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(54) **Title**: METHOD FOR PRODUCING MONOMETHYL FUMARATE COMPOUNDS

(57) **Abstract**: The present invention relates to a novel method for preparing monomethyl fumarate, which can preferably be used in the treatment and/or prevention of systemic diseases, autoimmune diseases, inflammatory diseases such as multiple sclerosis and psoriasis. Further, the present invention relates to the use of specific compounds as intermediates in the process for preparing a monomethyl fumarate prodrug.

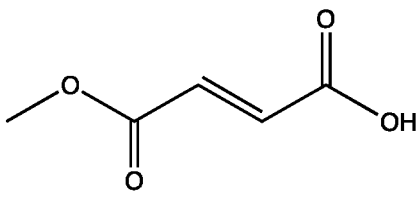
Method for producing monomethyl fumarate compounds

The present invention relates to a novel method for preparing monomethyl fumarate compounds, which can preferably be used in the treatment and/or prevention of systemic diseases, autoimmune diseases, inflammatory diseases such as multiple sclerosis and psoriasis. Further, the present invention relates to the use of specific compounds as intermediates in the process for preparing a monomethyl fumarate prodrug.

Background of the invention

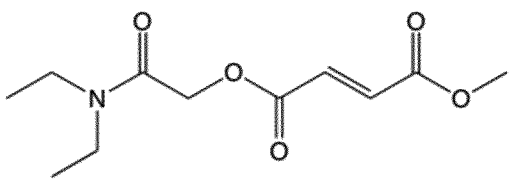
Dimethyl fumarate (hereinafter referred to as DMF) is an oral therapeutic agent which is reported to reduce the rejection often occurring in connection with an organ transplantation (host versus graft reaction). Further, DMF is approved to be suitable as medicament for the treatment or prevention of a variety of disease and is used in the treatment of autoimmune diseases such as multiple sclerosis and psoriasis.

When taken orally DMF is rapidly hydrolyzed for example by the acidic ambience of the stomach or by esterases in the intestine to monomethyl fumarate (hereinafter referred to as MMF), which can be regarded as a metabolite of DMF and which is characterized by the following chemical Formula (2):



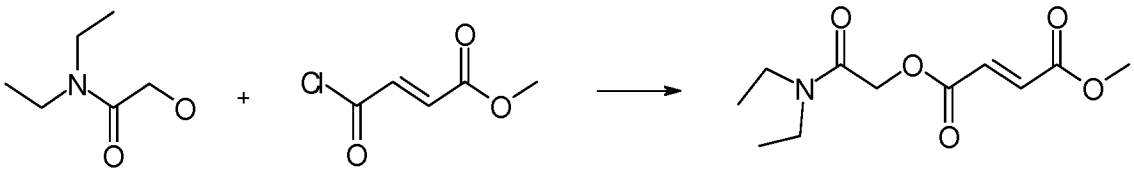
Formula (2)

In the art different MMF prodrugs are known. For example WO 2010/022177 A2 and WO 2013/181451 A1 disclose the following compound



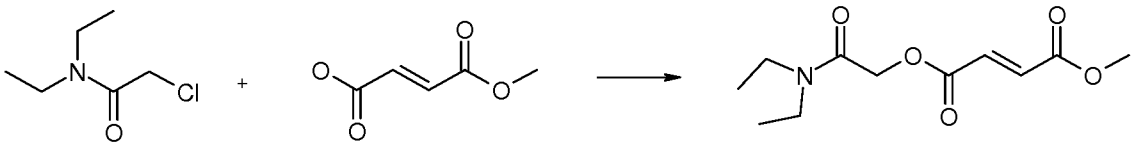
.

The compound can be prepared by the following route:



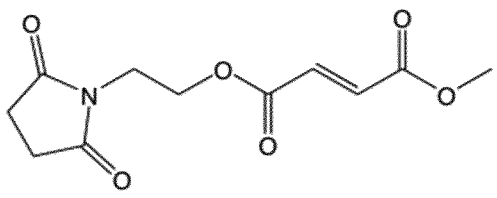
This process includes the use of the carboxylic acid chloride of monomethyl fumaric acid which is instable and difficult to handle. For these reasons the carboxylic acid chloride of monomethyl fumaric acid should not be stored but prepared freshly before use, which can be inconvenient, especially when required in a large scale production process. Additionally the yield of the above reaction seems to be disadvantageously low. Furthermore a chromatographic purification is necessary.

Alternatively the above compound can be synthesized by the following route:

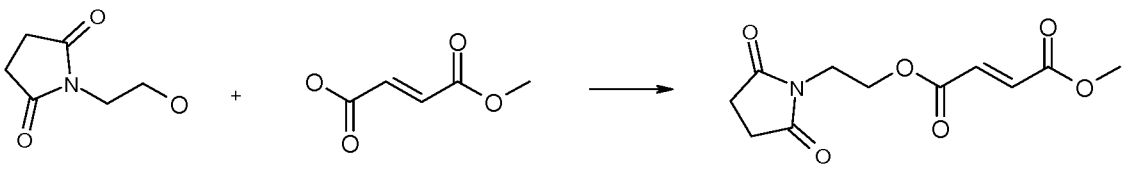


However, in the above methods the required auxiliary alkaline compound Cs_2CO_3 or $CsHCO_3$ is very expensive and thus the process is undesirable from an economic point of view. Further, a use of the less expensive alternative K_2CO_3 or $KHCO_3$ is reported to lead to a poor yield. Furthermore a chromatographic purification is necessary.

Further, US 8 669 281 B1 and WO 2014/152494 A1 disclose the following compound



The compound is reported to be prepared by the following route:



The above method requires the expensive coupling agent HBTU (*N, N, N', N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl) uronium hexafluorophosphate and the yield is reported to be about 30 to 40%. Furthermore, by-products deriving from coupling reagents are present in the reaction mixture, which have to be removed afterwards, which is done in the state of the art via chromatographic purification.

Consequently, there is still a need for a new route of synthesis, i.e. for a method for the preparation of MMF compounds such as MMF-prodrugs, which can be applied in a simple and effective manner.

Hence, it was an object of the present invention to overcome the drawbacks of the above-mentioned processes. In particular, it was an object of the present invention to provide a process for preparing specific unsymmetric fumaric acid esters with an advantageous yield and quality, even when used in a large scale process.

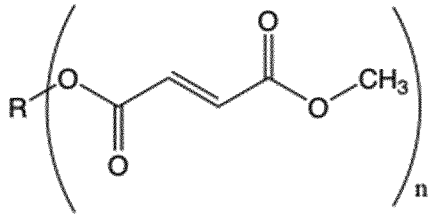
Further, the use and handling of instable carboxy acid chloride of monomethyl fumarate should be avoided.

It was a further object of the invention to provide a method for preparing fumaric acid esters, wherein expensive and/or so called "sophisticated" coupling agent should be avoided.

According to the present invention, the above objectives are achieved by the specific method described herein for preparing a compound according to Formula (I).

The present invention has unexpectedly solved the above objectives by the provision of a new synthetic approach for preparing a compound according to Formula (I).

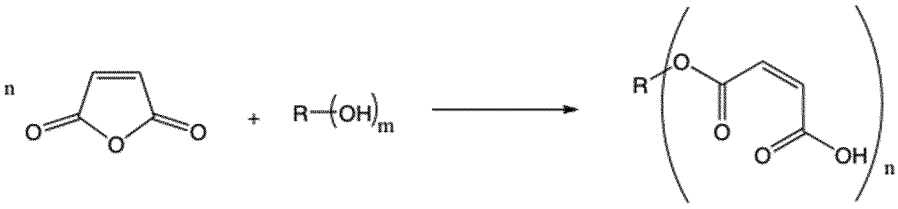
Hence, the subject of the present invention is a method for preparing a compound according to Formula (I)



Formula (I)

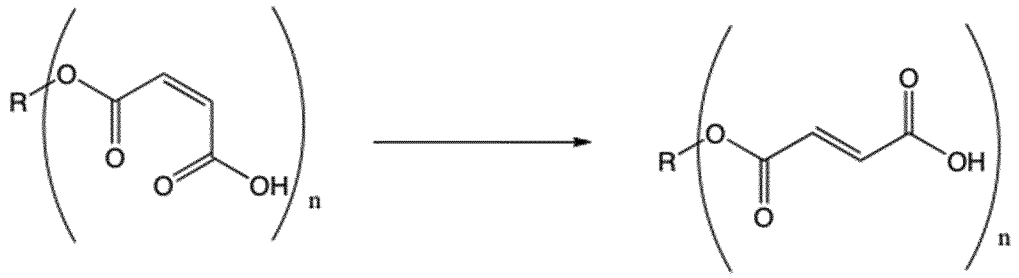
comprising the steps of

(a) reacting maleic acid anhydride with an alcohol according to Formula (IV) to give a compound according to Formula (III)



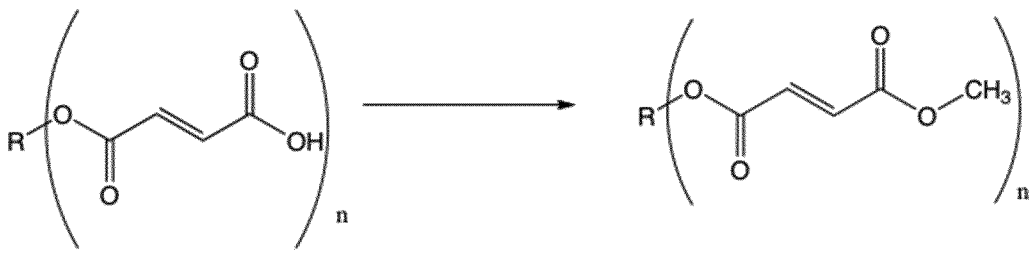
Formula (IV) Formula (III)

(b) isomerizing a compound according to Formula (III) to give a compound according to Formula (II)



Formula (III) Formula (II)

(c) esterifying a compound according to Formula (II) to give a compound according to Formula (I)



Formula (II) Formula (I)

wherein
R is an organic residue, provided that R is not hydrogen or methyl,
m is a natural number from 1 to 4 and
n is is natural number with $1 \leq n \leq m$.

It was unexpectedly found that the method of the present invention allows advantageous yields and quality of the resulting compounds. Additionally, with the method of the invention the use of labile carboxylic acid chlorides and/or expensive coupling agents can be advantageously avoided. Furthermore, the product is obtained in high crude product quality and in pharmaceutical quality through crystallisation and without the need of a chromatographic purification step.

A further subject of the present invention is the use of the compound according to Formula (II) and/or (III) as an intermediate in a process for preparing a MMF-prodrug.

Detailed description of the invention

The present invention relates to a method for preparing a compound according to Formula (I) comprising steps (a), (b) and (c). In a preferred embodiment of the invention the above mentioned steps (a), (b) and (c) can be carried out consecutively.

In the above Formulae (I), (II) and (III) generally R is an organic residue, provided that R is not hydrogen or methyl. In that regard the term "organic residue" generally refers to a residue known in organic chemistry. Preferably, the skeleton of the organic residue contains predominately carbon atoms, nitrogen atoms and/or oxygen.

In a preferred embodiment the atom of the residue R, which is covalently to the oxygen atom of the adjacent carboxylic group, is a carbon atom.

In a preferred embodiment of the invention R can be an aliphatic residue. An aliphatic residue is a non-aromatic hydrocarbon compound which can comprise, apart from carbons and hydrogen atoms, for example also oxygen, sulphur and nitrogen atoms.

In a preferred embodiment R can be a substituted or unsubstituted, linear, divalent or trivalent aliphatic residue with 2 to 30 carbon atoms. More preferably R comprises 3 to 20 carbon atoms, or 4 to 15 or 5 to 12 or 6 to 10 carbon atoms or combinations thereof.

In case that R is a substituted aliphatic residue, the one or more substituents can preferably be selected independently from one or more of the following substituents: alkyl groups with 1 to 6 carbon atoms, halogen, nitro, nitrile, carboxylic group, carboxylic esters and carboxylic amide, urea, phenyl, aldehyde, sulfate, amino, hydroxy, methoxy, mercapto, methylthio, phenyl and =O, such that the corresponding -CO-group is formed.

Examples of an alkyl group with 1 to 6 carbon atoms are methyl, ethyl, propyl, isopropyl, butyl, tert.butyl, isobutyl, pentyl, neopentyl and hexyl.

Further, in case that R is a substituted aliphatic residue, it is included that substituents are bonded with each other such that a cyclic residue is formed.

In a preferred embodiment R can be $-(CH_2CHXO)_t-(CH_2CHX)-OH$ or $-(CHXCH_2O)_t-(CHXCH_2)-OH$, wherein t is 1 to 10, preferably 2 to 5, and wherein X is selected from methyl and ethyl. It is further preferred that t is 3, such that the corresponding R is $-(CH_2CHXO)_3-(CH_2CHX)-OH$ or $-(CHXCH_2O)_3-(CHXCH_2)-OH$, wherein X is selected from methyl and ethyl.

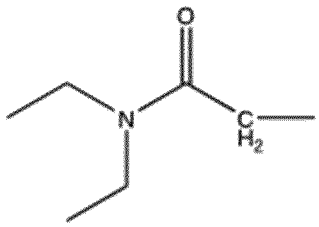
In an alternatively preferred embodiment R can be $-((CH_2)_3O)_t-(CH_2)_3-OH$, wherein t is 0 to 10, preferably 2 to 8. In a more preferred embodiment R is $-((CH_2)_2O)_t-(CH_2)_2-OH$, and t is 2, 3, 4, 5 or 6, in particular t is 3.

In a preferred embodiment R can be $-((CH_2)_2O)_t-(CH_2)_2-OH$, wherein t is 0 to 10, preferably 2 to 8. In a more preferred embodiment R is $-((CH_2)_2O)_t-(CH_2)_2-OH$, and m is 2, 3, 4, 5 or 6, in particular t is 3, such that the corresponding R is $-((CH_2)_2O)_3-(CH_2)_2-OH$.

In an alternative a preferred embodiment, R can be a substituted or unsubstituted aryl group or a substituted or unsubstituted hetero aryl group.

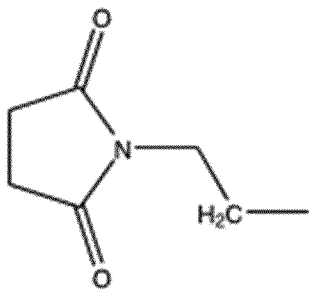
Generally, the term "unsubstituted aryl" group refers to a residue with an aromatic skeletal structure, wherein the ring atoms of the aromatic skeletal structure are carbon atoms.

In a particluarly referred embodiment residue R is 3-dimethylamino-3-oxoethyl. 3-dimethylamino-3-oxoethyl can be represented by the following Formula



In case that R is 3-dimethylamino-3-oxoethyl, the method of the invention is directed to the preparation of (E)-But-2-enedioic acid diethylcarbamoylmethyl ester methyl ester.

In an alternatively particularly preferred embodiment residue R is 2-(2,5 dioxopyrrolidin-1-yl)ethyl. 2-(2,5 dioxopyrrolidin-1-yl)ethyl can be represented by the follwing Formula



In case that R is 2-(2,5 dioxopyrrolidin-1-yl)ethyl, the method of the invention is directed to the preparation of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester.

Examples for aryl groups are phenyl, biphenyl, naphthyl, anthranyl, fluorenyl, indanyl, phenalenyl, acenaphthyl, indyl, pyryl and chrysenyl.

An unsubstituted heteroaryl group refers to a residue with an aromatic skeletal structure, wherein one or more of the ring atoms of the aromatic skeletal structure are not carbon atoms but hetero atoms such as nitrogen, oxygen, sulphur and/or phosphor.

Examples for heteroaryl groups are succinimidyl, pyrryl, pyrrazolyl, imidazolyl, triazolyl, furyl, oxalyl, thienyl, isothiazolyl, thiazolyl, pyridyl, pyrazidyl, pyrazyl, pyrimidyl, indolyl, isoindolyl, benzofuranyl, benzimidazyl, indazolyl, quinolinyl, isoquinolinyl, triazinyl and thienyl.

In another preferred embodiment, the aryl group or hetero aryl group can bear one or more substituents. Examples for substituents are unsubstituted or substituted alkyl groups with 1 to 6 carbon atoms, unsubstituted or substituted alkoxy groups with 1 to 6 carbon atoms, carboxylic acid, carboxylic acid esters, carboxamides, carbonyl, aryloxy groups, optionally protected amines, optionally protected monoalkyl amines, optionally protected monoarylamines, dialkylamines, diarylamines, silyl ethers, halogens or optionally protected hydroxyl groups.

In the method of the present invention protection groups can be used. Preferred protection groups for amines or mono-substituted amines are for example Boc (tert-butyloxycarbonyl), Z or Cbz (benzyloxycarbonyl), benzyl, benzhydryl and Fmoc (fluorenylmethylenoxycarbonyl).

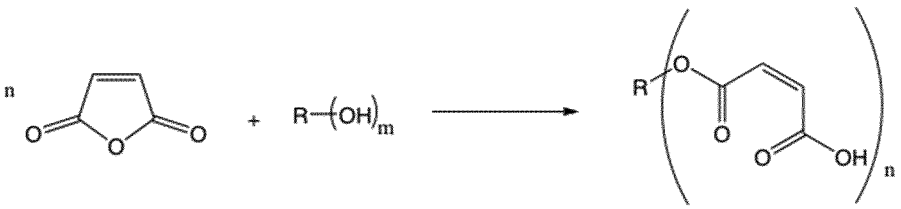
Preferred protection groups for hydroxyl groups are for example esters, such as benzoic acid esters or pivalic acid esters, and trisubstituted silylethers, such as trimethylsilyl-ether, triethylsilylether, tert-butyldimethylsilylether and tert-butyl diphenylsilylether.

Further, m is a natural number from 1 to 4; i.e. m is 1, 2, 3 or 4. That means R can preferably comprise from one up to four hydroxy groups. It is preferred that m is 1.

Further, n is a natural number with $1 \leq n \leq m$. n corresponds to the numbers of MMF-residues bonded to R. In case that n is smaller than m that means that not all of the

hydroxy groups comprised by R are reacted with maleic acid anhydride in step (a). It is preferred that n is 1.

In step (a) the reaction of maleic acid anhydride with an alcohol according to Formula (IV) to a compound according to Formula (III) can be represented by the following scheme:



Formula (IV) Formula (III)

The alcohol according to Formula (IV) can be submitted to an esterification with maleic acid anhydride. In case that m > n the one or more hydroxy groups which are considered to not react with maleic anhydride can preferably be protected with a protection group for alcohols as described above. Further, in case that R comprises amino or alkylamino groups these groups can preferably be protected with a protection groups for amines as described above. After the esterification reaction, the corresponding protection groups can preferably be removed by a suitable reaction.

In step (a) the reaction can be preferably carried out in an organic solvent, preferably an aprotic organic solvent.

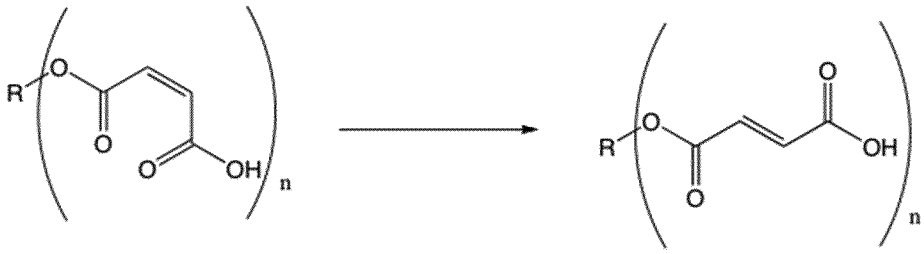
Suitable organic solvents can for example be toluene, benzene, xylene, dimethyl-formamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, acetone, ethylacetate, hexane, heptane, octane, cyclic and acyclic alkylethers, acetonitrile, benzonitrile, anisol, cumene, chlorobenzene, cyclohexane, methylcyclohexane, ethylacetate, dichloro-methane, dichloroethane, trichloroethane, tetrachloroethane, dimethoxyethane, diethoxyethane and combinations thereof. Particularly preferred are toluene, acetone and acetonitrile. In an alternatively particularly preferred embodiment step (a) can be carried out in the absence of a solvent.

The reaction in step (a) can be preferably carried out at a temperature from 0°C to 150°C, more preferably from 20°C to 140°C, still more preferably from 40° to 100°C, in particular from 50°C to 90°C. In case that the reaction is carried at temperatures below 23°C it is preferred that a catalyst is added. A catalyst can be an alkaline substance such as an amine. Amines being suitable as catalyst can for example be diethyl methylamine, triethylamine, diisopropyl ethylamine, dimethyl aniline, diethyl aniline. Particularly preferred is triethylamine.

Further, the reaction of step (a) can be preferably subjected to a mechanical movement such as stirring.

In a preferred embodiment the reaction time of step (a) can be between 2 hours and 24 hours, preferably between 4 hours and 15 hours, in particular between 6 hours and 12 hours. Subsequently, if used, the solvent can be removed under elevated temperatures and/or preferably under reduced pressure. If desired, the product can be further purified, for example by recrystallization.

In step (b) the isomerisation of a compound according to Formula (III) to a compound according to Formula (II) is represented by the following scheme:



Formula (III) Formula (II)

The isomerisation of a compound according to Formula (III) to a compound according to Formula (II) can be regarded as the isomerisation of a compound comprising maleic acid ester to a compound comprising a fumaric acid ester.

In step (b) the reaction can be preferably carried out in an organic solvent, preferably an aprotic organic solvent as described above with regard to step (a). Toluene, acetonitrile

and acetone are particularly preferred. Alternatively preferred step (b) can be carried out in the absence of a solvent.

The reaction in step (b) can be preferably carried out at a temperature from 0°C to 120°C, more preferably from 20°C to 100°C, still more preferably from 30° to 90°C, in particular from 50°C to 80°C. Further, the reaction of step (b) can be preferably subjected to a mechanical movement such as stirring.

In a preferred embodiment the reaction time of step (b) can be between 1 hour and 12 hours, preferably between 1.5 hours and 8 hours, in particular between 2 hours and 6 hours.

It is further preferred that the reaction of step (b) is carried out in the presence of a catalyst. Suitable catalysts can for example be a trialkylsilylchloride, a trialkoxy-silychloride and/or a carboxylic acid chloride of an organic acid containing 1 to 6 carbon atoms, preferably a trialkylsilylchloride and/or a carboxylic acid chloride of an organic acid containing 1 to 6 carbon atoms, in particular a carboxylic acid chloride of an organic acid containing 1 to 6 carbon atoms.

Alkyl can be preferably an alkyl group with 1 to 6 carbon atoms. Examples of an alkyl group with 1 to 6 carbon atoms are methyl, ethyl, propyl, isopropyl, butyl, tert.butyl, isobutyl, pentyl, neopentyl and hexyl. Preferred are methyl and ethyl, in particular methyl.

Alkoxy can preferably be an alkoxy group with 1 to 6 carbon atoms. Examples of an alkoxy group with 1 to 6 carbon atoms are methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert.butoxyl, isobutoxy, pentoxy. Preferred are methoxy and ethoxy, in particular methoxy.

Examples of organic acids with 1 to 6 carbon atoms are formic acid, acetic acid, oxalic acid, propionic acid, malonic acid, butyric acid, succinic acid, caproic acid, 1,6-hexanedicarboxylic acid. In particular preferred is acetic acid.

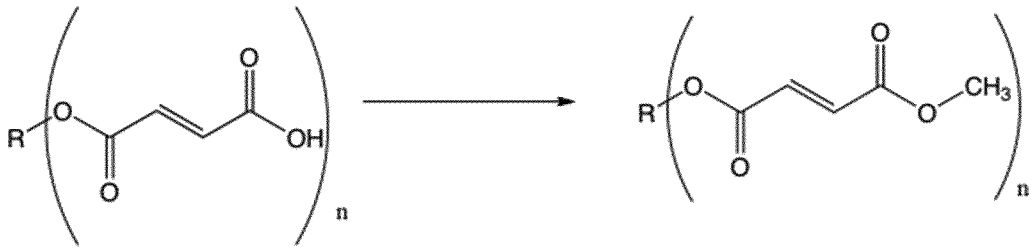
Thus, step (b) is preferably carried out in the presence of acetyl chloride as catalyst.

The catalyst can preferably be present in an amount from 0.01 to 1.0 equivalents, preferably from 0.02 to 0.1 equivalents, in particular from 0.03 to 0.07 equivalents of the compound according to Formula (III).

If desired, the product of step (b) can be further purified, for example by recrystallization.

In a preferred embodiment step (a) and step (b) can preferably be carried out as one-pot reaction. An one-pot reaction can be considered as a reaction wherein successive chemical reaction are carried in a single reactor thereby avoiding an intermediate work-up and/or purification process.

In step (c) the esterification of a compound according to Formula (II) to a compound according to Formula (I) is represented by the following scheme:



Formula (II) Formula (I)

The compound according to Formula (I) can be regarded as the methyl ester of the compound according to Formula (II). The part of the compound according to Formula (I) within the brackets can be regarded as mono methyl ester of fumaric acid (MMF). The compound according to Formula (I) generally are referred to herein as monomethyl fumarate compounds. In particular, they could be regarded as unsymmetric monomethyl fumarate compounds. In a preferred embodiment the monomethyl fumarate compound (I) is a monomethyl fumarate prodrug.

Generally, a prodrug can be regarded as a substance that is administered to a subject (preferably human) in a pharmacologically inactive or pharmacologically less than fully active form, and is subsequently converted in the body of the subject to an active drug, preferably through metabolic processes occurring in the body of the subject. In other words, a prodrug usually serves as a type of 'precursor' to the intended drug. In other words, a MMF prodrug defined as a compound, which is metabolized in the human body to give MMF. Further, a MMF prodrug preferably can be used in the treatment or prevention of systemic diseases, autoimmune diseases, inflammatory diseases such as multiple sclerosis and psoriasis. Concerning definition and use of MMF prodrugs it is additionally referred to WO 2015/158817, WO 2015/128488, and WO 2015/082590.

In step (c) the compound according to Formula (II) is reacted to give a compound according to Formula (I). Generally, the reaction can be carried out by adding a methyl-donating compound. Preferably the methyl-donating compound can be selected from e.g. methyl chloroformates, methyl halides, methyl sulfonates, methyl oxonium salts, dimethyl sulfates, dimethyl carbonates, tetramethylammonium salts, diazomethane, trimethylsilyldiazomethane, dimethyl acetals of N,N-dimethylformamide, O-methyl-caprolactams, trimethoxy orthoester or methanol in combination with esterification catalysts such as acids.

In a preferred embodiment of the invention step (c) is carried out in the presence of methanol, methyl chloroformate or MeX, wherein X is a leaving group.

In a more preferred embodiments step (c) is carried out in the presence of methanol in combination with an esterification catalyst. An esterification catalyst can for example be an acid such as hydrochloric acid, sulfuric acid or p-toluene sulfonic acid. Further, the reaction can be preferably subjected to a mechanical movement such as stirring. The reaction can be preferably carried out at a temperature from 0°C to 150°C. It is particular preferred to carry out the reaction under reflux conditions. In a preferred embodiment the reaction time can be between 30 minutes and 24 hours, preferably between 45 minutes and 18 hours, in particular between 1 hour and 4 hours.

In a more preferred embodiments step (c) is carried out in the presence of MeX, wherein X is a leaving group. Examples for leaving groups are halides such fluoro chloro, bromo, iodo; acycloxy groups such as acetoxy, benzoyloxy, alkoxycarbonyl, aryloxycarbonyl; sulfonates such as mesyloxy, tosyloxy, trifluormethansulfoxy, benzylsulfoxy; aryloxy groups such as 2,4-dinitrophenoxy. In a preferred embodiment X can be a sulfonate or a halide selected from chloride, bromide and iodide. Particular preferred is methyliodide.

The reaction can be preferably carried out in an organic solvent, preferably an aprotic organic solvent. Suitable aprotic solvents correspond to the ones described above. Preferred are cyclic alklyethers such as tetrahydrofuran and dioxane, acetonitrile, dimethyl sulfoxide, dimethylformamide, and N-methyl pyrrolidone (NMP). Further, the reaction can be preferably subjected to a mechanical movement such as stirring. The reaction can be preferably carried out at a temperature from 0°C to 100°, more preferably from 20°C to 90°C, in particular from 30°C to 80°C. In a preferred embodiment the reaction time can be between 30 minutes and 24 hours, preferably between 45 minutes and 18 hours, in particular between 1 hour and 4 hours.

In a particularly preferred embodiment of the invention step (c) is carried out in the presence of methyl chloroformate. The reaction with methyl chloroformate can be preferably carried out in an organic solvent, an aprotic organic solvent. Suitable aprotic solvents correspond to the ones described above in step (a). Preferred are toluene, acetone and ethylacetate, in particular ethylacetate and acetone. It is further preferred that the reaction with methyl chloroformate is carried out in the presence of an auxiliary alkaline compound. Suitable alkaline compounds are for example triethylamine, dimethylaminopyridin (DMAP), diisopropylethylamine, in particular DMAP or triethylamine. DMAP is especially preferred. Also triethylamine is especially preferred. Further suitable alkaline compounds are inorganic alkaline compounds such as phosphates, hydrogen phosphates, sulphates, carbonates and bicarbonates. Preferred are bicarbonates and carbonates of alkali and earth alkali metals. Particularly preferred is sodium carbonate. Further, the reaction with methyl chloroformate is preferably carried out at temperatures of -10°C to 45°C, preferably of -8°C to 35°C, more preferably

of -6°C to 25°C, in particular of -5°C to 5°C. Further, completion of the reaction takes preferably from 0.5 to 6 hours, more preferably from 1 to 5 hours, especially from 2 to 4 hours. Further, the reaction can be preferably subjected to a mechanical movement such as stirring.

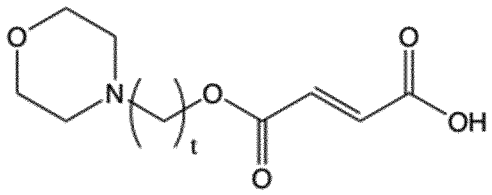
In a preferred embodiment of the invention step (a), step (b) and step (c) can preferably be carried out as one-pot reaction.

A further subject of the invention is the use of the compound according to Formula (II) and/or (III) as an intermediate in a process for preparing a monomethyl fumarate compound, in particular in a process for preparing a MMF-prodrug. As a consequence, a further subject of the invention is the use of the compound according to Formula (II) and/or (III) as an intermediate in a process for preparing a compound, in particular a monomethyl fumarate compound, suitable for use in the treatment and/or prevention systemic diseases, autoimmune diseases, inflammatory diseases such as multiple sclerosis and psoriasis. In the above mentioned use according to the present invention in particular the below illustrated compounds according to Formulae (II-1) – (II-12) are employed.

Still another subject of the invention is a method for preparing a monomethyl fumarate compound, in particular in a process for preparing a MMF-prodrug, wherein in said method the compound according to Formula (II) and/or (III) occurs as intermediate, and wherein said compound according to Formula (II) is subsequently methylated. Especially, the process includes the use of compounds according to Formulae (II/1) – (II/12) as illustrated below.

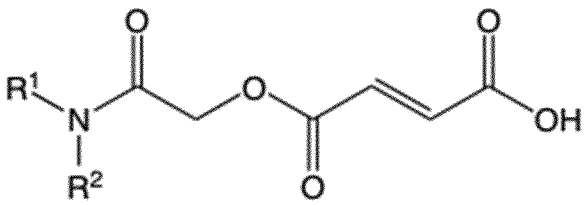
The compound according Formula (II) can be regarded as a fumaric acid ester and the compound according to Formula (III) as maleic ester. Contrary to the prior art processes in which the monomethyl fumarate is coupled to a complex residue, the compounds according to Formula (II) and/or (III) are already bonded with the complex organic residue. Thus, the free carboxylic group of the compound according to Formula (II) just has to be transferred to the corresponding methyl ester to achieve the MMF-prodrug.

In a preferred embodiment the compound according to Formula (II) is represented by the Formulae (II/1) to (II/12)



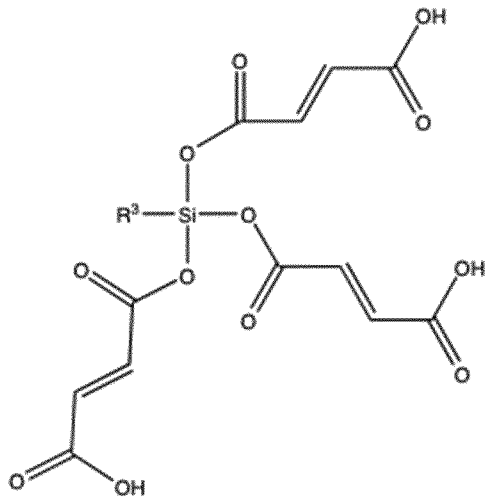
Formula (II/1),

wherein t is an integer from 1 to 6



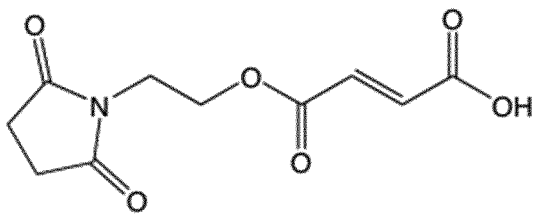
Formula (II/2)

wherein R^1 and R^2 are independently hydrogen or an alkyl with 1 to 6 carbon atoms

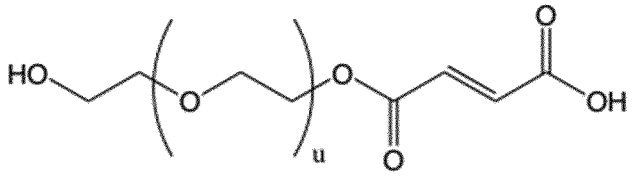


Formula (II/4)

wherein R^3 is an alkyl with 1 to 10 carbon atoms

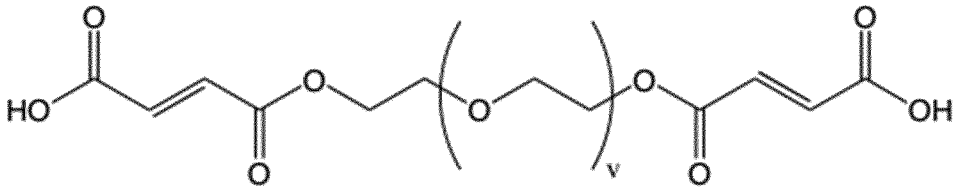


Formula (II/5)



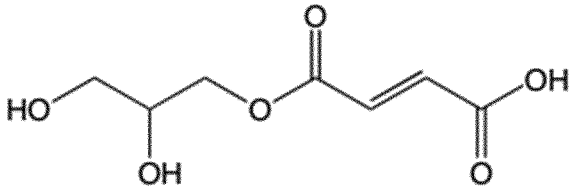
Formula (II/6)

wherein u is an integer from 1 to 10, preferably 2 to 6, in particular u is 3,

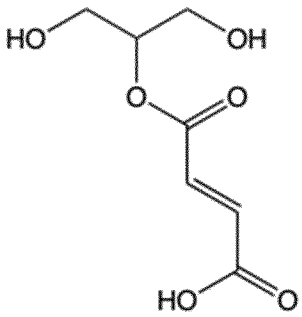


Formula (II/7)

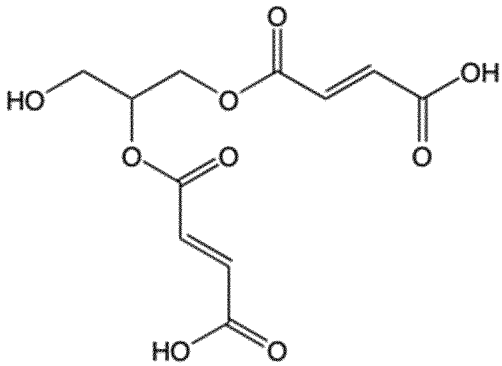
wherein v is an integer from 1 to 10, preferably 2 to 6, in particular v is 3,



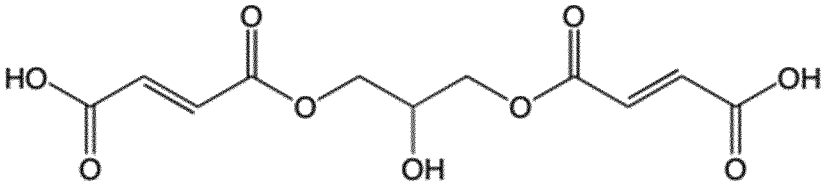
Formula (II/8)



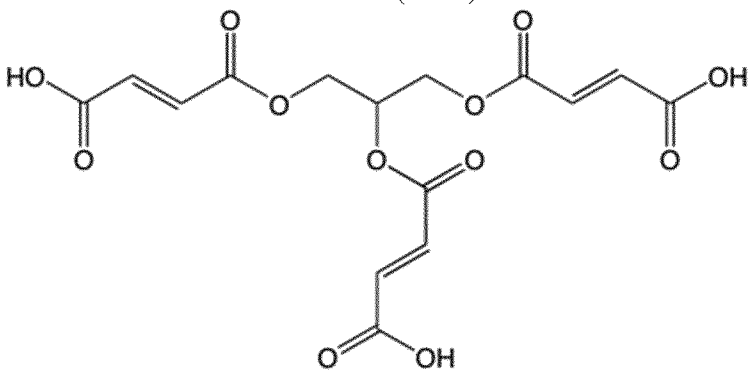
Formula (II/9)



Formula (II/10)



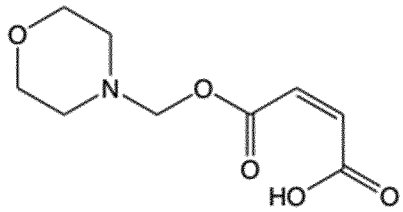
Formula (II/11)



Formula (II/12)

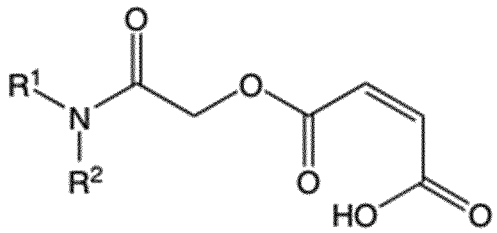
In particular, Formula (II/5) is particularly preferred.

In a preferred embodiment the compound according to Formula (III) is represented by Formulae (III/1) to (III/12)



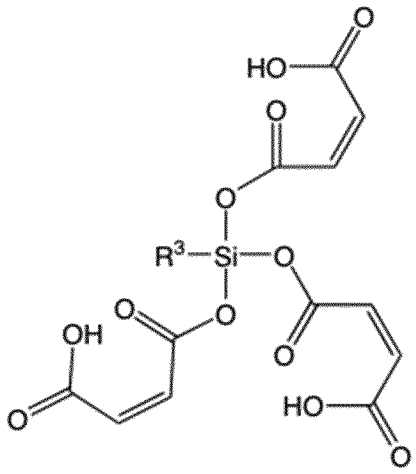
Formula (III/1)

wherein t is an integer from 1 to 6



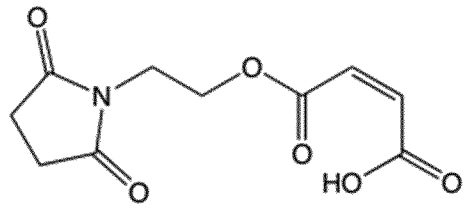
Formula (III/2)

wherein R^1 and R^2 are independently hydrogen or an alkyl with 1 to 6 carbon atoms

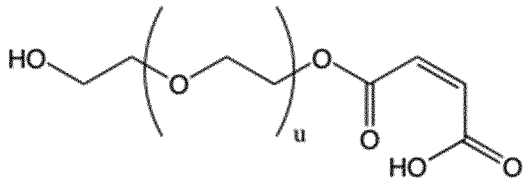


Formula (III/4)

wherein R^3 is an alkyl with 1 to 10 carbon atoms

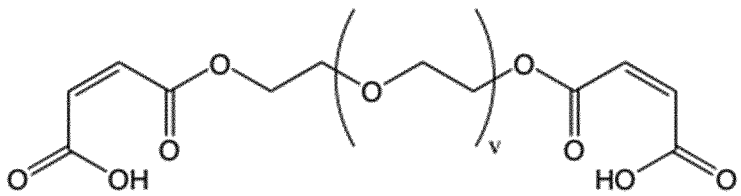


Formula (III/5)



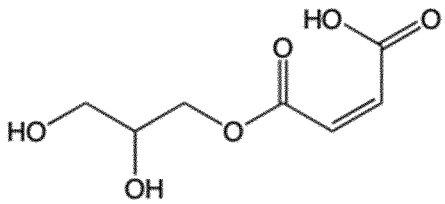
Formula (III/6)

wherein u is an integer from 1 to 10, preferably 2 to 6, in particular u is 3,

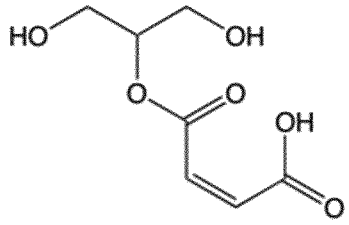


Formula (III/7)

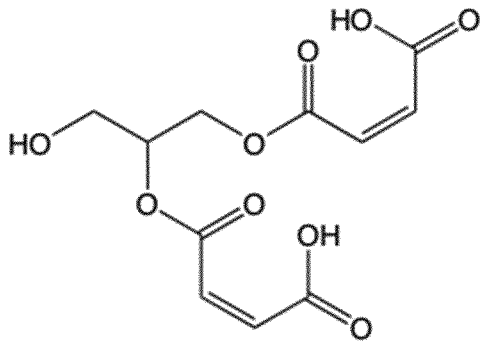
wherein v is an integer from 1 to 10, preferably 2 to 6, in particular v is 3,



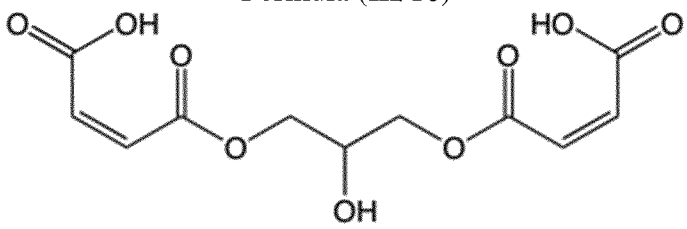
Formula (III/8)



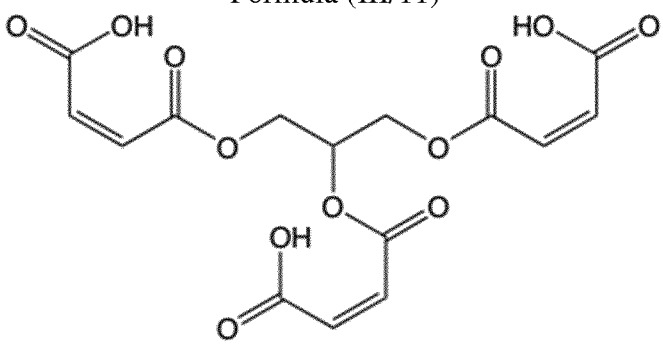
Formula (III/9)



Formula (III/10)



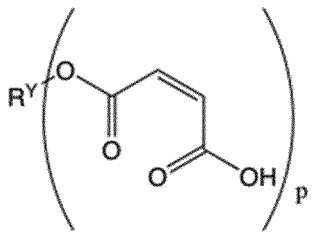
Formula (III/11)



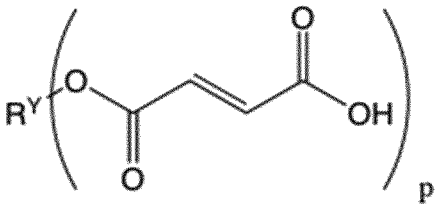
Formula (III/12)

In particular, Formula (III/5) is particularly preferred.

A further aspect of the invention concerns a method for isomerisation of



to give



wherein

R^Y is an organic residue with the proviso that R^Y is not hydrogen and

p is an integer from 1 to 4

and wherein preferably the isomerisation can be carried out in the presence of trialkylsilylchloride or trialkoxysilylchloride.

In the above mentioned formulae R^Y is an organic residue with the proviso that R^Y is not hydrogen. An organic residue R^Y can be defined as described above with regard to the residue R.

In a preferred embodiment R^Y can be an aliphatic residue as described above. In a particular preferred embodiment R^Y is methyl.

In the above mentioned formulae p can be an integer from 1 to 4, preferably 1, 2 or 3, in particular 1.

The isomerisation is preferably carried out in the presence of a trialkylsilylchloride or a trialkoxysilylchloride.

The trialkylsilychloride preferably comprises alkyl groups with 1 to 6 carbons atoms, respectively. Examples of an alkyl group with 1 to 6 carbon atoms are methyl, ethyl, propyl, isopropyl, butyl, tert.butyl, isobutyl, pentyl, neopentyl and hexyl. Especially preferred is methyl. In a preferred embodiment the three alkyl groups are identical. Thus, in this aspect the isomerisation is preferably carried out in the presence of trimethylsilylchoride.

Alternatively, the trialkoxysilylchloride preferably comprises alkoxy groups with 1 to 6 carbons atoms, respectively. Examples of an alkyl group with 1 to 6 carbon atoms are methoxy, ethoxyl, propoxy, isopropoxy, butoxy, tert.butoxy, isobutoxy, pentoxy, neo-pentoxy and hexoxy. Especially preferred is methoxy and ethoxy, in particular methyoxy. In a preferred embodiment the three alkyl groups are identical. Thus, in this aspect the isomerisation is preferably carried out in the presence of trimethoxysilyl-choride.

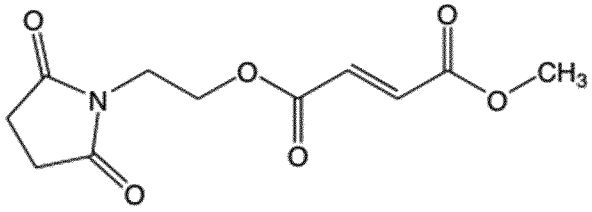
The isomerisation can be preferably carried out in an organic solvent, preferably an aprotic organic solvent as described above with regard to step (a). Toluene is particularly preferred. Alternatively preferred step (b) can be carried out in the absence of a solvent. Further, the isomerisation can be preferably carried out at a temperature from 0°C to 120°C, more preferably from 20°C to 100°C, still more preferably from 30° to 90°C, in particular from 50°C to 80°C. Further, the reaction of step (b) can be preferably subjected to a mechanical movement such as stirring. The reaction time might be between 1 hour and 36 hours, preferably between 1.5 hours and 24 hours, in particular between 2 hours and 6 hours.

In a particular preferred embodiment of this aspect of the invention R^Y can be methyl, p can be 1 and the isomerisation in carried out in the presence of trimethylsilychloride. In that case the present invention is related to the conversion of monomethyl maleate to monomethyl fumarate in the presence of trimethylsilychloride.

WO 2014/197860 describes the formation of monomethyl fumarate via isomerisation of monomethyl maleate in the presence of carboxy acid chloride, in particular in the presence of acetyl chloride. However, this process is reported to be improvable with respect to the yield of the product. It was unexpectedly found that the method for isomerisation of this aspect of the present invention provides a higher yield of the desired product.

In a further aspect the present invention relates to a method for preparing (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester and to different

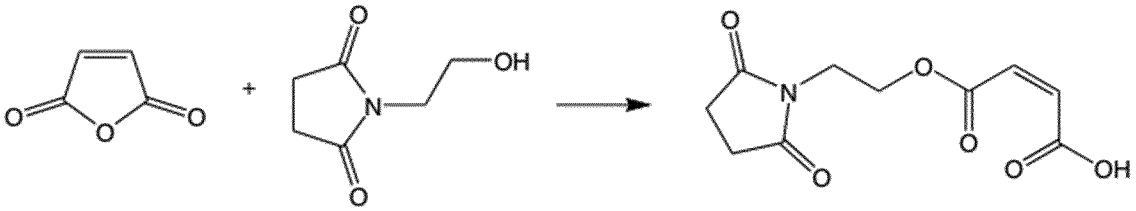
polymorphs of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester. (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester can be represented by the following Formula (I')



Formula (I')

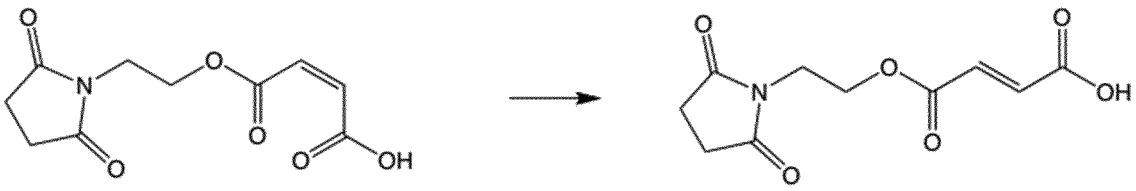
The method for preparing (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to Formula (I') comprises the steps of

(a') reaction of maleic acid anhydride with an alcohol according to Formula (IV') to a compound according to Formula (III')



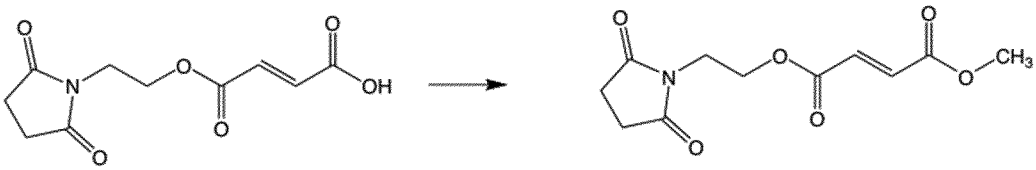
Formula (IV') Formula (III')

(b') isomerisation of a compound according to Formula (III') to a compound according to Formula (II')



Formula (III') Formula (II')

(c) esterification of a compound according to Formula (II') to a compound according to Formula (I')



Formula (II') Formula (I')

As far as the reaction conditions of steps (a'), (b') and (c') are concerned the same as described above with regard to steps (a), (b) and (c) applies.

The (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to Formula (I') can preferably be present in crystalline form.

A crystal form may be referred to herein as being characterized by data selected from two or more different data groupings, for example by a powder XRD pattern having a group of specific peaks or by a powder XRD pattern as depicted in a diffractogram or by "a combination thereof" (or "combinations thereof" or "any combination thereof"). These expressions, e.g. "any combination thereof", contemplate that the skilled person may characterize a crystal form using any combination of the recited characteristic analytical data. For example, the skilled person may characterize a crystal form using a group of three, four or five characteristic powder XRD peaks and supplement that characterization with one or more additional feature(s) observed in the powder X-ray diffractogram, e.g., an additional peak, a characteristic peak shape, a peak intensity or even the absence of a peak at some position in the powder XRD pattern. Alternatively, the skilled person may in some instances characterize a crystal form using a group of three, four or five characteristic powder XRD peaks and supplement that characterization with one or more additional feature(s) observed using another analytical method, for example using one or more characteristic peaks in a solid state IR spectrum, solid state NMR or characteristics of the DSC thermogram of the crystal form that is being characterized.

In the present application, the XRPD is measured as described below in the experimental section. Further, unless indicated otherwise, XRPD peaks are reported as degrees 2θ values with a standard error of ± 0.2 degrees 2θ.

A crystal form may be referred to herein as being characterized by graphical data "as depicted in" a particular figure. Such data include for example powder X-ray diffractograms. The skilled person will understand that such graphical

representations of data may be subject to small variations, e.g. in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data characterize the same crystal form or two different crystal forms.

Thus, the subject of the present invention is (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester having characteristic X-ray powder diffraction peaks at 11.6, 21.1, 24.4, 27.5 and 28.0 degrees 2θ (± 0.2 degrees 2θ). That form of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester is hereinafter referred to as polymorphic Form A of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester.

In a preferred embodiment the (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form A can be characterized by one or more further XRPD diffraction peak(s) at 13.5, 16.7, 18.0, 23.1 and/or 27.0 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form A can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ: 7.1, 11.6, 13.5, 13.7, 16.3, 16.7, 18.0, 18.4, 21.1, 22.1, 23.1, 23.9, 24.4, 25.5, 27.0, 27.5, 28.0, 28.6, 30.8, 31.2, 31.9, 32.3, 33.7, 34.2, 34.4, 34.9, 35.1, 35.7, 36.0, 36.8, 38.3, 40.1, 40.5, 41.7, 42.4, 43.0, 43.4, 45.0, 45.3, 46.2, 46.4, 47.0, 48.6, 49.4, 49.9 and 52.0

An XRPD diffraction pattern of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form A is shown in Figure 3.

A further subject of the present invention is (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester having characteristic X-ray powder diffraction peaks at 15.7, 17.6, 19.0, 24.5 and 28.6 degrees 2θ (± 0.2 degrees 2θ). This form of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester is hereinafter referred to as polymorphic Form B of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester.

In a preferred embodiment the (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form B can be characterized by one or more further XRPD diffraction peak(s) at 6.4, 12.6, 13.4, 18.0, 19.0, 21.3, 22.1, 23.0, 25.2, 27.4 and/or 37.3 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form B can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ: 6.4, 7.0, 11.6, 12.6, 13.4, 13.7, 15.1, 15.7, 16.1, 16.3, 16.7, 17.6, 18.0, 19.0, 19.4, 19.8, 21.0, 21.3, 22.1, 23.0, 23.8, 24.5, and 25.2.

An XRPD diffraction pattern of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form B is shown in Figure 4.

A further subject of the present invention is (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester having characteristic X-ray powder diffraction peaks at 6.4, 17.6, 19.0, 21.3 and 24.5 degrees 2θ (± 0.2 degrees 2θ). This form of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester is hereinafter referred to as purified polymorphic Form B of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester.

A purified polymorph form can be regraded as a polymorph form being present in a purity of more than of 95% preferably more than 97%, in particular more than 99% of one single polymorphic form. I.e. a purified polymorphic form contains

less than 5%, preferably less than 3%, and even more preferably less than 1 % of any different polymorphic form(s).

In a preferred embodiment (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in purified Form B can be characterized by one or more further XRPD diffraction peak(s) at 12.6, 15.7, 23.0 and/or 25.2 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in purified Form B can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ: 6.4, 12.6, 13.4, 15.7, 17.6, 19.0, 19.4, 19.8, 21.3, 23.0, 24.5 and 25.2.

An XRPD diffraction pattern of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in purified Form B is shown in Figure 4'.

A further subject of the present invention is (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester having characteristic X-ray powder diffraction peaks at 11.2, 11.8, 19.6, 26.5 and 30.3 degrees 2θ (± 0.2 degrees 2θ). That form of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester is hereinafter referred to as polymorphic Form C of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester.

In a preferred embodiment the (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form C can be characterized by one or more further XRPD diffraction peak(s) at 16.8, 18.1, 23.2, 24.3 and/or 27.6 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form C can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ: 11.2, 11.8, 13.0, 13.6, 13.6, 16.8, 18.1, 19.6, 20.6, 21.2, 21.5, 22.3, 23.2, 23.7, 24.3,

24.4, 25.2, 25.6, 26.5, 27.6, 28.4, 29.1, 30.3, 31.1, 32.0, 33.1, 33.8, 36.1, 36.7, 37.5, 38.4, 38.9, 41.6, 42.5, 43.2, 44.8, 46.5, 48.7, 49.6 and 49.9.

An XRPD diffraction pattern of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form C is shown in Figure 5.

A further subject of the present invention is (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester having characteristic X-ray powder diffraction peaks at 13.6, 20.9, 32.1, 32.4 and 38.4 degrees 2θ (± 0.2 degrees 2θ). This form of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester is hereinafter referred to as polymorphic Form D of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester.

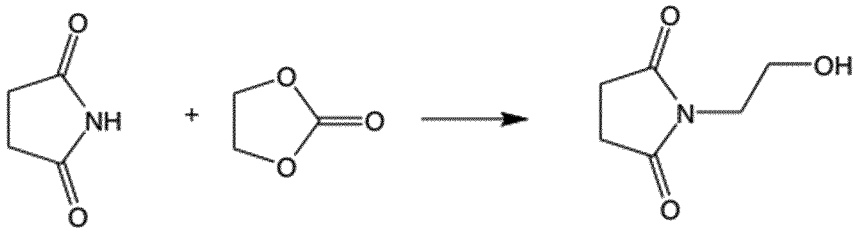
In a preferred embodiment the (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form D can be characterized by one or more further XRPD diffraction peak(s) at 18.2, 21.3, 23.3, 27.7 and/or 33.9 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form D can be characterized by the XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ: 6.9, 11.7, 13.6, 13.9, 16.4, 16.9, 18.2, 20.9, 21.3, 22.3, 23.3, 24.0, 24.6, 25.7, 27.5, 27.7, 31.0, 31.3, 32.1, 32.4, 33.9, 35.3, 35.7, 38.4, 41.9, 42.7, 43.1, 43.6, 44.4, 46.5 and 48.9.

An XRPD diffraction pattern of (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form D is shown in Figure 6.

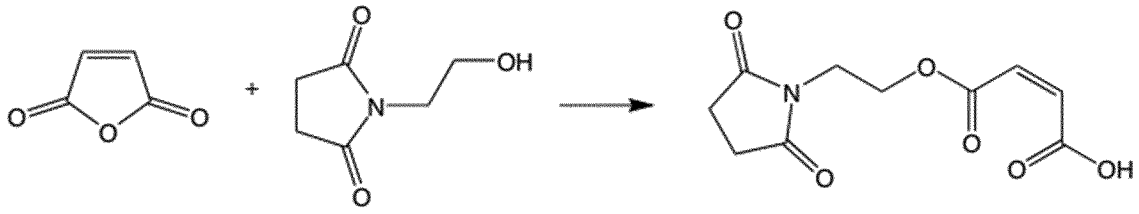
A further aspect of the invention is a method for preparing (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to Formula (I'), comprising the steps of

(0') reacting succinimide with ethylene carbonate to the compound according to Formula (IV')



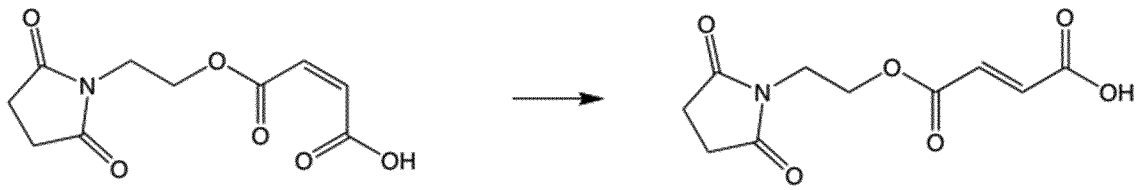
Formula (IV')

(a') reaction of maleic acid anhydride with an alcohol according to Formula (IV') to a compound according to Formula (III')



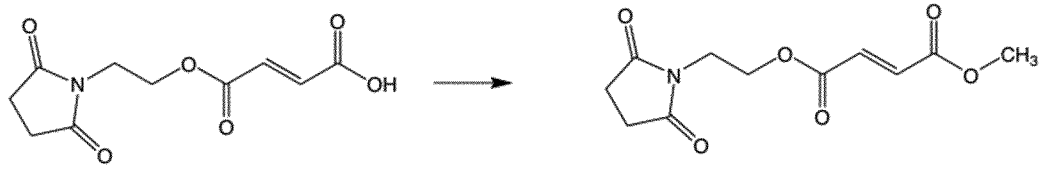
Formula (IV') Formula (III')

(b') isomerisation of a compound according to Formula (III') to a compound according to Formula (II')



Formula (III') Formula (II')

(c) esterification of a compound according to Formula (II') to a compound according to Formula (I')



Formula (II') Formula (I')

In step (0') the reaction can be preferably carried out in an organic solvent, preferably an aprotic organic solvent. Suitable organic solvents can be those as described above for example with reference to step (a).

In a more preferred embodiment step (0') can be carried out in the absence of a solvent.

The reaction in step (0') can be preferably carried out at a temperature of 50°C to 150°C, more preferably 70°C to 130°C, still more preferably 80° to 120°C in particular 85°C to 110°C.

It is preferred that a catalyst is added. A catalyst can be an alkaline substance. The alkaline can be an amine. Amines being suitable as catalyst can for example be diethyl methylamine, triethylamine, diisopropyl ethylamine, dimethyl aniline, diethyl aniline. Particularly preferred is triethylamine. Alternatively, further suitable alkaline compounds are inorganic alkaline compounds such as phosphates, hydrogen phosphates, sulphates, carbonates and bicarbonates. Preferred are bicarbonates and carbonates of alkali and earth alkali metals. Particularly preferred is sodium carbonate.

Further, the reaction of step (0') can be preferably subjected to a mechanical movement such as stirring.
In a preferred embodiment the reaction time of step (0') can be between 15 minutes and 48 hours, preferably between 30 minutes and 24 hours, in particular between 3 hours and 12 hours. If desired, the product can be further purified, for example by recrystallization.

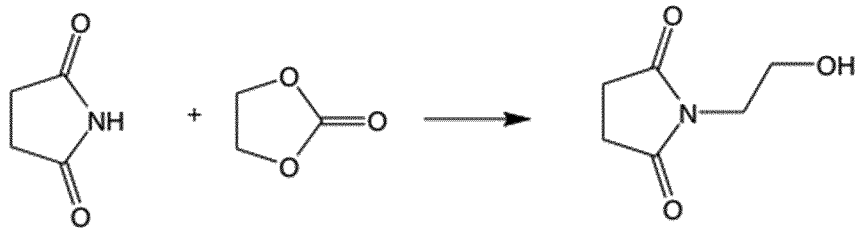
For steps (a'), (b') and (c') the same conditions as described in the context with steps (a), (b) and (c) apply.

In a preferred embodiment in steps (a'), (b') and (c') acetone, ethylacetate or acetonitrile is used as solvent.

In a preferred embodiment steps (0') and (a') can be carried out subsequently without the isolation of the product obtained from step (0').

In a preferred embodiment steps (0'), (a'), (b') and (c') can be carried out subsequently as one pot reaction, i.e. without the isolation of any intermediate obtained from steps (0') and (a'), (b').

A further aspect is a method for the preparation of a compound of Formula (IV') comprising the step of reacting succinimide with ethylene carbonate to a compound according to Formula (IV')



Formula (IV')

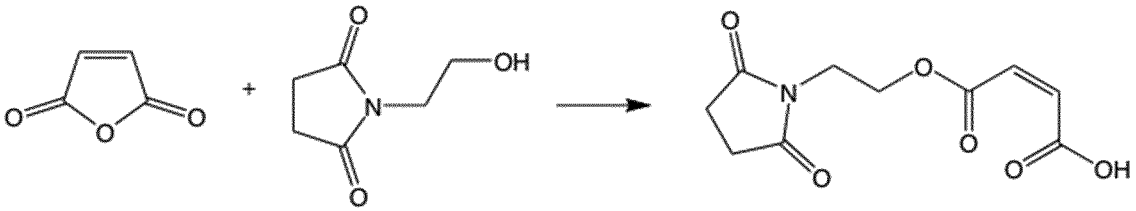
in the presence of a catalyst.

As far as the conditions for the method for the preparation of a compound of Formula (IV') apply, these correspond to the ones described with regard to above step (0'). In a preferred embodiment the catalyst can be triethylamine or sodium carbonate.

Further aspects and embodiments of the present invention are set out in the items 1 to 13.

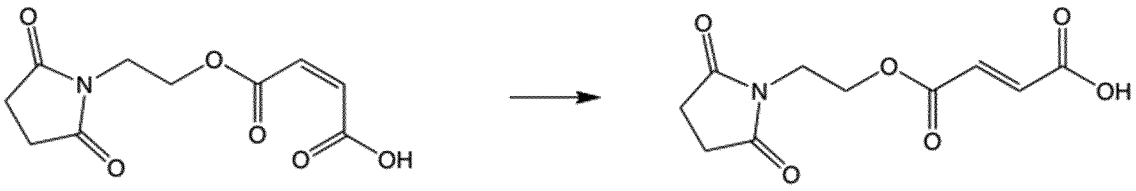
1. Method for preparing (E)-But-2 enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to Formula (I') comprises the steps of

(a') reaction of maleic acid anhydride with an alcohol according to Formula (IV') to a compound according to Formula (III')



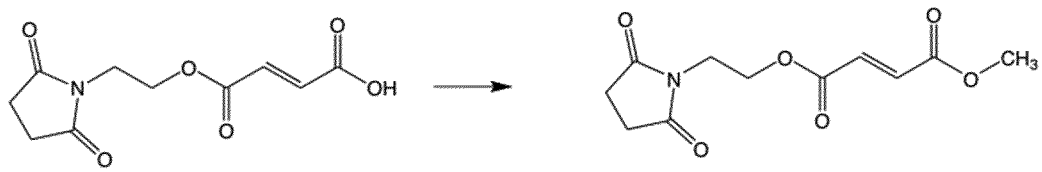
Formula (IV') Formula (III')

(b') isomerisation of a compound according to Formula (III') to a compound according to Formula (II')



Formula (III') Formula (II')

(c) esterification of a compound according to Formula (II') to a compound according to Formula (I')



Formula (II') Formula (I')

2. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester accroding to Formula (I'), characterised by the following XRPD diffraction peaks: 11.6, 21.1, 24.4, 27.5, 28.0 ± 0.2 degrees two theta.

3. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to item 2, further characterised by one or more peaks selected from the group consisting of 13.5, 16.7, 18.0, 23.1, 27.0 ± 0.2 degrees two theta.

4. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to item 2 or 3, wherein the habitus of the crystals is prismatic.

5. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to Formula (I'), characterised by the following XRPD diffraction peaks: 15.7, 17.6, 19.0, 24.5, 28.6 ± 0.2 degrees two theta.

6. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to item 5, further characterised by one or more peaks selected from the group consisting of 13.4, 18.0, 22.1, 23.0, 27.4 ± 0.2 degrees two theta.

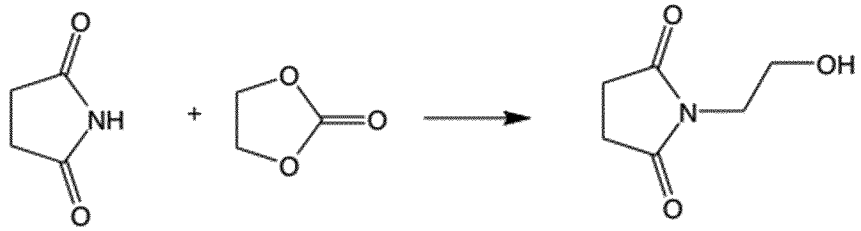
7. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester accroding to Formula (I'), characterised by the following XRPD diffraction peaks: 11.2, 11.8, 19.6, 26.5, 30.3 ± 0.2 degrees two theta.

8. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to item 7, further characterised by one or more peaks selected from the group consisting of 16.8, 18.1, 23.2, 24.3, 27.6 ± 0.2 degrees two theta.

9. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to Formula (I'), characterised by the following XRPD diffraction peaks: 13.6, 20.9, 32.1, 32.4, 38.4 ± 0.2 degrees two theta.

10. (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester according to item 9, further characterised by one or more peaks selected from the group consisting of 18.2, 21.3, 23.3, 27.7, 33.9 ± 0.2 degrees two theta.

11. Method according to item 1, further comprising step (0') of the reaction of succinimide with ethylene carbonate to the compound according to Formula (IV')



Formula (IV')

12. Method for preparing the compound according to Formula (IV'), wherein the method comprises reaction succinimide with ethylene carbonate in the presence of a catalyst.

13. Method according to item 12, wherein the catalyst is triethylamine or sodium carbonate.

The invention can be illustrated by the following examples.

EXAMPLES

Generally, all compounds are analyzed by the following analytical methods.

^{1}H-NMR Spectroscopy

Instrument: Varian Mercury 400 Plus NMR Spectrometer, Oxford AS, 400 MHz.

IR-spectroscopy

Instrument: Thermo Nicolet, Avatar 330 FT-IR.

HPLC/UV

Method A:

Instrument:	HP1200
Injection volume:	5 µl
Solvent A:	acetonitrile
Solvent B:	0.01M KH_2PO_4; pH = 2.3
Flow:	1.0 ml/min
Temperature:	RT
Column:	Supelco Discovery C18, 150 * 4.6 mm, 5 µm

time [min]	solvent B [%]
0.00	85
4.00	60
8.00	50
10.00	30
12.00	30
13.00	85
17.00	85

Method B:

Instrument:	Agilent 1200
Injection volume:	3 µl
Solvent A:	acetonitrile
Solvent B:	0.2% formic acid + 0.1% HFBA pH = 2.2
Flow:	0.8 ml/min
Temperature:	40°C
Column:	Phenomenex Kinetex phenyl hexyl 150*4.6mm 2.6u

time [min]	solvent B [%]
0.00	75
3.00	75
8.00	55
11.00	10
11.10	75
18.00	75

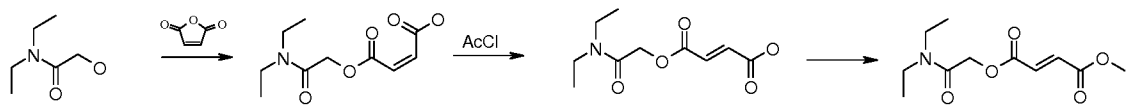
XRPD (X-Ray Powder Diffraction)

The sample was analyzed on a D8 Advance X-ray powder diffractometer (Bruker-AXS, Karlsruhe, Germany). The sample holder was rotated in a plane parallel to its surface at 20 rpm during the measurement. Further conditions for the measurements are summarized in the table below. The raw data were analyzed with the program EVA (Bruker-AXS, Germany). The samples were layered onto a silicon specimen holder.

	standard measurement
Radiation	Cu K_α (λ = 1.5406 Å)
Source	38 kV / 40 mA
Detector	Vantec
detector slit	Variable
divergence slit	v6
antiscattering slit	v6
2θ range / °	$2 \leq 2\theta \leq 55$
step size / °	0.017

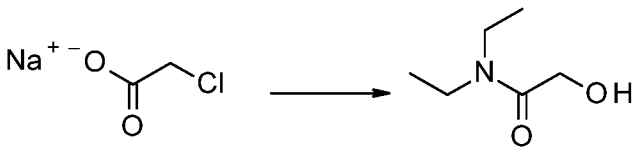
Example 1: Synthesis of (E)-But-2-enedioic acid diethylcarbamoylmethyl ester methyl ester

(E)-But-2-enedioic acid diethylcarbamoylmethyl ester methyl ester was synthesized according to the RoS is given in Scheme 1.



Scheme 1: RoS for preparation of (E)-But-2-enedioic acid diethylcarbamoylmethyl ester methyl ester

Synthesis of N,N-Diethyl-2-hydroxy-acetamide (starting material)

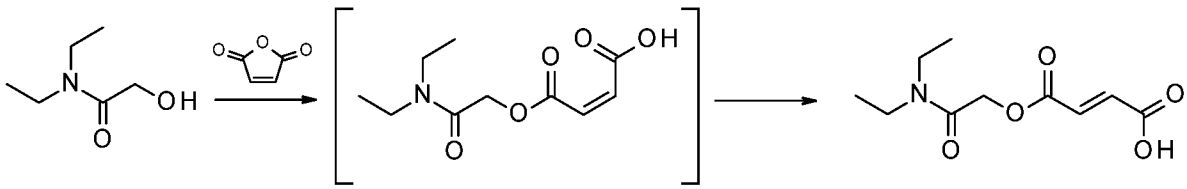


Sodium chloroacetate (30 g; 0.26 mol) was suspended in xylene (115 mL). Triethylamine (2.47 mL; 10 mmol) was added and the mixture was heated to reflux for 20 hours. After cooling to room temperature (RT), the solid was filtrated off and dried under vacuum at 60°C / 24 mbar for 2 hours. 30.82 g of a white/greyish solid was obtained. The solid was reacted with diethylamine (38.5 mL; 0.8 mol) in an autoclave at 150°C for 19 hours. The mixture was cooled to RT. Solids were filtrated off and the obtained black oil was distilled at 125°C/5 mbar. The compound was obtained at 87°C-92°C steam temperature as colorless liquid.

Yield: 19.01 g (56% of theory)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.14 - 1.21 (m, 6 H) 3.17 (q, J=7.17 Hz, 2 H) 3.45 (q, J=7.04 Hz, 2 H) 3.72 (br s, 1 H) 4.15 (s, 2 H)

Step 1: Synthesis of (E)-But-2-enedioic acid monodiethylcarbamoylmethyl ester



N,N-Diethyl-2-hydroxy-acetamide (51.5 g; 0.39 mol) and maleic acid anhydride (35 g; 0.36 mol) were heated to 60°C for 22 hours. Toluene (20 mL) and acetyl chloride (5 mL; 0.07 mol) were added and the reaction mixture was left stirring at 60°C overnight (O/N). A thick pasty substance was formed, to which toluene (40 mL) was added at 60°C. Stirring was continued for another 15 minutes before the product was filtered off. The white solid was washed with toluene (20 mL) and then dried at 50°C and 8 mbar for 3 hours.

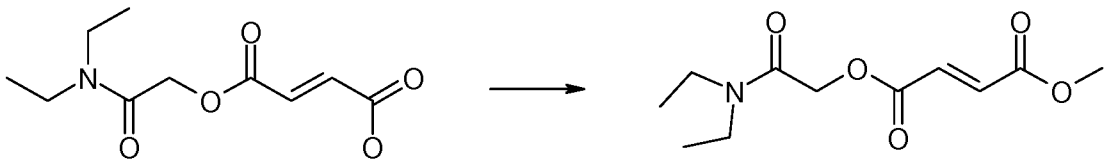
Yield: 62.69 g (77% of theory)

Purity: 96.2 area-% (HPLC/UV, method A, λ=200nm; t_r: 5.1 min).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.99 (t, J=6.84 Hz, 3 H) 1.11 (br t, J=7.04 Hz, 3 H) 3.24 (q, J=7.04 Hz, 4 H) 4.89 (s, 2 H) 6.74 (s, 2 H) 13.05 - 13.47 (m, 1 H)

IR (ATR) [cm^{-1}]: 2978, 2881, 2775, 2650, 2534, 2478, 1743, 1714, 1620, 1495, 1473, 1456, 1443, 1425, 1389, 1373, 1352, 1294, 1277, 1219, 1209, 1161, 1146, 1101, 1078, 1061, 1026, 987, 953, 914, 897, 806, 779, 764, 733, 702, 650, 615

Step 2: Synthesis of (E)-But-2-enedioic acid diethylcarbamoylmethyl ester methyl ester



Method A:

(E)-But-2-enedioic acid monodiethylcarbamoylmethyl ester (55 g; 0.24 mol) and triethylamine (38 mL) were dissolved in dichloromethane (310 mL) at 0°C. Methyl chloroformate (38 mL; 0.24 mol) was added within 30 minutes using a syringe pump. After completion, the mixture was stirred for 5 min at 0°C and dimethylaminopyridine (2.93 g) was added. The resulting solution was stirred at 0°C for 3 h, then the cold suspension was poured into water (400 mL), the reactor was washed with further dichloromethane (100 mL), which was added also to the dichloromethane water mixture. The organic layer was separated, washed with brine (100 mL) and dried over sodium sulfate. The solvent was evaporated at 60°C and the obtained brown/black oil crystallized upon cooling to RT. Acetone was added and the mixture was heated to 50°C, silica was added and the mixture was cooled to RT. A mixture of acetone and diethylether (1/4 v/v) was added and the suspension was stirred for 30 minutes. Silica was filtrated off and washed with another portion of diethylether. The organic layers were combined and evaporated to a yellow oil which crystallized upon cooling to RT. The solid was heated in diethylether to reflux until a clear solution was obtained. The

reaction mixture was cooled to RT and left stirring O/N. The product was filtrated off and dried under vacuum overnight.

Yield: 45.63 g (82%)

Purity: 98.67 area-% (HPLC/UV, method B, λ=218nm)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.00 (t, J=7.23 Hz, 3 H) 1.12 (t, J=7.23 Hz, 3 H) 3.25 (q, J=7.04 Hz, 4 H) 3.75 (s, 3 H) 4.90 (s, 2 H) 6.82 (d, J=1.56Hz, 2 H)

IR (ATR) [cm]$^{-1}$: 3080, 2980, 2962, 2941, 2879, 1718, 1649, 1487, 1454, 1441, 1381, 1363, 1352, 1306, 1271, 1221, 1194, 1161, 1144, 1099, 1051, 1016, 976, 960, 949, 906, 885, 806, 779, 766, 681, 642, 633, 615

Method B:

The starting material (0.5 g) was dissolved in dry N-methyl pyrrolidone (NMP) (3 mL) then methyliodide (0.2 mL) and Na_2CO_3 (0.4 g) were added. The solution was heated to 55°C and stirred for 16h. The formed yellow suspension was cooled to RT, diluted with ethyl acetate (60 mL) and washed with water (15 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To the brownish oil was added silica (40-63 um; 1.7 g), then diethylether (30 mL) was added. Stirring of the suspension was performed at RT for 15 minutes before filtrating the product (in organic layer). The solvent was evaporated at 60°C, yielding a colourless oil, which solidified upon standing at RT. The colourless oil was dissolved in diethylether (60 mL) and washed first with 0.05 M HCl (aq) (20 mL), then with water (20 mL). The organic layer was dried over sodium sulfate, then evaporated and dried under reduced pressure.

Yield: 147 mg (28%)

Purity: 96.7 area-% (HPLC/UV, method A, λ=200nm; t_r: 6.7 min)

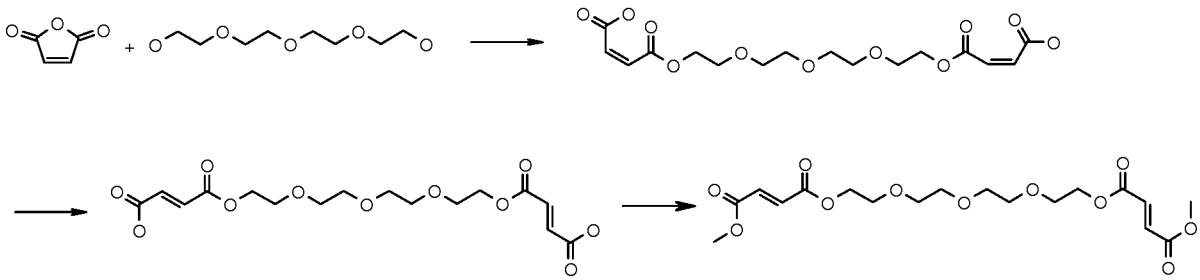
Example 1.1: Synthesis of (E)-But-2-enedioic acid diethylcarbamoylmethyl ester methyl ester (one-pot reaction)

Maleic acid anhydride (2.35 g) and N,N-diethyl-2-hydroxy-acetamide (3.46 g) were heated to 70°C overnight. Acetyl chloride (1 mL) was added and stirring was continued

at 80°C for 3.5 hours. The reaction mixture was cooled to RT, methanol (5 mL) was added and the mixture was stirred overnight at RT. The suspension turned into a yellow solution. The solvent was evaporated, and the yellow oil was stirred in a mixture of diethylether (10 mL) and n-heptane (10 mL) overnight at RT. The solid was filtrated off (mainly byproduct) and discarded. The mother liquor was evaporated to a colorless oil, diethylether (30 mL) was added. After filtration 1.3 g of silica (40-63 um) was added and the suspension was stirred for 15 minutes before being filtrated off. The solvent was evaporated, yielding the crude product as colourless oil.

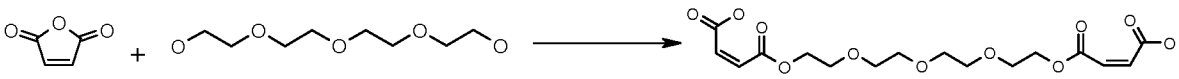
Yield: 2.78 g

Example 2: Synthesis of (E)-But-2-enedioic acid 2-(2-{2-[2-((E)-3-methoxycarbonyl-acryloyloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester methyl ester



Scheme 2: Synthesis of (E)-But-2-enedioic acid 2-(2-{2-[2-((E)-3-methoxycarbonyl-acryloyloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester methyl ester

Step 1: Synthesis of (Z)-But-2-enedioic acid mono-[2-(2-{2-[2-((Z)-3-carboxy-acryloyloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl] ester



Tetraethylene glycol (10 g; 0.051 mol), maleic acid anhydride (12.62 g; 0.129 mol) and dichloromethane (20 mL) were cooled to 0°C. Triethylamine (1.3 mL) was added to the cooled mixture and stirring was continued for 1 hour at 0°C, then the mixture was warmed to RT and stirring was continued for 1.5 hours. The solvent was evaporated and the brown oily residue was cooled to 0°C, saturated sodium bicarbonate solution (100 mL) was added. The aqueous solution was extracted with diethylether (100 mL).

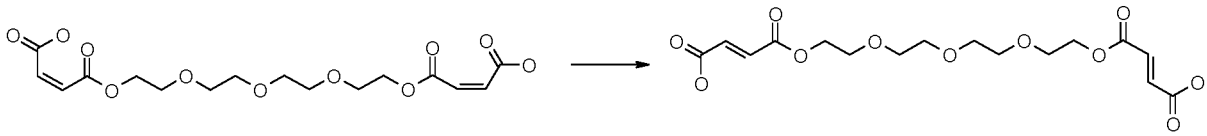
The organic layer was discarded, the aqueous layer was cooled to 0°C, acidified to pH 1 with half concentrated HCl, and extracted with ethyl acetate (200 mL). The organic layer was dried over Na_2SO_4, and after evaporation of the solvent, a red/brown transparent oil was obtained.

Yield: 14.83 g (74% of theory)

Purity: 92 area-% (HPLC/UV, method A, λ=200nm; t_r: 4.6 min.)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.62 - 3.81 (m, 12 H) 4.36 - 4.41 (m, 4 H) 6.26 - 6.34 (m, 2 H) 6.38 - 6.45 (m, 2 H) 10.22 (br s, 2 H)

Step 2: Synthesis of (E)-But-2-enedioic acid mono-[2-(2-{2-[2-((E)-3-carboxy-acryloyloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl] ester



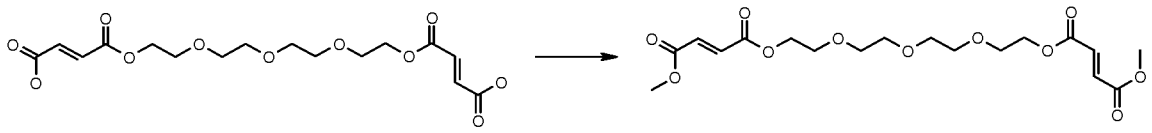
(Z)-But-2-enedioic acid mono-[2-(2-{2-[2-((Z)-3-carboxy-acryloyloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl] ester (11.4 g) was taken up in toluene (100 mL) and acetylchloride (1.83 mL; 0.026 mol) was added. The reaction mixture was heated to 80°C for 5h. To the reaction mixture was added ethyl acetate (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried over sodium sulfate, and then evaporated at 60°C and 52 mbar to yield a brown oil.

Yield: 11.57 g

Purity: 86 area-% (HPLC/UV, method A, λ=200nm; t_r: 5.3 min.)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.69 (s, 8 H) 3.75 - 3.82 (m, 4 H) 4.34 - 4.41 (m, 4 H) 6.78 - 7.02 (m, 4 H) 10.80 (br s, 2 H)

Step 3: Synthesis of (E)-But-2-enedioic acid mono [2-(2-{2-[2-((E)-3-methoxycarbonyl-acryloyloxy)-ethoxy]-ethoxy}-ethoxy)-ethyl ester] methyl ester



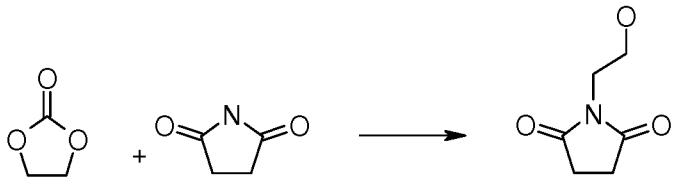
To a solution of the starting material (1 g) and triethylamine (0.8 mL) in methylene chloride at 0°C was added methyl chloroformate (0.4 mL). After 30 min of stirring at 0°C, dimethylaminopyridine (0.31 g) was added to the reaction mixture at 0°C, stirring was continued for 15 minutes, then the ice bath was removed and stirring was continued for 2 hours. The resulting solution was poured into water (60 mL) and extracted with ethyl acetate (60 mL). The organic layer was evaporated, yielding a brownish oil, containing the target compound as main ingredient (1.04 g). To the brown oil was added silica (40-63um; 700 mg)). Ethylacetate (20 mL) was added to the silica mixture and the resulting suspension was stirred for 15 minutes. Silica was filtrated off and washed with another portion of ethyl acetate (10 mL). The combined organic layers were evaporated to yield a colorless oil.

Yield: 0.83 g (77% of theory)

Purity: 89 area-% (HPLC/UV, method A, λ=200nm; t_r: 8.9 min.)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.50 - 3.54 (m, 8 H) 3.63 - 3.66 (m, 4 H) 3.73 (s, 6 H) 4.25 - 4.27 (m, 4 H) 6.69 - 6.83 (m, 4 H) 6.76 (s, 3 H)

Example 3a: Synthesis of 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione



Procedure A according to literature (Journal of Organic Chemistry, 24, 1121-2; 1959)

Ethylene carbonate (1.5 kg; 17 mol), Succinimide (1.687 Kg; 17 mol) and sodium carbonate (90.22 g; 0.9 mol) were heated to 90°C within ~2 hours (T in flask 85°C). The mixture was further heated to 100°C within 35 minutes, a moderate constant gas evolution was observed, the temperature was held overnight. The reaction mixture was transferred into a distillation (vigreux) apparature. Then the product was distilled off at 132-141°C at 7.2x10-2 to 9.9x10-2 mbar to yield the product as colorless product.

Yield: 2.094 kg (86% of theory)

Procedure B

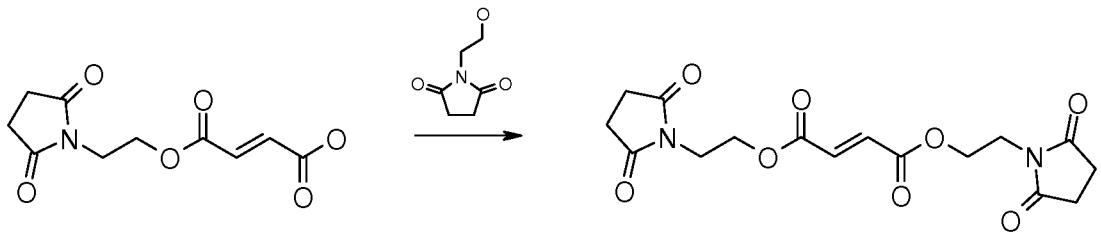
Ethylene carbonate (4.44 g; 50 mmol) and succinimide (5 g; 50 mmol) were heated to 100°C, after 4.5 h a sample was taken and analysed by NMR --> no conversion could be observed

Procedure C

Ethylene carbonate (1.07 g, 12.1 mmol), Succinimide (1.0 g; 10 mmol) and triethylamine (0.28 mL; 2 mmol) were heated to 115°C. Conversion was monitored by NMR. After 2.5 hours full conversion to the product was observed.

Impurity I

A potential impurity of the above reaction is (E)-But-2-enedioic acid bis-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl] ester, which may be formed according to the following reaction scheme.



Impurity I

This impurity is hard to remove from the final product and might lower the yield.

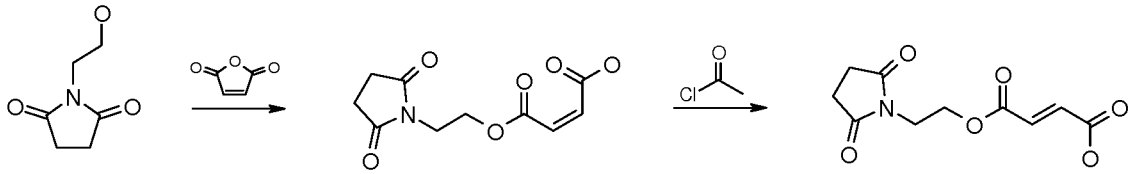
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.64 (s, 8 H) 3.69 (t, J=5.38 Hz, 4 H) 4.26 (t, J=5.38 Hz, 4 H) 6.65 (s, 2 H)

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 28.48 (CH2) 37.32 (CH2) 62.31 (CH2) 133.56 (CH) 164.64 (Cq) 178.11 (Cq)

m/z: 384 [M+NH4]+; 367 [M+H]+

HPLC: 5.4 minutes purity 100 area-% at 200 nm

Example 3b: Synthesis of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester



Procedure A:

Distilled 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (3 g; 20.96 mmol) and maleic acid anhydride (2.26 g; 23.1 mmol) in toluene (10 mL) were heated to 60°C under stirring for 29 hours. The temperature was raised to 80°C and heated for another 19 hours. Acetyl chloride (0.3 mL; 4.2 mmol) was added and heating (80°C) was continued for 24 hours. The reaction mixture was cooled to RT. The biphasic system was separated, the upper layer was discarded. The lower layer (viscous oil) crystallized. The crystallized compound was suspended in acetone (50 mL) and stirred for 15 minutes before being filtrated off. The product was dried at 50°C for 5 hours and 8 mbar to yield the 1st crop (1.65 g). The mother liquor was evaporated and the obtained oil/solid was suspended in acetone (5 mL) and stirred overnight at RT. The product was filtrated off and dried at 50°C for 5 hours and 8 mbar to yield the 2nd crop (1.41 g). The mother liquor was evaporated and the obtained oil/solid was suspended in a mixture of diethylether/acetone (5 mL/1 mL) and stirred overnight at RT. The product was filtrated off and dried at 8mbar/50°C for 3 hours (3rd crop, 0.37 g).

Yield: 3.43 g (68% of theory)

Purity: 1st crop 96.8 area%; 2nd crop 96.0 area-%; 3rd crop 85.4 area-% (HPLC/UV, method A, λ=200nm; t_r: 3.8 min.)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.61 (s, 4 H) 3.66 (t, J=5.47 Hz, 2 H) 4.23 (t, J=5.47 Hz, 2 H) 6.51 - 6.72 (m, 2 H) 6.60 (s, 1 H) 6.63 (s, 1 H) 13.21 (br s, 1 H)

Procedure B:

Reaction performed in a reactor (Mettler Toledo, Optimax):

Distilled 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (20 g; 0.14 mol) and maleic acid anhydride (15 g; 0.15 mol) in toluene (70 mL) were heated to 80°C under stirring (150 rpm) for 29 hours. Acetyl chloride (2 mL; 0.03 mol) was added and heating (80°C) was continued overnight. Stirring speed was raised to 200 rpm) after 15.5 hours (at 80°C) (product precipitated upon raising stirring speed. The reaction mixture was cooled to 20°C within 1 hour, directly after highering stirring speed. The reaction mixture was stirred for 4 hours, before being filtrated off. The filtrated precipitate was washed with toluene (30 mL) and then with heptane (70 mL), the product was dried at 60°C and 18 mbar. The crude product (26.26 g) with ~90% purity was suspended in a mixture of acetone (30 mL)/heptane (30 mL) and stirred at RT for 2 days. The product was filtrated off, washed with heptane (30 mL) and dried at 50°C and 7 mbar.

Yield: 24.12 g (72% of theory)

Purity: 97.4 area-% at 200 nm

Procedure C:

a) Ethylene carbonate (8.89 g; 0.1 mol), succinimide (10 g; 0.1 mol) and sodium carbonate (0.53 g, 5 mmol) were heated to 100°C, the temperature was hold overnight. The product was cooled down yielding a brownish solid (13.73 g) which was grinded in a mortar.

b) 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (10 g, 69.9 mmol) from sequence a) and maleic acid anhydride (6.85 g; 69.9 mmol) in toluene (33 mL) were heated to 80°C under stirring for 23 hours. Acetyl chloride (0.5 mL; 7 mmol) was added and heating

(80°C) was continued overnight. Heating was stopped and after stirring for another 2 hours the product was filtered off. The product was dried for 2 hours at 60°C and 8 mbar, yielding 15.82 g of crude product.

purity: 63 area-% at 200nm; 80 area-% at 220 nm

Procedure D

a) Ethylene carbonate (44.43 g; 0.5 mol), succinimide (50 g; 0.5 mol) and sodium carbonate (2.67 g; 25 mmol) were heated to 100°C. The reaction mixture was stirred at 100°C for overnight. The mixture was cooled to RT, yielding 72.4 g of the raw product. 40 g of the raw product were suspended in ethylacetate (40 mL) and heated to reflux for 30 minutes. The turbid mixture was cooled to RT and left stirring O/N. The product was filtrated off and dried under vacuum at RT to yield 29.19 g.

b) 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (10 g; 69.9 mmol) from sequence a) and maleic acid anhydride (6.85 g; 69.9 mmol) in toluene (30 mL) were heated to 80°C under stirring. Acetyl chloride (0.5 mL; 7 mmol) was added after 19 hours and heating (80°C) was continued overnight. Heating was stopped and stirring was continued for 2 days. The product was filtrated off and dried at 23 mbar and 60°C.

purity: 82 area% at 200 nm; 91 area-% at 220 nm

Procedure E:

a) Succinimide (500 g; 5.0 mol), ethylene carbonate (444.34 g; 5.0 mol) and sodium carbonate (26.74 g; 0.25 mol) were mixed and slowly heated to 130°C under stirring for 7 hours. The product was distilled via vacuum distillation to yield the product as colourless substance (628.14 g; 87% of theory)

b) The distilled 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (150 g; 1.05 mol) from sequence a) and maleic acid anhydride (102.76 g; 1.05 mol) in toluene (350 mL) were heated to 80°C under stirring for 23 hours. Acetyl chloride (7 mL; 0.01 mol) was added and heating (80°C) was continued. After 6 hours, the reaction mixture was cooled to 20°C within 30 minutes. The product was filtrated off and washed with toluene (200 mL), yielding 221.8 g of a white crystalline product (crude product).

purity: 91 area% at 200 nm; 92 area-% at 220 nm

Procedure F:

a) Ethylene carbonate (9.78 g; 0.11 mol), succinimide (10 g; 0.10 mol) and triethylamine (0.7 mL; 5mmol) were heated to 98°C. The reaction mixture was stirred at this temperature overnight. The mixture was cooled to RT, yielding a colourless liquid, which crystallizes upon standing at RT to a colorless solid (14.89 g).

b) The crude 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione from sequence a) (5 g; 35 mmol) and maleic acid anhydride (3.43 g; 35 mmol) in toluene (25 mL) were heated to 80°C under stirring for 24 hours. Acetyl chloride (0.25 mL; 3.5 mmol) was added and heating (80°C) was continued for ~4 hours. The reaction mixture was cooled to RT. The product was filtrated off washed with toluene and dried at 50°C and 8 mbar for 3 hours.
Yield: 6.52 g (77%)purity: 93 area% at 200 nm; 94 area-% at 220 nm

Procedure F'

Ethylene carbonate (161.50 g, 1.834 mol) was melted at 50°C in a reactor, succinimide (173.07 g, 1.747 mol) and Et_3N (12.2 mL, 87.350 mmol) were added and the reaction mixture was warmed up to 90°C and stirred for 24h. Reaction mixture was cooled to 50°C, 500 mL of acetone was added, followed by addition of maleic anhydride (164.19 g, 1.674 mol) and Et_3N (10.15 mL, 72.772 mmol). Reaction mixture was stirred at 50-55°C for 4h, cooled to 0°C and stirred for 20h. Resulting white suspension was filtered off and solid was washed with cold acetone (2×50 mL) and dried for 6h at 50°C and 30 mbar to afford crystalline (Z)-4-(2-(2,5-dioxopyrrolidin-1-yl)ethoxy)-4-oxobut-2-enoic acid.
Yield: 274 g (65%)
Purity: 97.23 area % at 200 nm

Procedure F''

(Z)-4-(2-(2,5-dioxopyrrolidin-1-yl)ethoxy)-4-oxobut-2-enoic acid (250 g, 1.036 mol) was suspended in acetone (500 mL) in 1-L reactor, acetyl chloride (5.53 mL, 77.736 mmol) was added drop wise at 20-25°C and reaction mixture was warmed up to 50-55°C and stirred for 20h. Reaction mixture was cooled to 0°C and stirred for 3h. Resulting white suspension was filtered off and solid was washed with cold acetone

(2×50 mL) and dried for 6h at 50°C and 30 mbar to afford crystalline (*E*)-4-(2-(2,5-dioxopyrrolidin-1-yl)ethoxy)-4-oxobut-2-enoic acid (Formula II).

Yield: 231.3 g (92.5%)

Purity: 99.47 area % at 200 nm

Summary:

Procedure B and E, using distilled 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione, showed purities of ~90-91 area-% of the crude product, ongoing crystallization of the target compound could improve the purity to ~97% also shown in procedure A. Distillation of 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione needs harsh conditions (Ex. 3a; procedure A). Using the crude 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione, produced with Na_2CO_3 lead to low product purities of 63 area-% (procedure C).

Crystallization of 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (procedure D) lead to product purities comparable to procedure A, B and E with distilled 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione, but crystallization is compounded by a significant product loss of ~ 25%.

The raw 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione could be used without any disadvantageous impact on product quality by substituting Na_2CO_3 with triethylamine as shown in procedure F with a purity of 93 area-%.

Procedure G

Two experiments were performed in parallel:

Each with 1 g (7 mmol) 1-(2-hydroxy-ethyl)-pyrrolidine-2,5-dione and 0.75 g (7.7 mmol) maleic acid anhydride in 6 mL acetonitrile in screw capped vials. To one of the reaction mixtures was given 0.1 mL triethylamine. Both mixtures were stirred at RT. Samples were taken and investigated by NMR (in DMSO).

product formation after 1 hour (quantified by NMR):

mixture without triethylamine: 0%

mixture with triethylamine: 55%

product formation after 2 hours:

mixture without triethylamine: 0%

mixture with triethylamine: 71%

Procedure H (isolation of cis intermediate):

1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (5 g; 35 mmol) and maleic acid anhydride (3.43 g; 35 mmol) in toluene (30 mL) were heated to 80°C under stirring for ~24 hours. The reaction was cooled to RT, first a biphasic layer was observed, then the product solidified (sticking to glass wall and stirrer). The product was filtrated off after 2.5 hours of stirring, washed with toluene (50 mL) and dried under vacuum. The dried product was milled and suspended again in toluene (60 mL) at RT, after 30 minutes the product was filtrated off and dried under atmospheric conditions to yield 7.24 g of the cis intermediate (86% of theory). The intermediate product was suspended in toluene (30 mL) and heated to 80°C, acetyl chloride (0.25 mL; 3.5 mmol) was added and heating (80°C) was continued for 5 hours. The reaction mixture was cooled to RT and stirred for 2 hours. The product was filtrated off, washed with toluene (30 mL) and dried at 50°C and 8 mbar O/N.

purity: 95.6 area-% at 200nm; (0.2% of Impurity I)

Procedure H (without isolation of cis intermediate):

1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione (5 g; 35 mmol) and maleic acid anhydride (3.43 g; 35 mmol) in toluene (30 mL) were heated to 80°C under stirring for 24 hours. Acetyl chloride (0.25 mL; 3.5 mmol) was added and heating (80°C) was continued for ~4 hours. The reaction mixture was cooled to RT. The product was filtrated off washed with toluene (30 mL) and dried at 50°C and 8 mbar for 3 hours.

purity: 93.2 area-% at 200nm; (1.3% of Impurity I)

Procedure I (scale-up without cis isolation)

Maleic acid (959.09 g; 9.8 mol) was added to a reactor under stirring, which was already loaded with toluene (7 L), then 1-(2-Hydroxyethyl)-pyrrolidine-2,5-dione

(1400 g; 9.8 mol) was added. Then the mixture was heated to 76°C within ~1 h (up to ~50°C the mixture is a suspension with the tendency of conglomeration of solids, very difficult consistency) at 50°C a turbid solution resulted. Stirring was continued at 80°C for 2 days. Acetyl chloride (138 mL; 1.96 mol) was added under enhanced stirring at 80°C. After ~5-10 minutes a crystalline precipitate was formed, which transformed into a pasty/syrupy solid, sticking to reactor walls (difficult handling). Heating was continued overnight (reaction completed after 5 hours as IPC showed). Mixture is still an emulsion, seeding was added and the product precipitated. Stirring at 80°C was continued for ~2 hours then the mixture was cooled to RT. The solid was filtrated off and dried at 50°C and 12 mbar overnight to yield 1818.74 g of the product.

purity: 96.34 area-% at 218 nm; (1.5% of Impurity I)

Procedure J:

2L flask (reaction volume ~1 L): Succinimide (460 g; 4.6 mol), ethylene carbonate (450 g; 5.1 mol) and triethylamine (32 mL; 0.23 mol) were heated to 85°C under stirring overnight. Temperature was raised to 95°-97C and heating was continued O/N. The mixture was cooled to 50°C. Acetonitrile (1600 mL) was charged into a 10 L reactor. To the reaction mixture was added acetonitrile (1000 mL) at 50°C and the solution was transferred to the reactor (reactor T ~22°C), triethylamine (35 mL) was added, then maleic acid anhydride (500.81 g; 5.1 mol). The mixture was heated to 55°C for 5.5 hours. A part of the solvent was distilled off (~1200 mL). Then toluene (1200 mL) was added. The mixture was heated to 90°C. The mixture was cooled to 50°C. At 60°C (clear solution), seeding was added ~300 mg, after ~3 minutes a suspension resulted. The mixture was further cooled down to 20°C within 10 hours and kept on stirring O/N. The white crystalline product was filtrated off, washed with toluene (1000 mL) and dried at 55°C and 9 mbar for 2 h to yield 908.99 g (81% yield).

905 g of the isolated, crystallized product was suspended in acetonitrile (2.9 L). Acetyl chloride (23 mL) was added and the mixture was heated to 80°C (clear, colorless solution) for 4 hours. Toluene (1000 mL) was added and the mixture was cooled to RT within 2 hours (linear). The mixture was further cooled to 0°C within 60 minutes. The

product was filtrated off and washed with toluene (1000 mL). The product was dried overnight at 9 mbar and 50°C.

Yield: 742.06 g (66%)

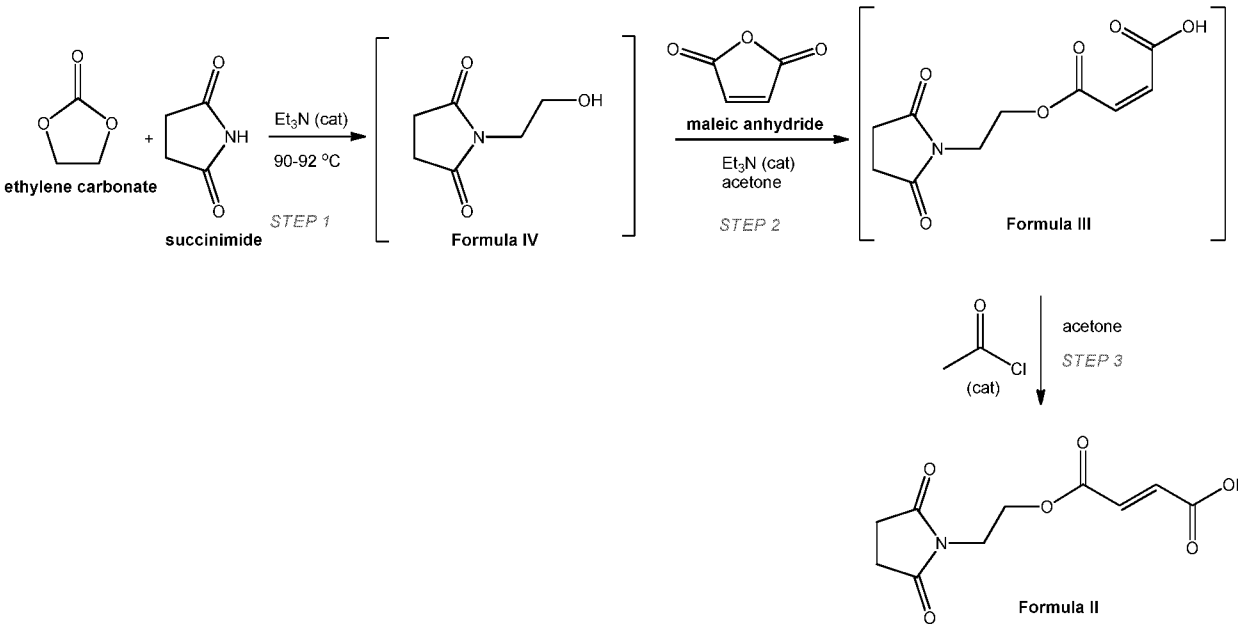
purity: 99.9 area% at 200 nm

Summary:

Isolation of the cis intermediate leads to a significantly lower content of impurities, in particular of Impurity I. Toluene as solvent leads to disadvantageous conditions regarding consistency of the reaction mixture (procedure H). The use of acetonitrile or acetone (procedure I/F) leads to improved reaction conditions and product quality.

Example 3c

Preparation of (*E*)-4-(2-(2,5-dioxopyrrolidin-1-yl)ethoxy)-4-oxobut-2-enoic acid (Formula II) from ethylene carbonate and succinimide (without isolation of intermediates)



Procedure

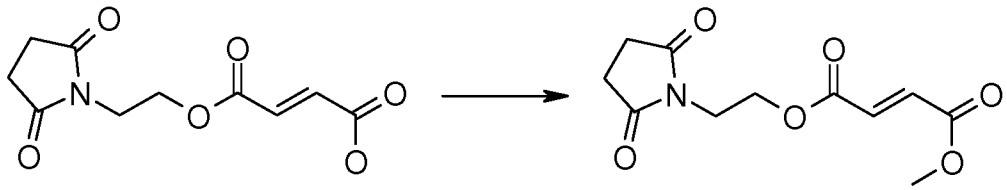
Ethylene carbonate (161.50 g, 1.834 mol) was melted at 50°C in an 1-L reactor, succinimide (173.07 g, 1.747 mol) and Et_3N (24.4 mL, 0.175 mol) were added and the reaction mixture was warmed up to 90-92°C and stirred for 24h. Distillation column

was set up on the reactor and the remaining Et_3N was distilled off. Reaction mixture was cooled to 40-45°C, 500 mL of acetone was added, followed by addition of maleic anhydride (184 g, 1.878 mol) and Et_3N (10.96 mL, 78.615 mmol). Reaction was stirred at 40°C for 6h (precipitation occurred after 3h), cooled to 20-25°C and acetyl chloride (20.86 mL, 0.293 mol) was added drop wise. Reaction mixture was then warmed up to 50-55°C and stirred for 20h. Orange solution crystallized upon seeding. Reaction mixture was cooled to 0°C and stirred for 3h. Resulting white suspension was filtered off and solid was washed with cold acetone (2×200 mL) and dried for 6h at 50°C and 30 mbar to afford (*E*)-4-(2-(2,5-dioxopyrrolidin-1-yl)ethoxy)-4-oxobut-2-enoic acid.

Yield: 352.8 g (83.7%)

Purity: 99.69 area % at 200 nm

Example 4: Synthesis of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester



Procedure A:

The starting material (E)-But-2-enedioic acid mono-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl] ester (5 g; 20 mmol) was suspended in dichloromethane (60 mL) and cooled to 0°C, triethylamine (3.16 mL; 22.8 mmol) was added, resulting a clear solution. To this solution methylchloroformate (3.3 mL; 20.7 mmol) was carefully added within 30 minutes via syringe (reaction very exothermic). After 15 min of stirring at 0°C, DMAP (0.25 g; 2.1 mmol) was added into the reaction mixture at 0°C, stirring was continued for 3 hours at 0°C. The reaction mixture was poured into water (200 mL) and additional dichloromethane (100 mL) was added. The organic layer was separated and the aqueous layer was extracted once again with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL). The solvent was evaporated at 52°C. To the brown oil, which solidified, was added acetone (20 mL) and the mixture was stirred overnight. The product was filtrated off (white solid, part I) (2.73 g) and to the mother

liquor silica was added, the mixture was evaporated. Acetone (50 mL) was added and silica was filtrated off. The solvent was evaporated and diethylether (30 mL) was added to the solid, the mixture was stirred for ~1 hour. The product was filtrated off (part II) (1.6 g).

Overall yield: 4.33 g (82%)
Purity: part I 100 area-% at 200 nm; part II 97.96 area-% at 200 nm

Procedure A'

(*E*)-4-(2-(2,5-dioxopyrrolidin-1-yl)ethoxy)-4-oxobut-2-enoic acid (Formula II) (200 g, 0.829 mol) was suspended in acetone (2000 mL) in 3-L reactor at 20-25°C and cooled to 0°C. Et_3N (150.31 mL, 1.078 mol) was added drop wise at 0-5°C. Into resulting solution, methyl chloroformate (83.27 mL, 1.072 mol) was added drop wise at 0-5°C. Reaction mixture was warmed up to 45°C and stirred for 2h. Upon completion, reaction mixture was cooled to 20-25°C and water (600 mL) was added drop wise with maintaining the temperature at 20-25°C resulting with off white to yellowish solution. pH was adjusted to 7 with 1M HCl. One more volume of water was added and pH corrected if needed. Part of acetone from the reaction mixture (5 volumes or 1000 mL) was distilled off under diminished pressure and reactor walls were washed with 1 more volume of water (200 mL), thus resulting in a solution of acetone/water mixture 1:1 (total 10 volumes). Reaction mixture was gradually cooled to 0°C and stirred for 20h. Resulting white suspension was filtered off and solid was washed with cold water (2×200 mL) and dried for 6h at 50°C and 30 mbar to afford crude 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (Formula I).
Yield: 183.7 g (86.8%)
Purity: 100.00 area % at 200 nm

Crude 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (170 g) was suspended in acetone (850 mL) at 20-25°C and warmed up to 50°C resulting with colorless solution. Water (850 mL) was added in portions at 50°C and solution was cooled gradually. Crystallization started at 32°C. Reaction mixture was stirred at crystallization temperature for 30 minutes and cooled further to 0°C, stirred at 0°C for 2h and resulting

white suspension was filtered off and solid was washed with cold water (2×170 mL) and dried for 6h at 50°C and 30 mbar to afford crystalline 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate.

Yield: 152.5 g (89.7%)

Purity: 100.00 area % at 200 nm

Procedure B:

The starting material (5 g, 20 mmol) was suspended in toluene (25 mL). Acetyl chloride (0.29 mL) and methanol (2.5 mL) were added, the reaction mixture was heated to 55°C and stirred for 3 hours. The reaction mixture was poured into water (100 mL) and extracted with ethylacetate (100 mL). The organic layer was separated and dried over sodium sulfate. The solvent was evaporated (crude product 4.7 g, main impurities dimetylfumarate (13%) and fumaric acid (1%) (HPLC at 200 nm)).

Yield: 4.7 g (88%)

Purity: 82.1 area-% at 200 nm

Procedure C:

(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in polymorphic form A; short: (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form A

The starting material (without isolation of (Z)-But-2-enedioic acid mono-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl] ester) (30 g; 0.12 mol) was suspended in dichloromethane (DCM, 160 mL) and cooled to 0°C, triethylamine (TEA, 19 mL; 0.14 mol) was added, resulting a clear solution. To this solution methyl chloroformate (19.74 mL; 0.12 mol) was added carefully within 30 minutes via syringe. Stirring was continued for ~2 hours. Water (200 mL) was added to the reaction mixture and stirring was continued for 5-10 minutes. The organic layer was separated and the aqueous layer was washed with another portion of DCM (100 mL). The combined organic layers were dried over sodium sulfate, before being evaporated. To the crude product was added acetone (50 mL) and the mixture was stirred for 3 hours before being filtered off. The product was washed with heptane (50 mL) and dried at 50°C and 21 mbar for 1 h.

Yield: 20.52 g (65%)

Purity: 98.7 area-% at 220 nm; (0.3% of Impurity I)

XRPD diffraction peaks: 7.1, 11.6, 13.5, 13.7, 16.3, 16.7, 18.0, 18.4, 21.1, 22.1, 23.1, 23.9, 24.4, 25.5, 27.0, 27.5, 28.0, 28.6, 30.8, 31.2, 31.9, 32.3, 33.7, 34.2, 34.4, 34.9, 35.1, 35.7, 36.0, 36.8, 38.3, 40.1, 40.5, 41.7, 42.4, 43.0, 43.4, 45.0, 45.3, 46.2, 46.4, 47.0, 48.6, 49.4, 49.9, 52.0 ± 0.2 degrees two theta.

The Form A according to Procedure C showed a habitus as depicted in Figure 7a

Procedure D:

(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form A

The starting material (10 g; 41.5 mmol) was suspended in toluene (70 mL) at 23°C, triethylamine (TEA; 6.3 mL; 45.6 mmol) was added. Methyl chloroformate (6.58 mL; 41.5 mmol) was slowly added within ~30 minutes. After stirring for 2 hours water (40 mL) was added and shortly after acetone (110 mL), stirring was continued for ~2 minutes. The organic layer was separated and washed with brine (15 mL). After drying over sodium sulfate, the solvent was evaporated, yielding a slightly grey solid as crude product (9.42 g). The raw product was suspended in acetone (20 mL) and heptane (20 mL). The mixture was heated to reflux for 15 minutes resulting in a clear solution with just a small amount of solid. The mixture was cooled to RT and stirred overnight (precipitation started at 45°C, cooling: flask left in cooling oil bath ~1h to RT). The resulting product showed polymorphic form A.

Yield: 7.83 g (74%)

Purity: 99.4 area-% at 200 nm

The form A according to Procedure D showed a habitus as depicted in Figure 7b

Procedure E:

The starting material (1 g; 4.15 mmol) was suspended in dichloromethane (50 mL) at RT. Methyl chloroformate (0.64 mL; 8.3 mmol) was added and stirring was continued overnight, in process control by HPLC showed no conversion.

Procedure F:

(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form A

The starting material (7 g; 0.03 mol) and Na_2CO_3 were suspended in ethylacetate (50 mL). To the suspension was added methyl chloroformate (3.37 mL; 0.04 mol) in one portion. The reaction mixture was heated to 70°C. The temperature was kept for 15.5 h. The reaction mixture was cooled to 20°C and ethyl acetate (70 mL) was added to the white suspension. The solids were filtrated off and the ethyl acetate layer was washed with water (40 mL), dried over Na_2SO_4 and evaporated to yield 6.4 g of the white crystalline crude product.

The crude product was suspended in a mixture of ethylacetate (10 mL) and heptane (10 mL). The suspension was heated to reflux for 30 minutes, then cooled to 23°C and stirred overnight. The product was filtrated off and dried at 8 mbar and 50°C overnight.

Yield: 5.62 g (75%)

Purity: 99.4 area-% at 200 nm

The form A according to Procedure E showed a habitus as depicted in Figure 7c

Procedure G:

(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in polymorphic form B; short: (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form B

(A) 9 g of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methylester was heated to 115°C. The melted compound was stirred for ~20 minutes and then dropped into a precooled mortar (0°C).

Purity of form B: 98.8 area-% at 200nm

XRPD-pattern: (Figure 4)

(B) 3.00 g of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester (form A) was suspended in 150 mL of dibutyl ether. Suspension was heated to 120° C while mixing. Solution was left at 25°C for 2 days. Crystallized material was filtered and dried at 23°C at 12 mbar.

XRPD-pattern: (Figure 4')

A measure of the relative volume change of a solid as a response to pressure change is called compressibility. An API should exhibit good compressibility which is dependent on the polymorphic state.

Experimental data:

The compressibility of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester form B and form A was assessed using a die and a flat-faced punch fitted on a TA-XT2 Texture analyser (Stable Micro Systems Ltd., Godalming, UK). 200 mg of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester sample is compressed in a steel mould (with the rate of displacement 0.03 mm/s). Cyclic procedure (similar to tapping) was performed: compressing, then retracting, relaxation for 15 s and then repeated compressive steps (altogether 10 steps). Each step exerts 0.2 MPa pressure on to the sample. Sample density is calculated by dividing the weight by the sample volume for each cycle. Maximum density is reached within 10 steps. Measurements were performed in duplicates for each sample, results are expressed as an average of duplicate measurements.

Results:

Sample	Density at 0.2 MPa / g/ml
(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form A	0.41 ± 0.02
(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form B	0.61 ± 0.00

Form B of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester exhibits a higher density at compression, indicating superior compressibility compared to form A.

Procedure H:

(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in polymorphic form C; short: (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form C

(E)-But-2-enedioic acid mono-[2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl] ester (10 g; 41.5 mmol) was suspended in dichloromethane (DCM; 100 mL) and cooled to 0°C, triethylamine (TEA; 6.3 mL; 45.6 mmol) was added, resulting a clear solution. To the reaction mixture was added methyl chloroformate (6.58 mL; 41.5 mmol) within 30 minutes via a syringe pump. After 15 min of stirring at 0°C, DMAP (0.51 g; 4 mmol) was added into the reaction mixture at 0°C. The resulting solution was stirred at 0°C for 2.5 hours, then the cold suspension was poured into water (70 mL), the reactor was washed with further DCM (20 mL), which was added also to the DCM/water mixture. The organic layer was separated and washed with HCl (32%aq) (5 mL) in water (60 mL), then with water (50 mL) and finally with brine (50 mL). To the obtained deep red to brown solution was added silica (40-63 um) and the mixture was stirred for 5 minutes, before being filtered off to yield a colorless solution, which was evaporated to yield a colorless oil (crude product). The obtained oil was dissolved in a mixture of ethyl acetate/heptane (1/4) (20 mL). The mixture was stirred for 2 days before being filtered off. The product was dried under vacuum.

Yield: 2.87 g (26%)

Purity: 90.9 area-% at 200 nm

XRPD diffraction peaks: 11.2, 11.8, 13.0, 13.6, 13.6, 16.8, 18.1, 19.6, 20.6, 21.2, 21.5, 22.3, 23.2, 23.7, 24.3, 24.4, 25.2, 25.6, 26.5, 27.6, 28.4, 29.1, 30.3, 31.1, 32.0, 33.1, 33.8, 36.1, 36.7, 37.5, 38.4, 38.9, 41.6, 42.5, 43.2, 44.8, 46.5, 48.7, 49.6, 49.9 ± 0.2 degrees two theta.

Procedure I:

(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in polymorphic form D; short: (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form D

(E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester Form B (1 g) was suspended in acetonitrile (3 mL). The suspension was stirred for 7 days in a closed screw cap vials followed by slow evaporation of the solvent under ambient conditions within 3 days.

Purity of form D: 96.3 area-% at 200 nm

XRPD diffraction peaks: 6.9, 11.7, 13.6, 13.9, 16.4, 16.9, 18.2, 20.9, 21.3, 22.3, 23.3, 24.0, 24.6, 25.7, 27.5, 27.7, 31.0, 31.3, 32.1, 32.4, 33.9, 35.3, 35.7, 38.4, 41.9, 42.7, 43.1, 43.6, 44.4, 46.5, 48.9 ± 0.2 degrees two theta.

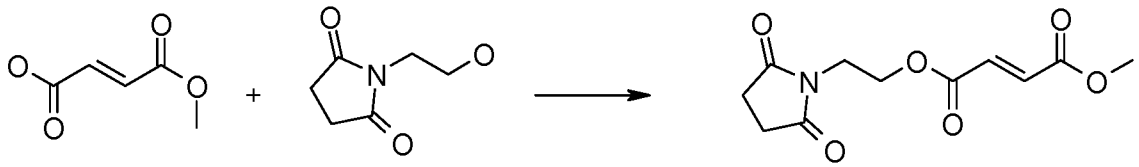
Procedure J:

The starting material (obtained via isolation of (Z)-But-2-enedioic acid mono-[2-(2, 5-dioxo-pyrrolidin-1-yl)-ethyl] ester) (400 g; 1.7 mol) and Na_2CO_3 (264 g; 2.5 mol) were suspended in ethylacetate (2.7 L). To the suspension was added methyl chloroformate (193 mL; 2.5 mol) at 20°C. The reaction mixture was heated to 45°C within 90 minutes (linear heated). The mixture was kept on stirring for 5.5 hours. Ethylacetate (4 L) was added to the white suspension (at 45°C). The suspension was stirred for 15 minutes before being filtrated off (45°C suspension). The reactor was rinsed with another portion of ethylacetate (1 L). The filtrated solids were discarded. To the ethylacetate solution was added a mixture of HCl_{aq} (32%) (50 mL) and water (1 L) and the mixture was vigorously stirred for 10 minutes (at 35°C). Then the ethylacetate layer was separated (at ~35°C). The ethylacetate layer was transferred back to the reactor and stirred over sodium sulfate for 30 minutes, sodium sulfate was filtrated off and the ethylacetate layer was reduced to 900 mL. The suspension was transferred into a 3 L flask, equipped with a KPG stirrer and reflux condenser. The mixture was heated to reflux (stirring speed 160 rpm), the suspension was stirred until a clear solution was obtained (~30 minutes). Then heptane (550 mL) was added dropwise within 30 minutes

under reflux conditions. Then the mixture (still solution) was slowly cooled to RT. The mixture was stirred O/N. The product was filtrated off and the filter cake was rinsed with heptane (500 mL) to yield the crystalline product (362.56 g; 86%).

purity: 99.8 area% at 218 nm (no Impurity I).

Alternative Procedure: Synthesis of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester



Procedure A

Monomethylfumarate (20 g, 0.15 mmol) was suspended in dry dichloromethane (400 mL) at RT, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid hydrochloride (32.42 g, 0.17 mol), N-(2-hydroxyethyl)succinimide (21.57 g, 0.15 mol) and dimethylaminopyridine (0.94 g, 7.7 mmol) were added. The solution was stirred O/N at RT. The formed yellow solution was diluted with dichloromethane (300 mL) and washed twice with water (2x500 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. To the crude product was added methyl tert. butyl ether (850 mL) and the reaction mixture was refluxed for 2.5 hours, cooled to RT, then filtrated and heated to reflux again for ~2 hours. After cooling to RT, the mixture was stored at ~5°C for 4 days. The white precipitate was filtrated off and washed with isopropylacetate (25 mL). The crystalline product was dried at 50°C and 7 mbar.
Yield: 10.8 g (28%)

Procedure B

Monomethylfumarate (1.5 g; 11.5 mmol) was suspended in dry DCM (30 mL) at 0°C. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid hydrochloride (2.47 g; 12.8 mmol), N-(2-hydroxyethyl)succinimide (1.62 g; 11.3 mmol) and DMAP (0.07 g; 0.6 mmol) were added. The solution was stirred overnight at RT. The formed yellow solution was diluted with DCM (50 mL) and washed with water twice (2x35 mL). The organic layer

was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (n-heptane:ethyl acetate 1:1->1:2). The final product showed polymorphic form A. The form A according to alternative Procedure B showed a prismatic habitus as depicted in Figure 7d

Yield: 2.3 g (78%)
Purity: 99.5 area-% at 200 nm

Example 5: Kinetic investigations

Monomethyl maleate was prepared in analogy to WO 2014/197860. Samples of 13.2 grams of monomethyl maleate in 50 mL of toluene and 0.1 equivalents of the isomerization catalyst were reacted at 80°C. Samples were taken after the given times and analyzed by HPLC at 200 nm. The absorbance ratio of monomethyl fumarate (3.8 min.) to monomethyl maleate (2.8 min.) was taken as conversion parameter. The results are shown in Figure 1. As it can be seen from Figure 1 the conversion of monomethyl maleate to monomethyl fumarate in the presence of is TMS (trimethylsilylchloride) is advantageously enhanced compared to the one in the presence of AcCl (acetyl chloride).

Example 6: Yield determination

Six samples of 13.2 g (0.1 mol) monomethyl maleate were diluted with toluene (50 mL) and 0.1 eq of the isomerization catalyst (trimethylsilylchloride or acetyl chloride) were added, three samples with trimethylsilylchloride and three samples with acetyl chloride. The resulting reaction mixtures were heated to the temperatures of 45°C, 51°C and 80°C. After 22 hours the reaction mixtures were cooled to room temperature, the product was filtrated off and dried at 50°C/8-16 mbar overnight. The results are shown in Figure 2 As it can be seen from Figure 2 the isolated yields of the conversion of monomethyl maleate to monomethyl fumarate in the presence of TMS (trimethylsilylchloride) is at any of the reaction temperature higher compared to the one in the presence of AcCl (acetyl chloride).

Short description of the Figures:

Figure 1: Time dependent conversion of monomethyl maleate to monomethyl fumarate (y- axes absorbance ratio of monomethyl fumarate to monomethyl maleate at 200 nm vs time) at 80°C.

Figure 2: Isolated yields after 22 hours of reaction time at given temperatures in %.

Figure 3: Polymorphic form A of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methylester.

Figure 4: Polymorphic form B of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methylester

Figure 4': XRPD pattern of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methyl ester in purified Form B.

Figure 5: Polymorphic form C of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methylester.

Figure 6: Polymorphic form D of (E)-But-2-enedioic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester methylester.

Figure 7a: Form A according to Procedure C.

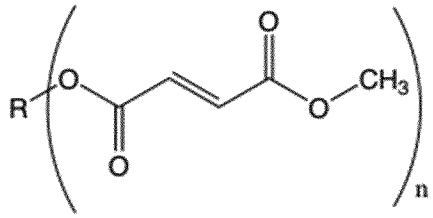
Figure 7b: Form A according to Procedure D.

Figure 7c: Form A according to Procedure E.

Figure 7d: Form A according to Alternative Procedure B.

Claims

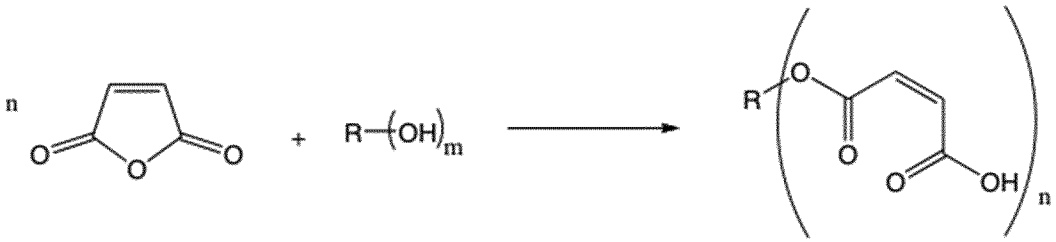
1. Method for preparing a compound according to Formula (I)



Formula (I)

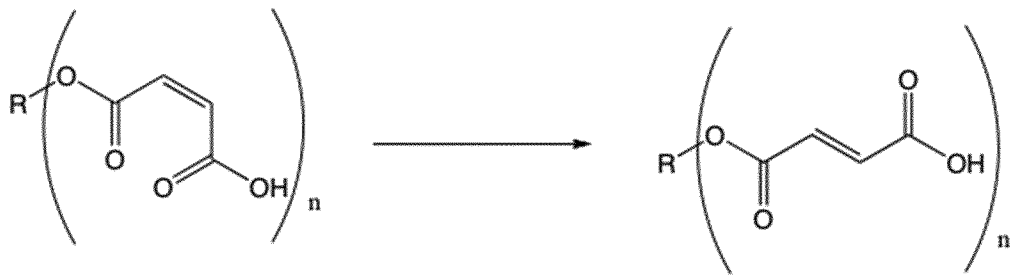
comprising the steps of

(a) reaction of maleic acid anhydride with an alcohol according to Formula (IV) to a compound according to Formula (III)



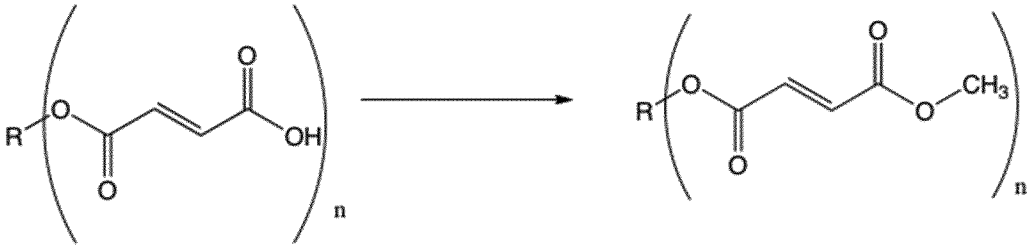
Formula (IV) Formula (III)

(b) isomerisation of a compound according to Formula (III) to a compound according to Formula (II)



Formula (III) Formula (II)

(c) esterification of a compound according to Formula (II) to a compound according to Formula (I)



Formula (II) Formula (I)

wherein

R is an organic resiude, provided that R is not hydrogen or methyl,

m is a natural number from 1 to 4 and

n is is natural number with $1 \leq n \leq m$.

2. Method according to claim 1, wherein residue R is 3-dimethylamino-3-oxoethyl.

3. Method according to claim 1, wherein residue R is 2-(2,5 dioxopyrrolidin-1-yl)ethyl.

4. Method according to any one of claims 1 to 3, wherein step (a) is carried at a temperaure from 0° to 150°C.

5. Method according to any one of claims 1 to 4, wherein step (b) is carried out in the presence of a trialkylsilylchoride and/or a carboxilic acid chloride of an organic acid containing 1 to 6 carbon atoms.

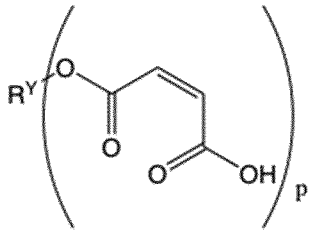
6. Method according to any one of claims 1 to 5, wherein steps (a) and (b) are caried out as one pot reaction.

7. Method according to any one of claims 1 to 6, wherein step (c) is carried out in the presence of methanol, methyl chloroformate or MeX, wherein X is a leaving group.

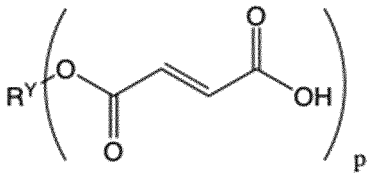
8. Method according to claim 7, wherein X is sulfonate or a halogenide selected from chloride, bromide and iodide.

9. Method according to anyone of claims 1 to 8, wherein steps (a), (b) and (c) are caried out as one pot reaction.

10. Method for isomerisation of



to



wherein

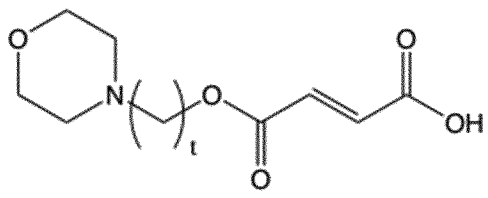
R^Y is an organic residue with the proviso that R^Y is not hydrogen and

p is an integer from 1 to 4,

and wherein the isomerisation is carried out in the presence of trialkylsilylchloride or trialkoxysilylchloride.

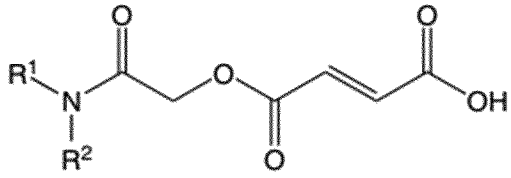
11. Use of the compound according to Formula (II) and/or (III) as an intermediate in a process for preparing a MMF-Prodrug.

12. Use according to claim 11, wherein the compound according to Formula (II) is represented by the Formulae (II/1) – (II/12)



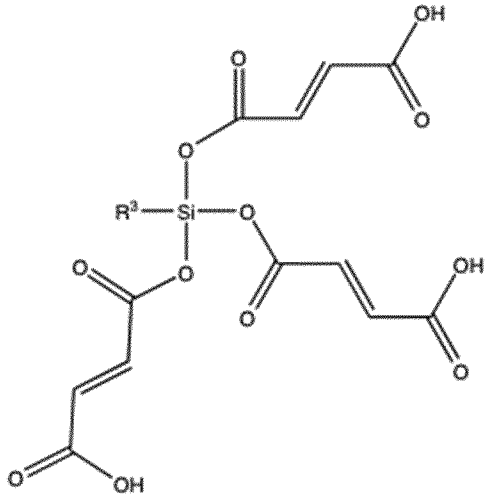
Formula (II/1),

wherein t is an integer from 1 to 6



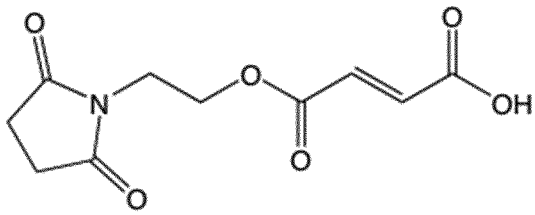
Formula (II/2)

wherein R^1 and R^2 are independently hydrogen or an alkyl with 1 to 6 carbon atoms

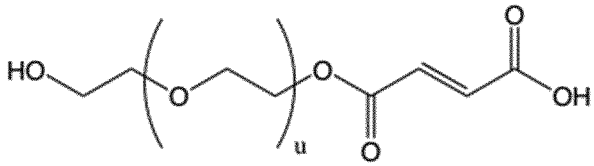


Formula (II/4)

wherein R^3 is an alkyl with 1 to 10 carbon atoms

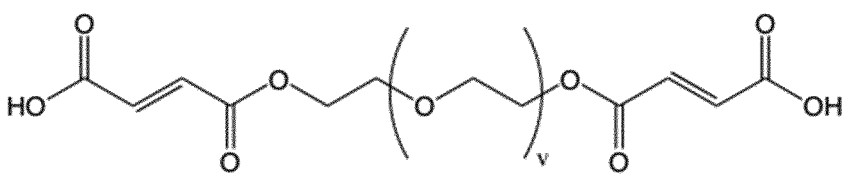


Formula (II/5)



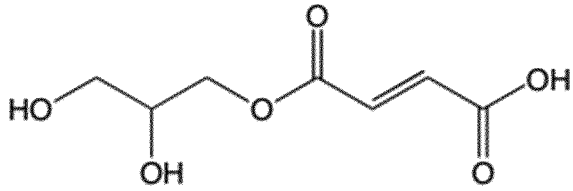
Formula (II/6)

wherein u is an integer from 1 to 10

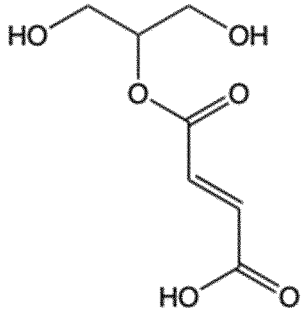


Formula (II/7)

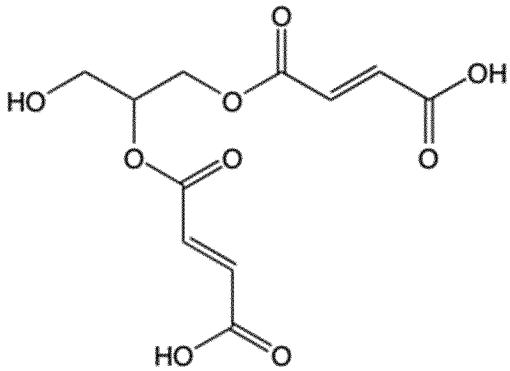
wherein v is an integer from 1 to 10



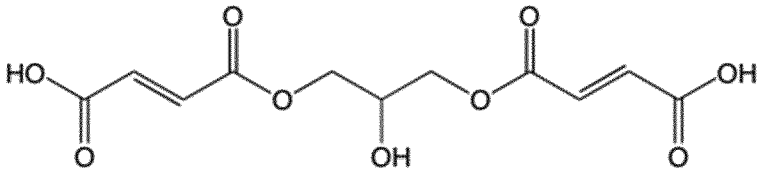
Formula (II/8)



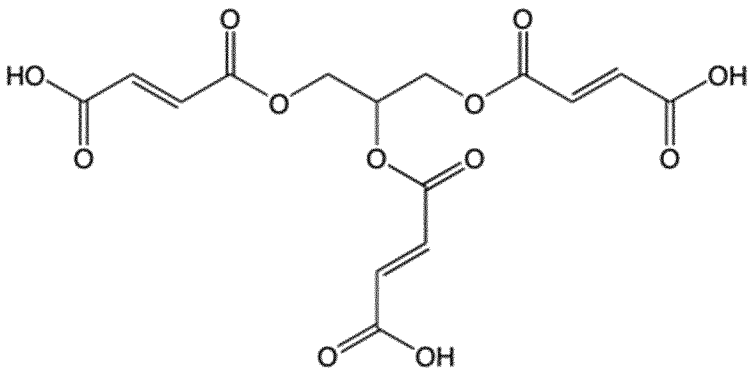
Formula (II/9)



Formula (II/10)

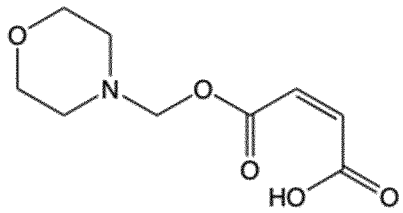


Formula (II/11)



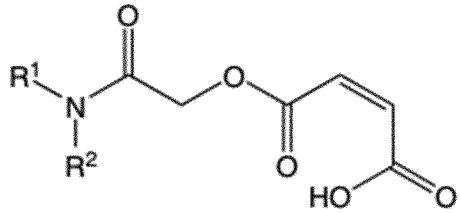
Formula (II/12)

13. Use according to claim 11, wherein the compound according to Formula (III) is represented by Formulae (III/1) to (III/12)



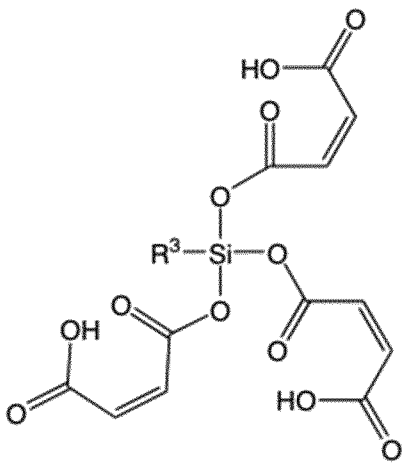
Formula (III/1),

wherein t is an integer from 1 to 6



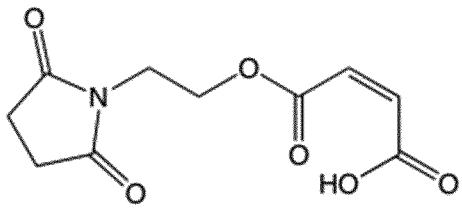
Formula (III/2)

wherein R^1 and R^2 are independently hydrogen or an alkyl with 1 to 6 carbon atoms

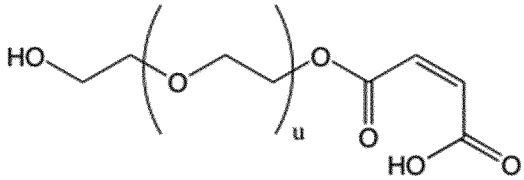


Formula (III/4)

wherein R^3 is an alkyl with 1 to 10 carbon atoms

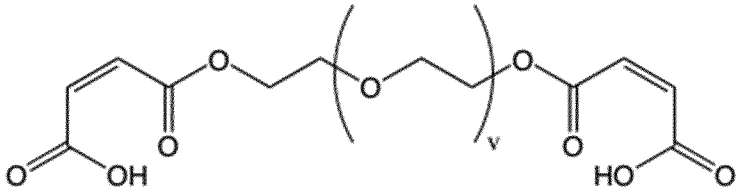


Formula (III/5)



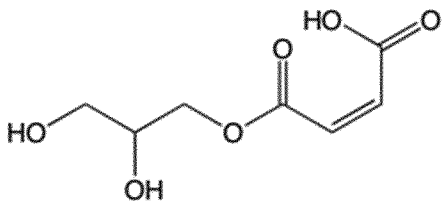
Formula (III/6)

wherein u is an integer from 1 to 10, preferably 2 to 6, in particular u is 3,

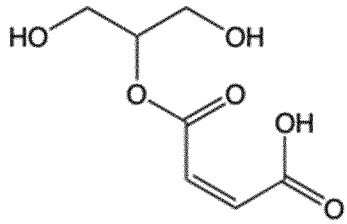


Formula (III/7)

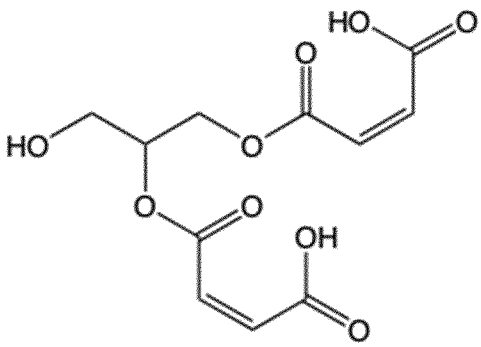
wherein v is an integer from 1 to 10, preferably 2 to 6, in particular v is 3,



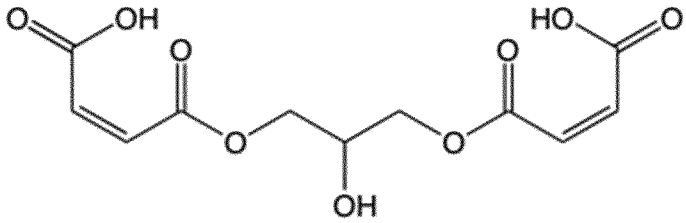
Formula (III/8)



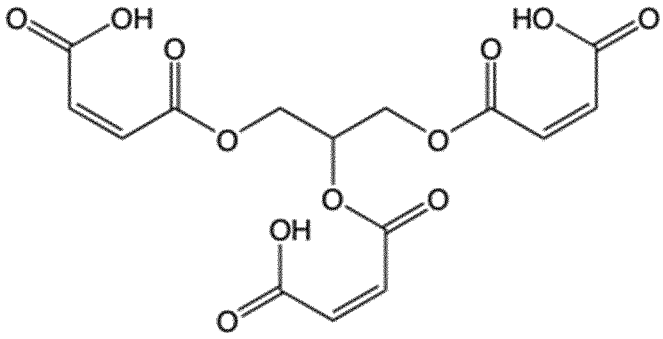
Formula (III/9)



Formula (III/10)



Formula (III/11)



Formula (III/12)

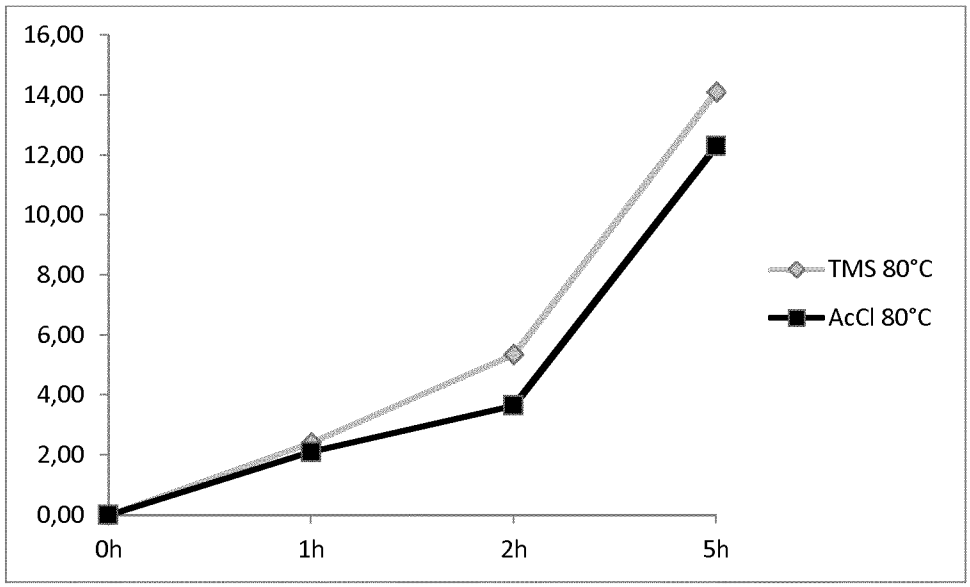


Figure 1

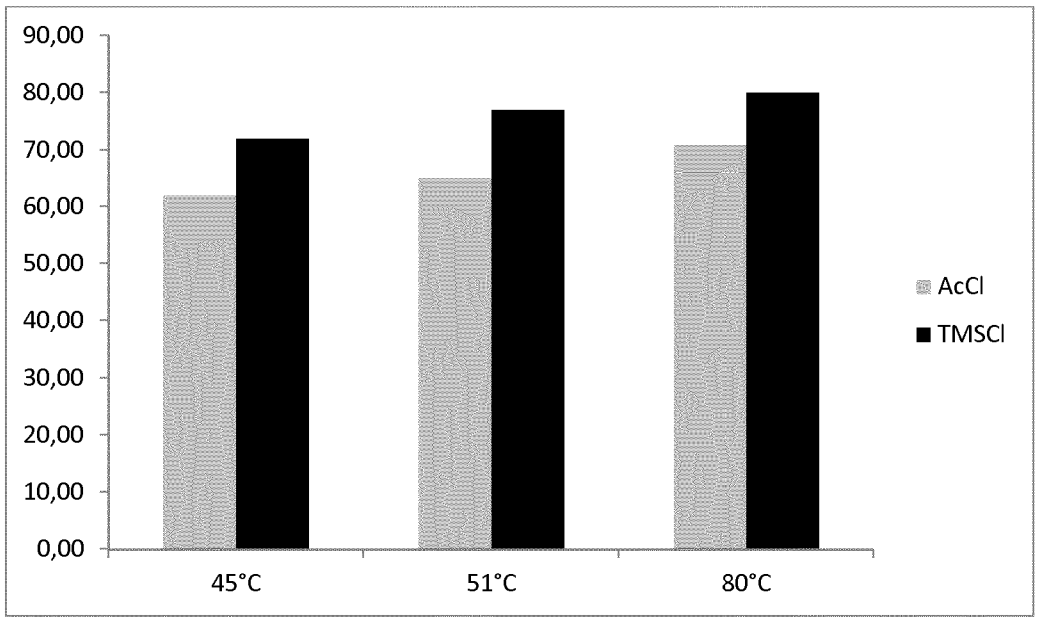


Figure 2

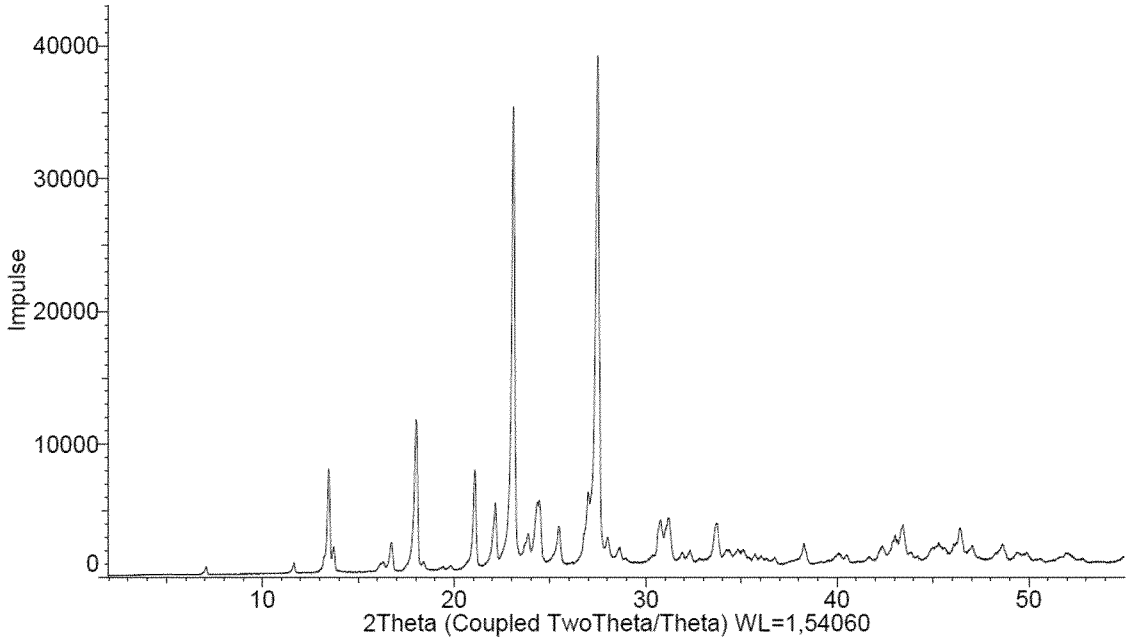


Figure 3

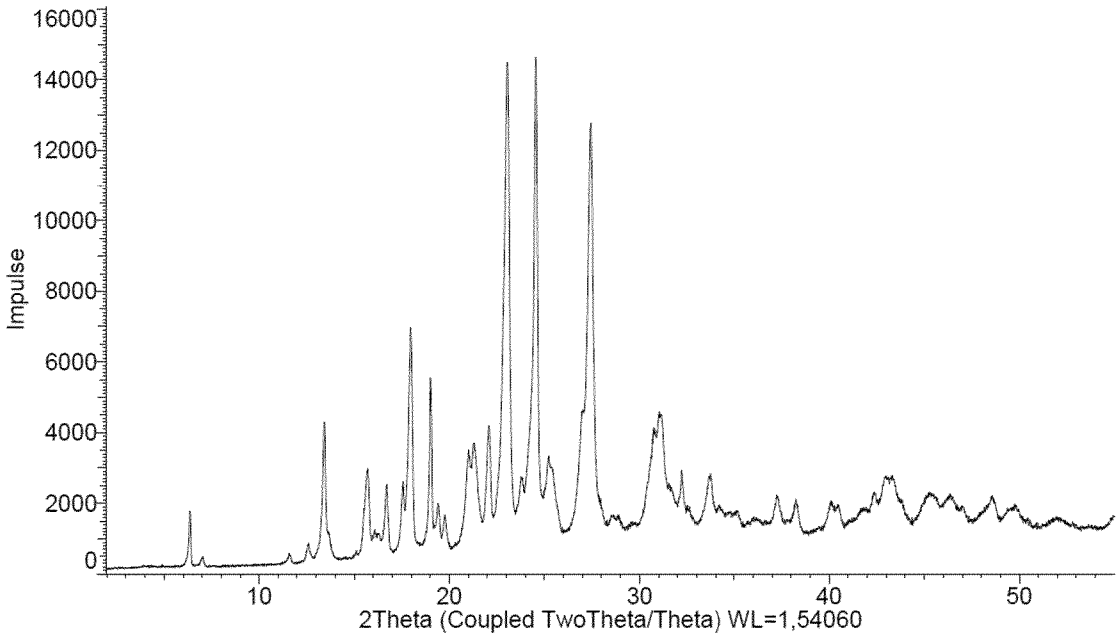


Figure 4

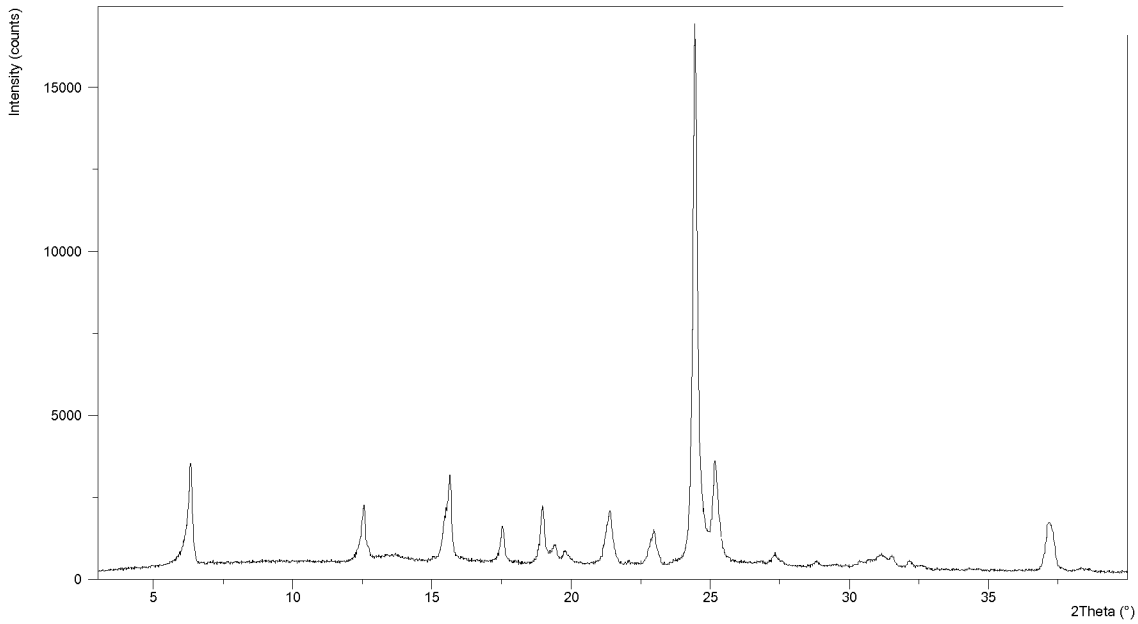


Figure 4'

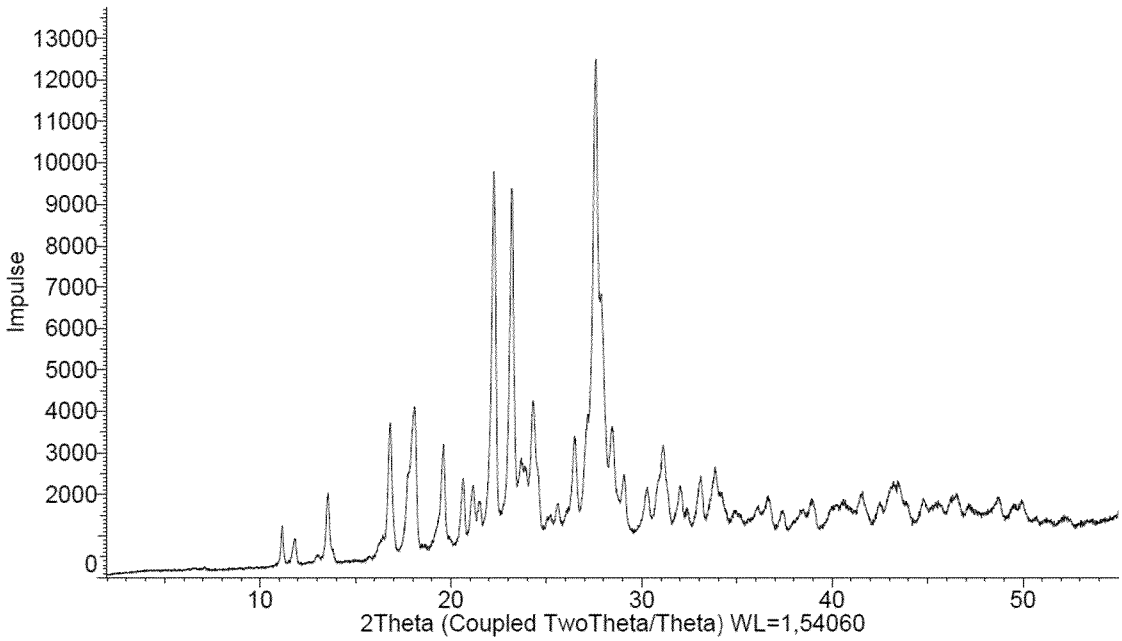


Figure 5

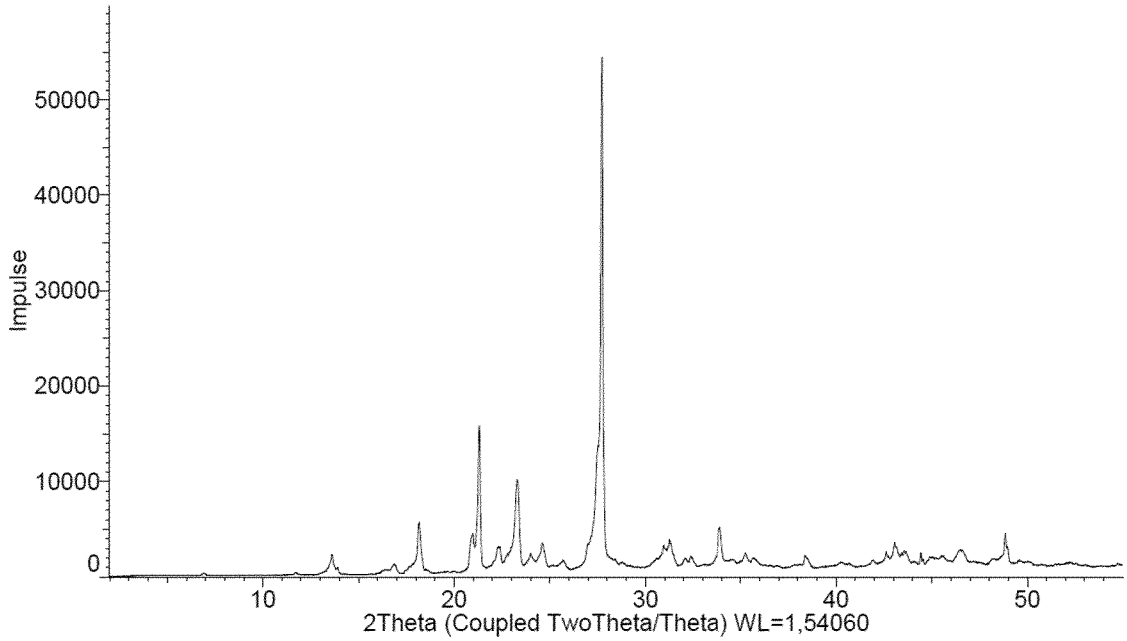


Figure 6

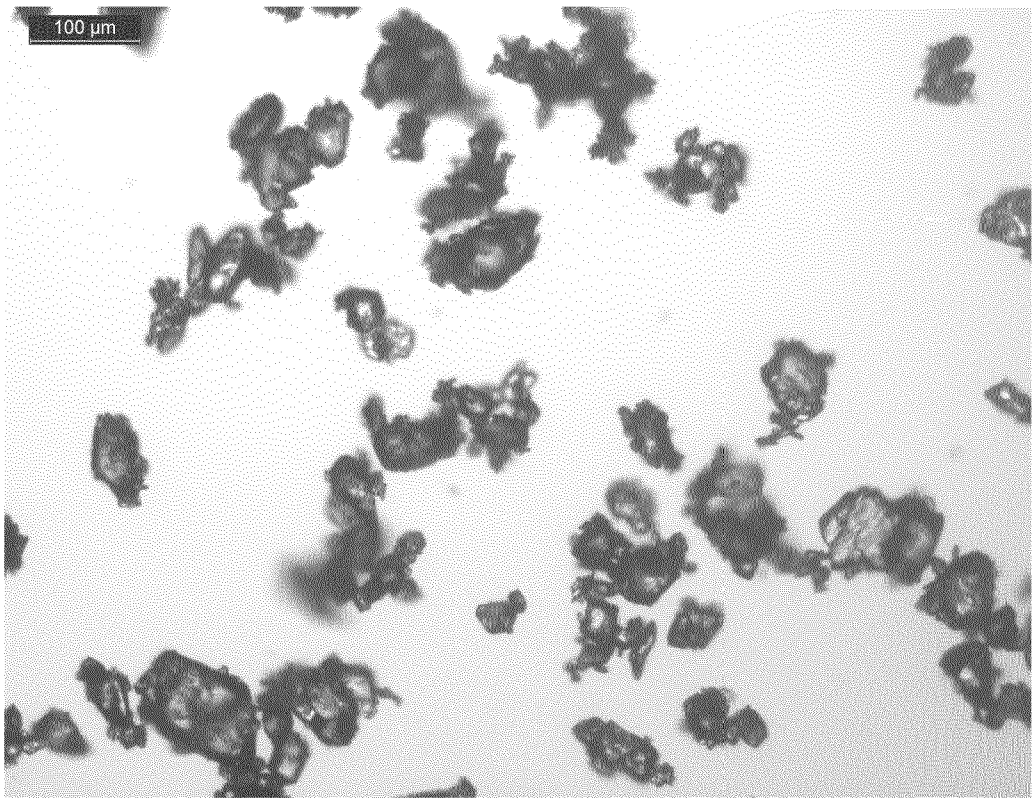


Figure 7a

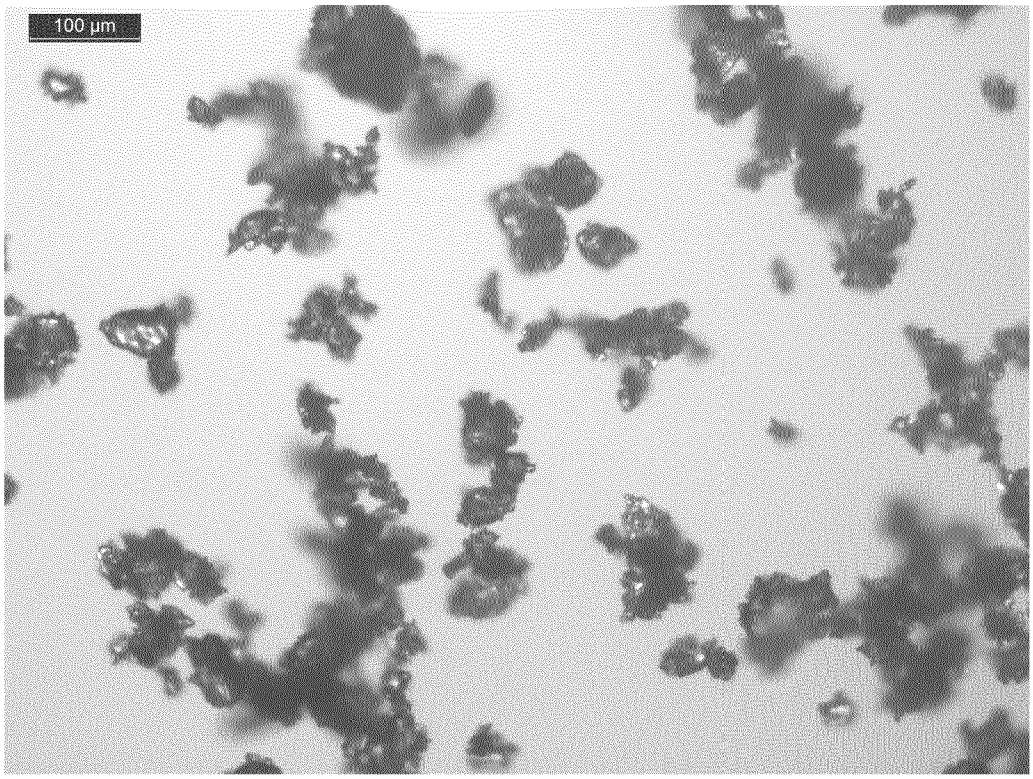


Figure 7b

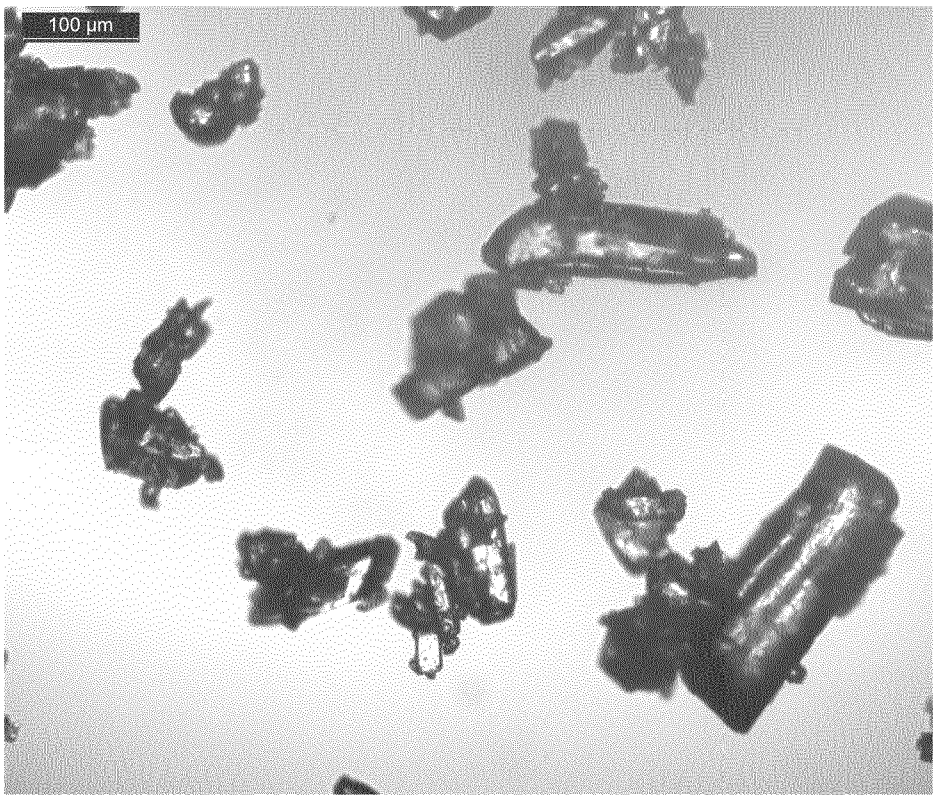


Figure 7c

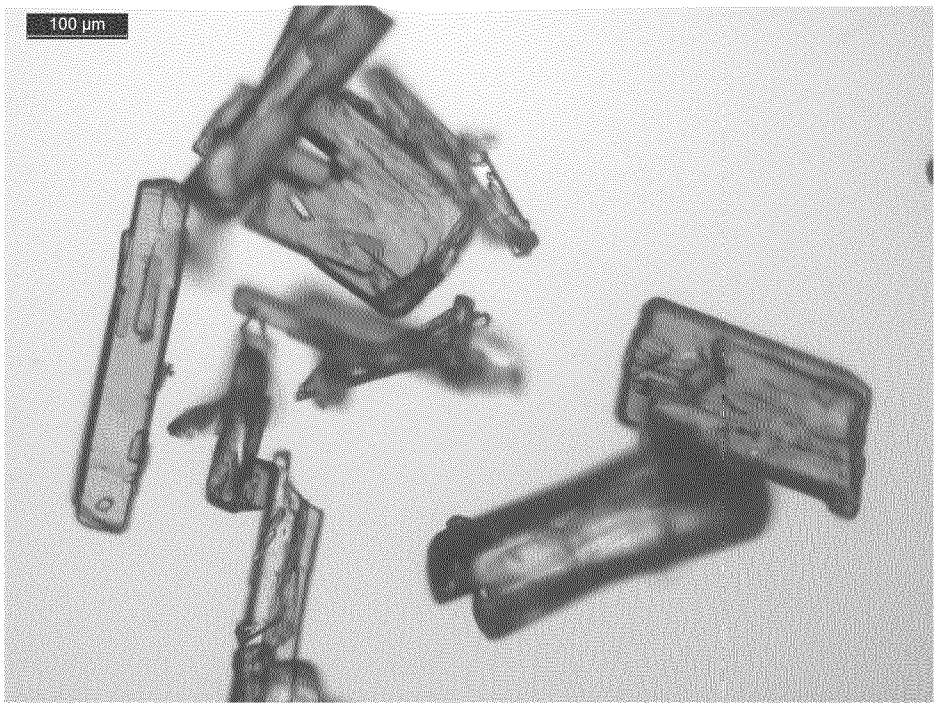


Figure 7d

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/082196

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C67/08 C07C67/11 C07C67/333 C07C231/12 C07D207/404
C07C69/90
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 C07D

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHAN YU, NING ZHENG-XIANG: "Synthesis Technology and Antimicrobial Activity of Cinnamyl Fumarate", JOURNAL OF YUNNAN AGRICULTURAL UNIVERSITY, vol. 21, no. 2, 2006, pages 239-242, XP008180300, abstract	1-9,11
X	WO 2014/197860 A1 (XENOPORT INC [US]) 11 December 2014 (2014-12-11) cited in the application	11-13
A	the whole document	10

-/--

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

[X] See patent family annex.

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

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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
9 March 2017	17/03/2017

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	Tabanella, Stefania

1

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LI NA ET AL: "Study on synthesis of preservative benzyl methyl fumarate", ADVANCED MATERIALS RESEARCH, TRANS TECH PUBLICATIONS LTD, CH, [Online] vol. 236-238, no. Pt. 2, Application of Chemical Engineering, 1 January 2011 (2011-01-01), pages 1970-1973, XP008183609, ISSN: 1022-6680 Retrieved from the Internet: URL:http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.927.7515&rep=rep1&type=pdf> figure 1 -----	1,4-7,9, 11
X	US 2010/048651 A1 (GANGAKHEDKAR ARCHANA [US] ET AL) 25 February 2010 (2010-02-25) examples 25, 48 -----	11

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Information on patent family members

International application No
PCT/EP2016/082196

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