group of the alpha-keto carboxylic acid and/or alpha-keto carboxylic acid ester is first reduced to a secondary alcohol. Two molecules of the resulting alpha-hydroxy acid or alpha-hydroxyester are then reacted by forming a cyclic dimeric ester of the lactide type. This cyclic dimeric ester is further reduced, thereby yielding two molecules of 1,2-alkanediol. The cyclic ester can be isolated and optionally purified before conversion to the 1,2-alkanediol. In a

preferred embodiment, the cyclic ester is formed in situ and directly converted to the 1,2-alkanediol without prior isolation or purification. By forming a dimeric ester of two alpha-hydroxy carboxylic acids and its subsequent reduction to the corresponding 1,2-alkanediol, the two consecutive steps 5 and 6 of the invention are combined in one step.

Preferably, the reductions during step 6 are carried out by means of a catalytic hydrogenation in the presence of a suitable metal catalyst. Hydrogenation of the alpha-carbonyl function to a secondary alcohol function is generally not challenging for reduction by catalytic hydrogenation. Further hydrogenolysis of the carboxyl group to a primary alcohol requires significantly harsher conditions, such as higher temperature and/or higher pressure of hydrogen gas. More than one type of catalyst can be used in case of a stepwise reduction. In a preferred embodiment, all reduction reactions are catalysed by the same catalyst.

Examples for suitable catalysts for the hydrogenation of alpha-keto carboxylic acids and/or of alpha-keto carboxylic acid esters to 1,2-alkanediols comprise heterogenous and/or homogenous metal catalyst.

Suitable heterogenous hydrogenation catalysts contain one or more of the following metals: Copper, Chromium, Cobalt, Cerium, Nickel, Iron, Ruthenium, Palladium, Platinum, Rhodium, Tantalum, Niobium, Iridium, Osmium, Rhenium, Gold, Silver, Manganese, Tin, Boron, Indium, Vanadium, Molybdenum and Tungsten. The metals are provided in their metallic form and/or in another catalytically active oxidation state, for example as (potentially reducible) metal oxides. Optionally, the heterogenous metal catalyst is provided on a solid support and/or in combination with a binder. Examples comprise carbon, aluminium oxide (alumina), silicium dioxide (silica, also fumed), silicic acid, silicium carbide, zinc oxide, zirconium oxide, barium oxide, magnesium oxide, titanium dioxide, cerium oxide, zirconium oxide, hydroxyapatite, aluminosilicates such as Mordenite and Zeolite, magnetic nanoparticles, polymers, or combinations thereof. The catalyst can also be of the RANEY® type, where one compartment (usually aluminium) is removed from an alloy of metals by treatment with a base (for example an aqueous solution of alkali hydroxide), thereby providing a sponge like metal catalyst.

Preferred heterogeneous catalysts for the hydrogenation of alpha-keto acids comprise noble metal catalysts based on Ruthenium, Platinum, Rhenium, Palladium, Rhodium and/or Iridium, and non-noble metal catalysts based on Copper, Nickel,

Cobalt and/or Molybdenum. The catalysts are preferably designed to minimize leaching of metal into the reaction medium. Combinations of different metals, as well as metal/metal oxide combinations and/or the use of suitable supports and/or promoters can be employed to improve reactivity and selectivity with respect to the desired diol.

Preferred heterogeneous catalysts for the hydrogenation of alpha-keto esters comprise noble metals, optionally in combination with promoters, most preferably bimetallic catalysts such as Pd/Re and Pt/Re. In particular, catalysts combining at least one hydrogenation metal (e.g. Ru, Pt, Pd, Rh) and at least one promoter metal (e.g. tin, rhenium, molydenum) and exhibiting a synergistic effect are preferred. Copper, silver and gold can also act as promoters to platinum group metals. The catalyst support and the optional solvent system may further promote the catalytic transformation. Support materials such as for example TiO2 and/or ZnO may assist in carbonyl group and/or dihydrogen activation.

Further preferred heterogeneous catalysts for the hydrogenation of alpha-keto esters are non-noble metal catalysts. Examples for suitable catalysts comprise:

- Copper chromite and zinc chromite catalysts (Adkins type), as well as Cu–Fe spinel and Cu-Fe-Al mixed oxide systems substituting the Cr component for Fe.
- Supported copper catalysts such as Cu/ZrO_2, Cu/SiO_2, $Cu/SiO_2/ZnO$, or Cu/SiO_2 hybrid catalysts containing the zeolite H-ZSM-5.
- RANEY® copper and RANEY® nickel catalysts.

The heterogenous catalyst(s) can be activated prior to application in the synthesis of 1,2-alkanediols, for example by heating in the presence or absence of hydrogen and/or water steam and/or an inert carrier gas.

In a preferred embodiment, the heterogenous catalyst is reused several times in consecutive batches and/or used for a longer time in a continuous hydrogenation reaction.

Particularly preferred heterogenous catalysts for the hydrogenation of alpha-keto esters to 1,2-alkanediols are Ruthenium catalysts.

In a further embodiment, homogeneous hydrogenation catalysts are employed which are soluble in at least one compartment of the reaction medium. They typically are

organometallic complexes consisting of at least one metal-center which is coordinated to one or more ligands. These ligands may have oxygen, nitrogen, phosphorus, or sulphur at the binding site which bind to the metal through a lone pair of electrons. They may also contain a carbon group that binds to the metal via a σ-bond or via π-interactions, such as benzene, diene, or allyl-groups. Carbenes are another type of viable ligands, having an electron sextet at a carbon atom.

Preferably, homogenous catalysts for hydrogenation of esters are selected from organometallic pincer-type complexes, such as those described in a review by Nielsen et al. (Catalysts 2020, 10, 773). Pincer ligands bind to a metal with two donor atoms (for example phosphorus, nitrogen, or sulphur) and one σ-bond. Phosphines (P), nitrogen (N) or sulphur (S) are often used as donors. For example, if the pincer ligand is bonded to the metal via two phosphorus donors and with a carbon-metal σ-bond, it is called a PCP pincer ligand. Similarly, nitrogen-metal σ-bonds are possible (PNP). Other common types are NCN (nitrogen-carbon nitrogen) and SCS (sulphur-carbon sulphur) ligand systems. Phenyl systems usually serve as the ligand backbone, but aliphatic systems are also known. If the ligands are bonded to a metal, the resulting coplanar structure is very rigid. This leads to an increased thermal stability of the homogenous catalyst.

Ligands containing phosphine and amine moieties, such as Ru-MACHO developed at Takasago, are known as effective catalysts for the conversion of esters to alcohols (WO2011048727A). Suitable organometallic complexes are shown in Fig. 5. Ru-MACHO (**C1**) and similar catalysts require the addition of a base, typically an alkali or earth alkali alcoholate such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, or potassium tert-butoxide. Replacing the chloride in Ru-MACHO by hydride-BH_3 affords Ru-MACHO-BH (**C2**) that is also effective in the absence of an additional base. The pincer Ruthenium complex **C3** bearing a monodentate N-heterocyclic carbene ligand demonstrated high efficacy under low pressure of hydrogen gas (Organic Letters 2016, 18/15, 3894-3897). Pincer-type catalysts developed by MILSTEIN et al. are another type of suitable catalysts. Examples comprise PNN-complexes such as **C4** and **C5**, and PNP-complexes like **C6** (WO2012052996 A2; Angew. Chem. Int. Ed. 2006, 45, 1113-1115). GUSEV et al. replaced one of the phosphine ligands by the hemilabile Npyr-NH-$P(iPr)_2$ ligand containing a pyridyl moiety (**C7**). The obtained monomeric Ru and Os complexes react with bases such as potassium tert-butoxide, to form dimeric structures that are able to convert esters to alcohols without further addition of a

base (Organometallics 2012, 31, 5239). GUSEV et al. also replaced the phosphines for sulphur in a so-called SNS pincer complex. The corresponding Ruthenium complex with structure **C8** shows high activity in the hydrogenation of esters and ketones (Angew. Chem. Int. Ed. 2013, 52, 2538). Another type of catalysts containing two amino-phosphino-bridged ligands (example: **C9**) were developed by researchers at Firmenich (Angew. Chem. Int. Ed. 2006, 45, 1113-1115).

The list of catalysts given herein is provided as an example only and is not intended to be limiting.

Particularly preferred homogenous catalysts for the hydrogenation of alpha-keto esters to 1,2-alkanediols are the Ruthenium-complexes C7 and C8.

The source of hydrogen for the hydrogenation of carboxylic acid and/or esters and ketones is selected from either hydrogen gas or from organic substances that act as hydrogen donors. The hydrogen gas can be produced, for example, by steam reforming of hydrocarbons or by electrolysis of water. Another option is the generation of hydrogen in situ by catalytic transfer of hydrogen from a donor molecule. Suitable hydrogen donors for transfer hydrogenation include formate, as well as alcohols such as 2-propanol, but any other suitable molecule can also be used as a donor.

The hydrogenation reactions can be either carried out in a liquid phase or in a gaseous phase. The conversions can be carried out batch-wise, for example in a stirred vessel. They can also be carried out in equipment suitable for continuous hydrogenation, for example by introducing the reactants to a trickle-bed or fixed bed tube-reactor or a loop reactor (such as BUSS loop or similar), or a fluidised bed reactor.

The hydrogenation can be carried out in the presence or absence of a suitable solvent that may act as transporter, mediator, and diluent. Examples of protic solvents are water, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, or mixtures thereof. Examples of aprotic solvents are ethers such as methyl-tert-butyl ether or 2-methyltetrahydrofuran, as well as hydrocarbons such as cyclohexane, heptane, octane or decalin.

The hydrogenation reaction is preferably carried out at a temperature of between -20°C and 300°C, more preferably between 0°C and 250°C.

In cases where gaseous hydrogen is used as hydrogen donor, the hydrogenation of alpha-keto carboxylic acids, alpha-keto esters or a mixture thereof is preferably carried out under hydrogen partial pressure of between 1 bar and 300 bar hydrogen, preferably between 5 bar and 100 bar hydrogen, more preferably 5 to 50 bar hydrogen. In a further preferred embodiment, the hydrogenation is carried out under a total pressure of between 1 bar and 300 bar, preferably between 5 bar and 100 bar, more preferably 5 to 50 bar. In a preferred embodiment, the hydrogen partial pressure is at least 75% of the total pressure, more preferably at least 80% of the total pressure, more preferably at least 85% of the total pressure, more preferably at least 90% of the total pressure, more preferably at least 95% of the total pressure, more preferably at least 97% of the total pressure, more preferably at least 98% of the total pressure, more preferably at least 99% of the total pressure, more preferably at least 99.5% of the total pressure.

In an optional seventh step, any of the intermediates formed in the course of the production process, during any of the aforementioned steps 1-6, may undergo a distillation step to refine the substance prior to the subsequent chemical reaction. The 1,2-alkanediol formed in the final stage 6 may also undergo a final distillation step to refine the 1,2-alkanediol. The aim of the purification step 7 is to remove undesired impurities or fractions. Preferably, the final 1,2-alkanediol is distilled under reduced pressure, most preferably at a pressure not exceeding 20 mbar and/or at temperatures not exceeding 150 °C. Such conditions effectively avoid thermal degradation of the diols and the formation of malodorous decomposition products.

The overall process preferably yields at least about 50% to about 99% of the 1,2-alkanediol, and more preferably yields at least about 70% to about 99% of the 1,2-alkanediol.

The 1,2-alkanediols obtained by the production process described herein have a carbon chain of between 4 and 30 carbon atoms. In one embodiment of the process, the 1,2-alkanediols have a carbon chain of from about 5 to about 14 carbon atoms. The 1,2-alkanediols may have a carbon chain length of from about 5 to about 10 carbon atoms. The 1,2-alkanediol may be, for example, 1,2-pentanediol and/or 1,2-hexanediol and/or 1,2-heptanediol and/or 1,2-octanediol and/or 1,2-decanediol.

The obtained 1,2-alkanediols can be straight-chain or branched molecules. Preferably, they are straight-chain molecules. In addition, the 1,2-alkanediols may contain one or more functional or substituted groups, such as sulphate or sulfonate groups, hydroxyl groups, ether groups, amine groups, halogenated groups, aryl or arene or other aromatic groups and similar functional groups, without any limitation being intended.

In a particularly preferred embodiment of the first aspect of the invention, the process for the production of 1,2-alkanediols comprising the steps of:

1) providing a dialkyl oxalate (component A);

2) providing an ester or an aldehyde (component B), which is characterised by having at least one hydrogen atom bound to the second (alpha-)carbon atom;

3) reaction of the dialkyl oxalate (component A) with an ester or aldehyde (component B) in the presence of a base (component C), thereby forming at least one new carbon-carbon bond and obtaining an intermediate;

3.1) preferably separating excess component A, component B, alcohol, solvent, or a mixture thereof by vacuum distillation; optionally recycling said excess component A, component B, alcohol, solvent, or a mixture thereof,

3.2) preferably purifying said obtained intermediate by aqueous extraction,

4) conversion of the obtained intermediate to an alpha-keto carboxylic acid, an alpha-keto ester or a mixture thereof; preferably by reacting said obtained intermediate with water at a temperature of at least 150°C thereby obtaining said alpha-keto carboxylic acid, said alpha-keto ester or said mixture thereof;

5) optionally, esterification of obtained alpha-keto carboxylic acid, preferably no esterification of said alpha-keto carboxylic acid;

6) reduction of said alpha-keto carboxylic acid, said alpha-keto ester or said mixture thereof to the corresponding 1,2-alkanediol;

6.1) preferably said alpha-keto carboxylic acid, said alpha-keto ester or said mixture thereof is not isolated prior to the reduction thereof;

6.2) preferably said alpha-keto carboxylic acid, said alpha-keto ester or said mixture thereof is reduced by hydrogenation with H_2, preferably the hydrogenation comprises a H_2 partial pressure between 5 and 100 bar, preferably the hydrogenation is carried out over a catalyst, more preferably

a ruthenium catalyst, most preferably ruthenium complexes C7 and / or C8, preferably at a hydrogenation temperature between 0 and 250°C,

7) optionally, purification of the obtained 1,2-alkanediol and/or any of the intermediates formed during the prior steps 1-6.

The preferred features and steps of this embodiment may be present or absent independently from one another. Most preferably, all preferred features are present. The vacuum distillation of preferred step 3.1 allows for an (energy) efficient method to separate the excess reagents (and solvent), without the need to purify the intermediate to a higher degree. This further advantageously allows the excess reagents and solvent to be integrally recycled, reducing the requirement for (virgin) reagents and solvent. The aqueous extraction of step 3.2 allows for quick and efficient removal of basic and / or alkaline impurities. The preferred reaction with hot water as described in step 4) advantageously favours the formation of the alpha-keto ester and limits the production of alpha-keto carboxylic acid as well as undesired side-reactions. The resulting product is sufficiently pure to integrally reduce, preferably hydrogenate, according to step 6. There is thus no need for optional step 5, nor the need for purification of the alpha-keto carboxylic acid or the alpha-keto ester.

Regarding their application, the 1,2-alkanediols obtained via a process according to the first aspect of the invention can be used alone, as combination of different types of 1,2-alkanediols, or in mixtures with other natural or conventional antimicrobials and/ or further solvents or additives.

In a second aspect, the invention relates to a **method of providing antimicrobial activity** to a composition, including incorporating an antimicrobial system into the composition, wherein the antimicrobial system comprises at least one 1,2-alkanediol having a carbon chain length of from about 4 to about 21 carbon atoms synthesized by conversion of at least one aldehyde or carboxylic acid ester having a carbon chain of from about 3 to about 20 carbon atoms.

In a third aspect, the invention relates to the **use of 1,2-alkanediols** obtained by a process according to the first aspect of the invention **as antimicrobial ingredients in compositions**. Such compositions may include cosmetic, pharmaceutical, dermatological, hygienic, agrochemical or other industrial preparations. Non-limiting examples of compositions include:

a) Solutions (aqueous, organic, hydro-alcoholic, hydro-glycolic)

b) suspensions,
c) emulsions (oil in water, water in oil, silicon in water, water in silicon, microemulsions)
d) gels,
e) ointments,
f) pastes,
g) syrups,
h) solids and/or powders,
i) foams,
j) soaps,
k) capsules,
l) perfumes,
m) hydrosols,
n) shampoos,
o) creams,
p) micellar waters,
q) microencapsulated systems,
r) liposome-based systems,
s) wipes and towelettes,
t) combinations of a – s.

These compositions may be intended for use as, for example, skin care, hair care, oral care, health care, fabric care or cleaning products.

Such compositions may optionally further include at least one solubilizing agent in a ratio of about 1:10 to 10:1 by weight of the solubilizing material versus the 1,2-alkanediol(s). Suitable solubilizing agents may include for example alkanediols, as well as derivatives of polyethylene glycol, polypropylene glycol and/or polyglycerol. The 1,2-alkanediols obtained by the process according to the first aspect of the invention can be added to compositions at any time during the production process. The addition preferably takes place towards the end of the formulation process, in order to ensure a high concentration of 1,2-alkanediol in the water phase of the formulation. When used in a composition, the 1,2-alkanediols of the invention are preferably incorporated in an amount of about 0.1 to about 10 weight percent, and preferably 0.3 to about 2 weight percent, of the total composition.

In a fourth aspect, the invention relates to a cosmetic, pharmaceutical, dermatological or hygienic **product containing at least one 1,2-alkanediol** obtained by the process according to the first aspect of the invention, wherein the product passes a microbial challenge test according to the norm ISO 11930.

In a fifth aspect, the invention relates to **antimicrobial systems** containing one or more 1,2-alkanediols obtained by a process according to the first aspect of the invention. The antimicrobial systems may further contain at least one additional component with antimicrobial activity, such as, but not limited to:

- Alkanediols that were made by another process than the one according to the first aspect of the invention. These diols can be either derived from bio-based or petrochemical feedstock. Examples of suitable alkanediols comprise 1,2-propanediol, 1,3-propanediol, 1,2-butanediol, 1,3-butanediol, 2,3-butanediol, 3-methyl-1,3-butanediol (isopentyl diol), 1,2-pentanediol, 1,4-pentanediol, 1,5-pentanediol, 2-methyl-2,4-pentanediol (hexylene glycol), 1,2-hexanediol, 1,2-heptanediol, 1,2-octanediol, 1,2-decanediol, and 1,2-dodecanediol.
- Aromatic alcohols and/or phenylpropanoids such as benzyl alcohol, 2-phenylethanol, 2-phenylethanal, 3-phenylpropan-1-ol, cinnamaldehyde, cinnamyl alcohol, 3-phenylpropanal.
- Glyceryl mono and/or di-esters and/or glyceryl mono-ethers such as, but not limited to, glyceryl caprylate, glyceryl caprate, glyceryl caprylate/caprate, glyceryl laurate, 2-ethylhexyl glyceryl ether (ethylhexylglycerin), n-hexyl glyceryl ether, cyclohexyl glyceryl ether, n-octyl glyceryl ether, decyl glyceryl ether and lauryl glyceryl ether. Each of these substances can be of petrochemical and/or bio-based origin.
- Lower aliphatic alcohols such as ethanol, 1-propanol, 2-propanol.
- Carboxylic acids such as levulinic acid, benzoic acid, sorbic acid, cinnamic acid, p-anisic acid, salicylic acid, as well as the corresponding alkali or earth alkali salts and/or corresponding esters with lower alcohols or with aromatic alcohols.
- Essential oils obtained by extraction or steam distillation of vegetable material, such as but not limited to cassia oil, cinnamon oil, tea tree oil, citrus peel or flower oils, Peru balm, lemon grass oil.
- Extracts and botanicals obtained by immersion of natural materials of vegetable and/or marine origin in a solvent or supercritical fluid,

optionally followed by removal of the extraction medium by evaporation or sublimation or solvent exchange.

- Fermentation products.
- Preservatives and/or microbicides, such as parabens (methyl, ethyl, propyl, and butyl), Quaternium 15, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin, 2-bromo-2-nitropropane-1,3-diol (Bronopol), sodium hydroxyglycinate, sodium hydroxymethylglycinate, phenoxyethanol, methylisothiazolinone and/or methylchloroisothiazoline, benzylisothiazolinone, dehydroacetic acid, sodium dehydroacetate, formaldehyde and/or formaldehyde releasing agents, MDM hydantoin, iodopropynyl butylcarbamate chloroxylenol, methyldibromo glutaronitrile, chlorphenesin, triclosan, triclocarban, benzalkonium chloride, chlorhexidine, polyaminopropyl biguanide, 5-bromo-5-nitro-1,3-dioxane (bronidox), hexamidine diisethionate, o-cymen-5-ol, as well as any other compound listed in Annex V of the EU Regulation 1223/2009/EC on Cosmetic Products.

The 1,2-alkanediols are preferably present in the antimicrobial systems in a ratio of the 1,2-alkanediol(s) to any other antimicrobial component(s) of from about 99:1 to about 1:99, and preferably from about 75:25 to about 25:75 in the antimicrobial system.

These antimicrobial systems may be characterized by having a synergistic antimicrobial effect that exceeds the additive antimicrobial effects of their individual components by at least 5%, preferably at least about 10%, and more preferably at least about 20%. Such so-called "boosting" effects and antimicrobial effects in a formulation are evaluated using microbiological testing protocols known as "challenge tests." Preservatives and antimicrobials used in cosmetic, toiletry and pharmaceutical formulations must enable the products to successfully pass such tests. Challenge tests are conducted by adding known amounts of microorganisms to a product and measuring the increase or decrease in the microorganism population over time. The microorganisms added include Gram-positive bacteria, Gram-negative bacteria, yeast(s) and mold(s). A widely accepted standard for challenge testing is defined by ISO 11930. Other suitable test protocols and acceptance criteria are described in the European Pharmacopoeia (Efficacy of Antimicrobial Preservation) and the Japanese Pharmacopoeia (Preservation Effectiveness Tests). Other appropriate challenge test protocols may be used.

Also disclosed herein are **methods of using 1,2-alkanediols for the creation of self-preserving compositions.** Each of such methods includes incorporating into the composition at least one 1,2-alkanediol, combination(s) of at least two different 1,2-alkanediols, or combination(s) of at least one 1,2-alkanediol with at least one other compound different from the at least one 1,2-alkanediol. The 1,2-alkanediol(s) either act as an antimicrobial agent or boost the antimicrobial efficacy of the overall composition. In a preferred embodiment, such compositions are self-preserved against microbial infestation without the need for adding further preservatives.

Personal care and pharmaceutical formulations containing 1,2-alkanediols will also preferably contain water. The formulations may further contain any other functional or active ingredients, such as but not limited to flavours and/or fragrances, fats and/or oils, surfactants, thickeners, emollients, humectants, emulsifiers, chelating agents, gelling agents, binders, texturizing agents, solvents, mineral and/or organic UV filters and/or UVA and/or UVB blocking agents, antioxidants, waxes, polymers, inorganic and/or organic pigments, colouring agents, clays and/or other mineral powders, vegetable materials, natural extracts, essential oils, APIs and other additives commonly used in such formulations. In water-based formulations, it is preferred that about 20 wt% to about 95 wt% water be present therein. The various additives in addition to the water and the preferred antimicrobial systems described herein make up the remaining amount. Preferably, each additive is present in an amount up to about 75% by weight of the total formulation, and more preferably up to about 40% by weight, with the total amount of such additives preferably not exceeding about 50% by weight.

Household product compositions containing 1,2-alkanediols may include both household cleaners and fabric care compositions. Cleaning compositions (whether solids or liquids) may contain detergents that are active ingredients for cleaning, such as quaternary ammonium compounds, bleaching agents, or basic or acidic cleaning agents. Commercially available cleaning agents based on quaternary ammonium compounds include various antibacterial cleaners for disinfection or sanitization. Such compositions may contain other antimicrobial agents and/or other preservatives to maintain adequate shelf life. Therefore, such compositions may also benefit from the addition of 1,2-alkanediols as described herein.

The 1,2-alkanediols described herein may also be used in the treatment of textiles

and/or fibres or yarns. Textiles may include woven and non-woven tissues, or combinations thereof.

The 1,2-alkanediols described herein may further be used for the protection of agrochemical compositions.

In a sixth aspect, the invention relates to 1,2-alkanediols obtainable by a process according to the first aspect of the invention. Preferably, the invention relates to 1,2-alkanediols obtained by the process according to the first aspect of the present invention. More preferably, the invention relates to bio-1,2-alkanediols obtainable, preferably obtained, by the process according to the first aspect of the present invention.

EXAMPLES

Example 1: Synthesis of 2-oxo-methyl/ ethyl octanoate

Diethyl oxalate (88 g) and sodium methanolate (190 g of a 30% solution in methanol) are filled into a dry flask. Ethyl heptanoate (79 g) is added and the reaction mixture is warmed to about 40 °C. The methanol and ethanol being present or released during the reaction are removed by distillation under vacuum.

The reaction is stopped as soon as analysis by GC shows a sufficient conversion of the ethyl heptanoate. The reaction mixture is cooled, and formic acid (52 g) is slowly added under vigorous stirring and temperature control (<40°C), followed by water (200 mL). The two phases are separated. The aqueous phase is extracted with ethyl acetate (2 x 50 mL). All organic phases are combined and washed with saturated hydrogen carbonate solution (50 mL) and portions of demineralised water (50 mL) until the pH of the aqueous phase is neutral (pH indicator paper Tritest®). The solvents and excess oxalate ester are removed by vacuum distillation.

The oily residue is filled into a stainless-steel autoclave and mixed therein with the same volume of demineralised water. The autoclave is closed and heated to 150-200°C for 30 min. After cooling to ambient temperature, the overpressure is carefully released. The phases are separated, and the organic phase is purified by fractional vacuum distillation to afford a mixture of 2-oxo-ethyl octanoate and 2-oxo-methyl octanoate (104 g, 98.1 area-% combined purity by GC-FID).

Example 2: Synthesis of 2-oxo-ethyl/ methyl hexanoate

Diethyl oxalate (88 g) and sodium methanolate (190 g of a 30% solution in methanol) are filled into a dry flask. Excess methanol is removed by vacuum

distillation. The oily residue is diluted with MTBE (150 mL). The mixture is warmed to about 35-40 °C. Ethyl valerate (65 g) is slowly added over 2 hours and stirring is continued for 2 hours at 35-40°C.

The reaction is stopped as soon as analysis by GC shows a sufficient conversion of the ethyl valerate. The reaction mixture is cooled, and formic acid (52 g) is slowly added under vigorous stirring and temperature control (<40°C), followed by water (200 mL). The two phases are separated. The organic phase is washed with saturated hydrogen carbonate solution (50 mL) and portions of demineralised water (50 mL) until the pH of the aqueous phase is neutral (pH indicator paper Tritest®). The solvents and excess oxalate ester are removed by vacuum distillation.

The oily residue is filled into a stainless-steel autoclave and mixed therein with the same volume of demineralised water. The autoclave is closed and heated to 150-200°C for 30 min. After cooling to ambient temperature, the overpressure is carefully released. The phases are separated, and the organic phase is purified by fractional vacuum distillation to afford a mixture of 2-oxo-ethyl hexanoate and 2-oxo-methyl hexanoate (62 g, 97.8 area-% combined purity by GC-FID).

Example 3: Synthesis of 1,2-octanediol

A mixture of 2-oxo-ethyl octanoate and 2-oxo-methyl octanoate (approx. 0.5 mol) is filled into a stainless-steel autoclave. 5% Ru-catalyst on alumina is added (1 g, Noblyst® P3061) and the autoclave is closed. The reaction mixture is heated to 150 °C with stirring under an atmosphere of 50 bar hydrogen. The mixture is stirred further until the end of the hydrogen absorption. Following that the reaction mixture is inertised with nitrogen and the catalyst is removed by filtration. The obtained crude product is fractionally distilled in vacuo. The obtained 1,2-octanediol (131 g isolated yield; purity: 99.9 area-% by GC-FID) is practically free from oxo-impurities and therefore has a very faint waxy odour. It also contains no regioisomers such as 2,3- or 3,4-octanediol.

Example 4: Synthesis of 1,2-hexanediol

A mixture of 2-oxo-ethyl hexanoate and 2-oxo-methyl hexanoate (approx. 0.5 mol) is filled into a stainless-steel autoclave. Catalyst Ru-SNS catalyst C8 (155 mg) and sodium methanolate (9 g of a 30 % solution in methanol) are added. The autoclave is then closed. The reaction mixture is heated to 50 °C with stirring under 15-20 bar hydrogen atmosphere. The mixture is stirred further until the end of the hydrogen absorption. Following that the reaction mixture is inertised with nitrogen and neutralised with 10% sulphuric acid (24,5 g). The obtained crude product is

fractionally distilled in vacuo. The obtained 1,2-hexanediol (53,2 g isolated yield; purity: 99.9 area-% by GC-FID) is practically free from oxo-impurities and therefore practically odourless. It also contains no regioisomers such as 2,3- or 3,4-hexanediol.

CLAIMS

1. Process for the production of 1,2-alkanediols comprising the steps of:
   1) providing a dialkyl oxalate (component A);
   2) providing an ester or an aldehyde (component B), which is characterised by having at least one hydrogen atom bound to the second (alpha-)carbon atom;
   3) reaction of the dialkyl oxalate (component A) with an ester or aldehyde (component B) in the presence of a base (component C), thereby forming at least one new carbon-carbon bond and obtaining an intermediate;
   4) conversion of the obtained intermediate to an alpha-keto carboxylic acid, an alpha-keto ester or a mixture thereof;
   5) optionally, esterification of obtained alpha-keto carboxylic acid;
   6) reduction of the alpha-keto carboxylic acid, its ester or a mixture thereof to the corresponding 1,2-alkanediol;
   7) optionally, purification of the obtained 1,2-alkanediol and/or any of the intermediates formed during the prior steps 1-6.

2. Process according to claim 1, wherein the two alkyl groups of component A are independently chosen from straight or branched alkyl groups with 1 to 8 carbon atoms.

3. Process according to any of claims 1 or 2, wherein component A is chosen from the list of: diethyl oxalate, dimethyl oxalate, di-n-propyl oxalate, di-n-butyl oxalate, methyl ethyl oxalate, methyl n-propyl oxalate or methyl n-butyl oxalate; preferably component A is diethyl oxalate or dibutyl oxalate.

4. Process according to any of claims 1-3, wherein component A and/or component B is bio-based, preferably component A and B are bio-based.

5. Process according to any of claims 1-4, wherein component B is an aldehyde or an ester derived from a C3-C24 carboxylic acid, preferably a C3-C15 carboxylic acid, more preferably a C3-C12 carboxylic acid, more preferably a C3-C10 carboxylic acid, more preferably a C3-C8 carboxylic acid.

6. Process according to any of claims 1-5, wherein component B is the ethyl ester or n-butyl ester of a carboxylic acid.

7. Process according to claim 6, wherein component B is the ethyl ester or n-butyl ester of a carboxylic acid obtained through the reaction of a bio-based carboxylic acid with bio-based ethanol or bio-based butanol.

8. Process according to any of claims 1-7, wherein component C (base) is an alkali or earth alkali alkoxide of an alcohol chosen from the list of: methanol, ethanol, 1-propanol, 2-propanol, n-butanol, sec-butanol, tert-butanol or other isomers thereof.

9. Process according to any of claims 1-8, wherein component C (base) is chosen from the list of: sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, or potassium tert-butoxide, wherein the molar ratio of component C (base) to component B (ester or aldehyde) is at least 3:2.

10. Process according to any of claims 1-9, wherein step 4) comprises the conversion of the obtained intermediate in water at a reaction temperature of at least 150°C, thereby obtaining said alpha-keto ester and / or said alpha-keto carboxylic acid.

11. Process according to claim 10, wherein the intermediate obtained in step 3) is purified by aqueous extraction prior to step 4).

12. Process according to any of claims 1-11, wherein the alpha-keto carboxylic acid is esterified by reaction with a C1-C8 alcohol, preferably methanol or ethanol or n-propanol or n-butanol.

13. Process according to any of claims 1-12, wherein the reduction of the alpha-keto carboxylic acid or its ester to the corresponding 1,2-alkanediol according to step 6 comprises the hydrogenation of said alpha-keto carboxylic acid, said alpha-keto ester or the mixture thereof, preferably in the presence of a ruthenium catalyst.

14. Use of an 1,2-alkanediol obtained by a process according to any of claims 1-13.

15. Use of an 1,2-alkanediol obtained by a process according to any of claims 1-13 in a cosmetic or pharmaceutical composition.

FIGURES

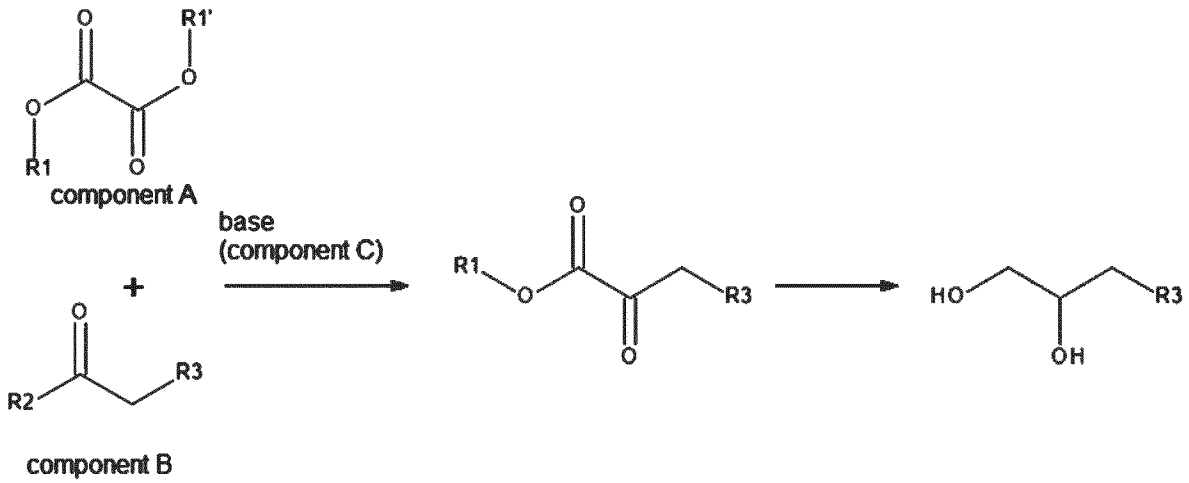


Fig. 1

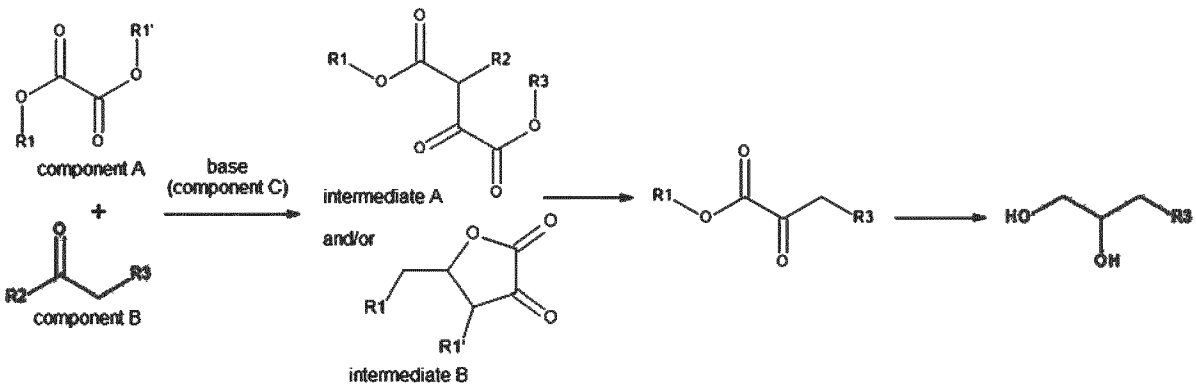
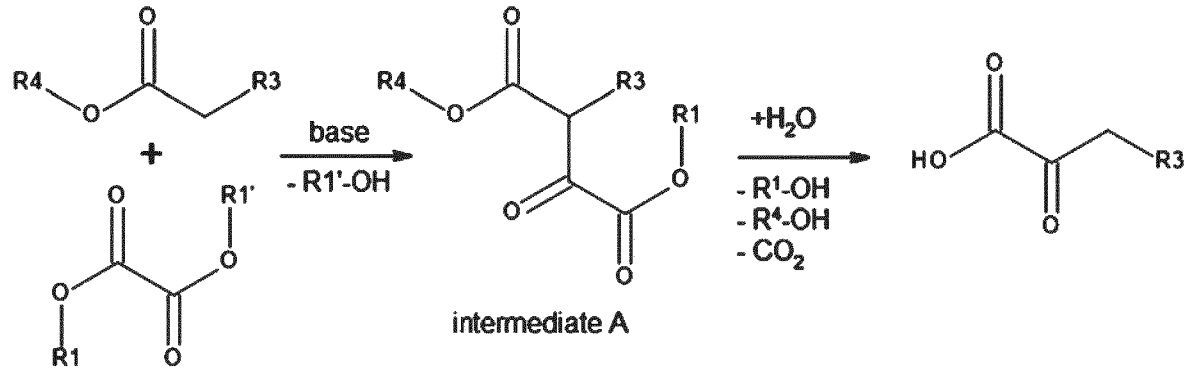


Fig. 2


R4
R3
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- R1'-OH
R1'
R1
intermediate A
+H2O
- R1-OH
- R4-OH
- CO2
HO

Fig. 3

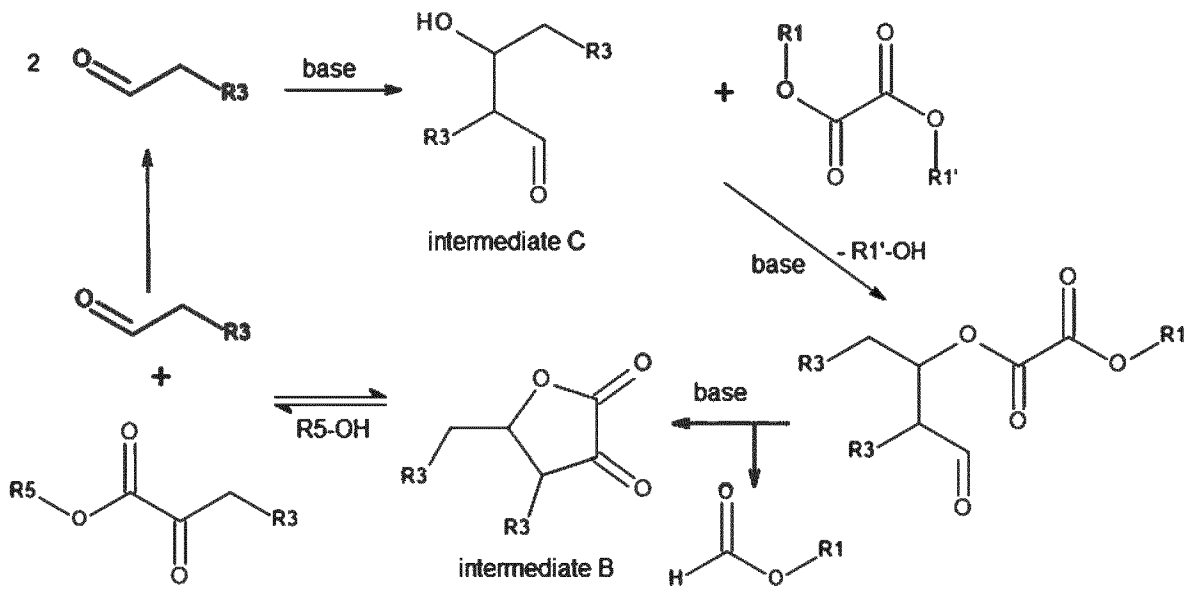
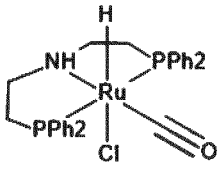
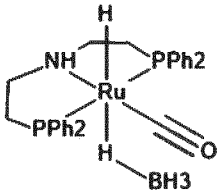

2
base
HO
R3
intermediate C
R1
R1'
- R1'-OH
R5-OH
R5
intermediate B
H

Fig. 4

Takasago:



C1



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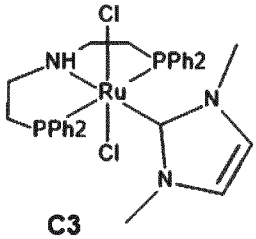

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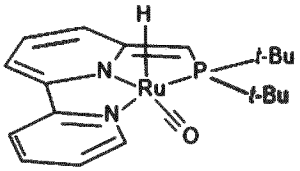

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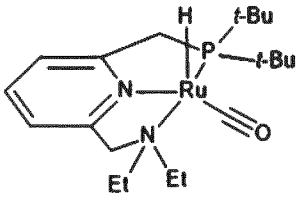

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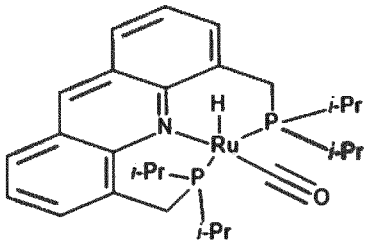
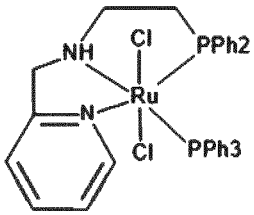


C6

Gusev:



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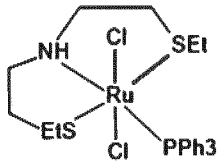
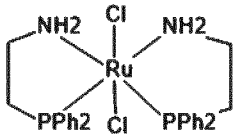


C8

Firmenich:



C9

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/066838

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C67/32 C07C29/147 C07C31/20 C07C69/738
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)
C07C

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, 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	Nakamura Kaoru ET AL: "Stereochemical Control on Yeast Reduction of a-Keto Esters. Reduction by Immobilized Bakers' Yeast in Hexane1", J. Org. Chem, 1 January 1988 (1988-01-01), pages 2589-2593, XP055862720, Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/jo00246a035?casa_token=g_q3h6S6EdAAAAAA:NKaNMa-kvUErY4B_jadBSMdJoDnG2BgXt9jUjuHdTPuz3-z4qS5KSBEBoLOs4Ro5qe6F871gTh6CqGXJ [retrieved on 2021-11-17] page 2592; table I; compounds 1d, 2d page 2593 ----- -/--	1-13

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

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2022	23/08/2022

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/066838

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019/029808 A1 (SYMRISE AG [DE]) 14 February 2019 (2019-02-14)	14,15
Y	paragraphs [0002], [0017] - [0021], [0088] - [0095]; claims 1-4,10	1-13
X	WO 2019/152569 A2 (INOLEX INVESTMENT CORP [US]) 8 August 2019 (2019-08-08) cited in the application	14,15
Y	the whole document	1-13
Y	GAO SHAOCHAN ET AL: SYNLETT , vol. 27, no. 11 1 January 2016 (2016-01-01), pages 1748-1752, XP055826996, DE ISSN: 0936-5214, DOI: 10.1055/s-0035-1561971 Retrieved from the Internet: URL:https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0035-1561971.pdf products 2, conditions A; examples 17-18; table 2	1-13

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/066838

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		KR 20190016877 A	19-02-2019
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		US 2021085579 A1	25-03-2021
		WO 2019029808 A1	14-02-2019
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		US 2020189995 A1	18-06-2020
		WO 2019152569 A2	08-08-2019