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(71) Applicant (for all designated States except US): **LONZA LTD** [CH/CH]; Lonzastrasse, CH-3930 Visp (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NOTI, Christian** [CH/CH]; Gliserallee 105, CH-3902 Brig-Glis (CH). **SCHMID, Leo** [CH/CH]; Wickertweg 78, CH-3902 Brig-Glis (CH). **RITTINER, Bruno** [CH/CH]; Kirchweg 7, CH-3902 Brig-Glis (CH). **HANSELMANN, Paul** [CH/CH]; Holzachra 25, CH-3902 Brig-Glis (CH). **BIERSTEDT, Anja** [DE/CH]; Gliserallee 179, CH-3902 Brig-Glis (CH).

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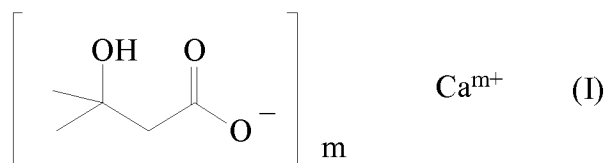
(54) Title: PROCESS FOR THE PREPARATION OF 3-HYDROXY-3-METHYLBUTYRIC ACID OR ITS CALCIUM SALTS

(57) Abstract: A new process for preparing calcium salts of 3-hydroxy-3-methylbutyric acid is described. Lactones obtained from ketene and acetone are hydrolyzed in selective and scalable manners. The 3-hydroxy-3-methylbutyric acid or its calcium salts are useful in preparations for inhibiting protein depletion or as immuno-stimulating feedstuff additives for mammals.



Process for the preparation of 3-hydroxy-3-methylbutyric acid or its calcium salts

The invention discloses a new process for the preparation of calcium salts of 3-hydroxy-3-methylbutyrate and/or hydrates and/or solvates of general formula



wherein m is 1 or 2.

10 Calcium 3-hydroxy-3-methylbutyrate (Ca-HMB compound of formula (I), m= 1 and/or 2) is a nutritional supplement, which represents a calcium salt of 3-hydroxy-3-methylbutyrate (HMB).

HMB and its salts have been found to be useful within the context of a number of applications. Ca-HMB may help muscles to combat protein breakdown, assist in muscle
15 repair and support increased endurance. HMB is described as useful for reducing blood levels of total cholesterol (US20100179112A1 and references cited herein).

HMB has been shown to increase strength and lean mass gains in humans undergoing resistance-exercise training (Applied and Environmental Microbiology (1997), 63(11), 4191-4195).

20 US4992470A (Nissen) describes HMB as a more potent activator of the immune function of T lymphocytes than the standard α -ketoisocaproate. HMB is usable as an immuno-stimulant in human and veterinary medicine. Diet supplementation with 0.05% Ca-HMB (referred to body weight), for one week prevented some of the lung damage associated with mycoplasmosis, induced by Mycoplasma hypopneumoniae injection.

25 Most of the prior art documents describing the preparation of HMB or its salts start with 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol) as starting material. For example in US4992470A (Nissen), HMB was prepared by refluxing 4-hydroxy-4-methyl-2-pentanone with NaClO and NaOH in 1,4-dioxane (haloform reaction). HMB was converted into the
30 calcium salt by neutralization with $\text{Ca}(\text{OH})_2$. A drawback of this method is the high dilution required due to the poor stability of aqueous NaClO.

US6248922B1 discloses a method for preparation of Ca-HMB via the oxidation of 4-hydroxy-4-methyl-2-pentanone using an external heat exchanger. All these procedures using oxidation reagents have the disadvantage of using hazardous chemicals for the oxidation.

- 5 Alternatively a study investigated the microbial conversion of 3-methylbutyric acid (MBA) to HMB by cultures of *Galactomyces reesii* (Applied and Environmental Microbiology (1997), 63(11), 4191-4195). Optimal concentrations of MBA were in the range of 5 to 20 g/L for HMB production. Experiments indicated that HMB yields were sensitive to dissolved oxygen levels and that cell growth decreased significantly as MBA concentrations increased.
- 10 Degradation of HMB was faster at acidic pH, and pH 7.0 was optimal for HMB production. Resting cells obtained from media without MBA could convert MBA to HMB. Hence, a drawback of this method is the high dependence to the pH. Another drawback of this method is that a maximum HMB concentration of 38 g/L was obtained after a very long time of 136 h, and the molar conversion yield was only slightly higher than 0.50 mol of HMB/mol of
- 15 MBA during the fermentation. These drawbacks prevent large scale industrial applicability.

- EP1399138B1 discloses the preparation of silica formulated sodium 3-hydroxy-3-methylbutyrate (Na-HMB) from 4,4-dimethyloxetan-2-one with aqueous sodium hydroxide. However due to the poor solubility of Ca(OH)_2 in water (1.7 g/L in water at 20°C) this
- 20 method can't be applied to the large scale preparation of Ca-HMB. The low solubility furthermore leads to low reactivity and long reaction and filtration time. In addition such process applied to the preparation of Ca-HMB can form side products difficult to remove from the reaction mixture, such as mesityl oxide (abbreviated MoX, with the formula $\text{CH}_3\text{C(O)CH=C(CH}_3)_2$) and 3,3-dimethylacrylic acid (abbreviated DMA, with the formula
- 25 $\text{HOC(O)CH=C(CH}_3)_2$).

- WO98/34897 discloses a method for preparation of 3-hydroxy-3-methylbutyric acid by reacting ketene with acetone to yield the 6 membered ring dioxanone, which is then hydrolysed under basic conditions. This hydrolysis produces two products: the desired
- 30 product 3-hydroxy-3-methylbutyric and acetone as side product. Two molecules acetone react under the basic conditions of the hydrolysis to yield MoX, resulting in prohibitively high MoX content, which can be higher than 1000 ppm.

CN 1417190 A discloses a haloform reaction between 4-methyl-4-hydroxy-2-pentanone (diacetone alcohol) as raw material and aqueous NaOBr solution with the presence of water, followed by acidification to a pH of 2 to 3, only thereafter iso-butanol is added and the extraction with iso-butanol gives an extract containing HMB acid. The HMB acid in the
5 extract is directly salified with $\text{Ca}(\text{OH})_2$ to give the HMB-Ca (calcium beta-hydroxy-beta-methylbutyrate).

The specification discloses one example which is not reproducible:

The example was repeated twice, see below Examples 15 and 16. The yield was only 3.6% of HMB-Ca, instead of the 49.6% given by the disclosure of CN 1417190 A, the solid obtained
10 was not white but brown, and the DMA value was far above specification (DMA: 497 ppm instead of 12 ppm or less).

US 6090978 B discloses a process of the preparation of HMB by a haloform reaction between diacetone alcohol and hypochlorite or hypobromite, followed by acidification to a pH of 3.5
15 or lower. Only thereafter a solvent is added for the extraction of HMB.

There was a need for a simplified process which does not have the disadvantages of the current processes. The process of the instant invention provides a solution. The reaction mixture is concentrated which allows high throughput production. The filtration of the
20 product is rapid and easy. No excess of reagent is required; no hazardous reagents are used and the reagents are readily available. The reaction times are short in each of the process steps and the temperature ranges are close to room temperature. Each process step is highly selective, the basic medium of the method of the invention warrants no formation of pH dependent side products which further can degrade the starting material (DMA promotes the
25 degradation of 4,4-dimethyloxetan-2-one into isobutene and carbon dioxide).

The process should be free of the use of hypochlorite or hypobromite, i.e. should not use a haloform reaction, no chloroform or bromoform should be present, since chloroform is mutagenic and is anticipated to be a human carcinogen. Bromoform is a confirmed animal carcinogen and is detrimental for ozone.

30 The process should give a product with low value of DMA and MoX, preferably DMA content should be 12 ppm or less, and MoX content should be 6 ppm or less.

Preferably, the process should be free of halogenated solvents.

In the following, “OTf” means trifluoromethanesulfonate, also known by the trivial name triflate.

In the following, “OTs” means para-toluenesulfonate, also known by the trivial name tosylate.

5

In the following, “OMs” means methanesulfonate, also known by the trivial name mesylate.

In the following, “OBz” means benzenesulfonate, also known by the name bezylate.

10 In the following, “montmorillonite” means a hydrated sodium calcium aluminium magnesium silicate hydroxide, such as montmorillonite K 10, CAS number 70131-50-9.

In the following, “MTBE” means methyl tert-butyl ether.

15 In the following, “THF” means tetrahydrofuran.

In the following, “proton sponge” means 1,8-bis(dimethylamino)naphthalene, CAS number 20734-58-1.

20 In the following, “TMEDA” means tetramethylethylenediamine.

In the following, “DBU” means 1,8-diazabicycloundec-7-ene.

In the following, “DABCO” means 1,4-diazabicyclo[2.2.2]octane.

25

In the following, “-HMDS” means the hexamethyldisilazide moiety.

In the following, “DMAP” means 4-dimethylaminopyridine.

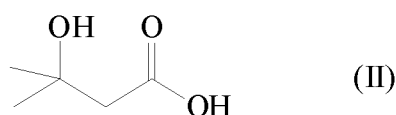
30 In the following, “aryl” represents an optionally substituted aromatic or heteroaromatic group, selected from the group consisting of phenyl, naphth-1-yl, naphth-2-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, benzo[b]furan-2-yl and benzo[b]thiophen-2-yl.

In the following, "C₁₋₆ alkyl" represents for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl or hexyl.

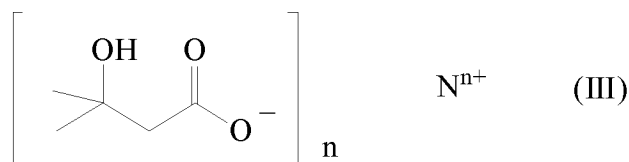
In the following, the "C₁₋₄ alkyl" moieties are independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

Subject of the invention is a process for the preparation of a compound of formula (I) and/or a suitable hydrate and/or solvate thereof comprising a step (1) and a step (2);

step (1) comprises the preparation of a compound of formula (II)



characterized by protonation of a compound of formula (III),



wherein N is Na, Li, K, Ag, Ni, Mg, Cu, Zn, Cs, Ni, Ba, Fe or a mixture thereof;

n is 1, 2 or a mixture thereof;

in the presence of a solvent (1) and an acid (1);

the solvent (1) being selected from the group consisting of water, acetonitrile, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene, dioxane, C₁₋₄ alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof;

the acid (1) being an organic or an inorganic acid;

step (2) comprises the preparation of a compound of formula (I) characterized by deprotonation of a compound of formula (II) in the presence of a solvent (2) and a salt (2);

the solvent (2) being selected from the group consisting of water, acetonitrile, ethanol, 2-methyl-1-propanol, isopropanol, MTBE, THF, acetone, methanol and mixtures thereof;

the salt (2) being an organic or an inorganic salt;

with the proviso, that compound of formula (III) is not prepared by a haloform reaction from diacetone alcohol.

- 5 In step (1), no chloroform and no bromoform and no iodoform is present. Preferably, in step (1) and in step (2) no chloroform and no bromoform and no iodoform is present. Preferably, compound of formula (III) is not produced by a haloform reaction from diacetone alcohol.

- 10 The acid (1) is selected from the group consisting of polymeric sulfonic acid resin, aqueous HCl, HCl gas, HBr, HI, HF, HCN, H₂SO₄, HNO₃, HNO₂, MsOH, TsOH, TfOH, BzOH, trifluoroacetic acid, ammonium chloride, phosphoric acid and mixtures thereof. Preferably acid (1) is an inorganic acid, more preferably acid (1) is aqueous HCl, H₂SO₄ or a mixture thereof, even more preferably acid (1) is aqueous HCl.

- 15 Preferably acid (1) is used in such an amount, that a pH of from 3.5 to 6.2 is attained for the protonation, i.e. the protonation is preferably done at a pH of from 3.5 to 6.2. More preferably, the pH is of from 3.6 to 6.1, even more preferably from 3.7 to 6.1, especially from 3.8 to 6.1, more especially from 3.9 to 6.1, even more especially from 4 to 6.1, in particular from 4.0 to 6.1.

20

Preferably, the reaction temperature of step (1) is of from -78 to 100 °C, more preferably of from -20 to 40 °C, even more preferably of from -5 to 20 °C.

- 25 Preferably, the reaction of step (1) is done at a pressure of from 1 to 10 bar, more preferably of from 1 to 5 bar, even more preferably of from 1 to 2 bar.

Preferably, the reaction time of step (1) is of from 1 min to 10 h, more preferably of from 1 min to 2 h, even more preferably of from 1 min to 1 h.

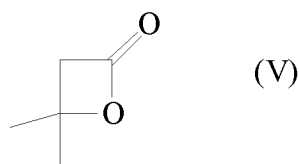
- 30 Preferably, the reaction of step (1) is done in a solvent (1).

More preferably, the solvent (1) is selected from the group consisting of water, acetonitrile, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene, dioxane, C₁₋₄ alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof,

even more preferably, the solvent (1) is selected from the group consisting of water, acetonitrile, hexanes, heptanes, toluene, xylene, mesitylene, dioxane, C₁₋₄ alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof, especially of water, MTBE or a mixture thereof.

5

Preferably, the amount of solvent (1) is of from 0 to 100 parts, more preferably of from 1 to 10 parts, even more preferably of from 3 to 5 parts, the parts being a weight factor of the parts by weight of compound of formula (V). Wherein compound of formula (V) is



10

Preferably, of from 0.55 to 5, more preferably of from 0.95 to 2, even more preferably of from 1.1 to 1.5 mol equivalents, of acid (1) are used, the mol equivalents being based the mol of compound of formula (V).

15

Preferably after the step (1), the compound of formula (II) is not isolated.

Preferably, any aqueous phase can be separated from any organic phase before or after the addition of acid (1), more preferably after the addition of acid (1).

20

Compounds of formula (I) are obtained in a pure form, as hydrates, as solvates and mixtures thereof. Preferably the solvates are formed with solvents listed in the US Food and Drug Administration Guidance for Industry Q3C, selected from the group consisting of class 2, class 4, class 3 and mixtures thereof, more preferably of class 4, class 3 and mixtures thereof, even more preferably of class 3. Solvents of class 2 are for example acetonitrile, methanol, THF and toluene. Solvents of class 4 are for example isopropyl ether, 2-methyltetrahydrofuran and methylisopropyl ketone. Solvents of class 3 are for example ethanol, acetone, MTBE, ethyl acetate and isopropanol. Preferably the hydrates are monohydrates, more preferably compounds of formula (I) is obtained as a monohydrate.

30

m is 1 or 2, preferably m is 2.

Preferably, the salt (2) is selected from the group consisting of CaCO_3 , $\text{Ca}(\text{HCO}_3)_2$, $\text{Ca}(\text{OTf})_2$, $\text{Ca}(\text{OMs})_2$, $\text{Ca}(\text{OTs})_2$, $\text{Ca}(\text{OBz})_2$, CaBr_2 , CaF_2 , CaI_2 , CaNO_3 , CaSO_4 , $\text{Ca}(\text{HSO}_4)_2$, $\text{Ca}(\text{OAc})_2$, $\text{Ca}(\text{O-aryl})_2$, $\text{Ca}(\text{O-C}_{1-6} \text{ alkyl})$, CaS , $\text{Ca}(\text{SH}_2)$, $\text{Ca}_3(\text{PO}_4)_2$, $\text{Ca}(\text{HPO}_4)$, $\text{Ca}(\text{H}_2\text{PO}_4)_2$, CaCl_2 , CaO ,
5 $\text{Ca}(\text{OH})_2$ and mixtures thereof, more preferably the salt (2) is CaCO_3 , $\text{Ca}(\text{HCO}_3)_2$, CaBr_2 , CaCl_2 , CaO , $\text{Ca}(\text{OH})_2$, even more preferably the salt (2) is CaCl_2 , CaO , $\text{Ca}(\text{OH})_2$.

Preferably, the reaction of step (2) is done in a solvent (2).

More preferably, the solvent (2) is selected from the group consisting of water, acetonitrile,
10 ethanol, 2-methyl-1-propanol, isopropanol, MTBE, THF, acetone, methanol and mixtures thereof,
even more preferably the solvent (2) is a mixture of ethanol and water.

In the preferred embodiment where the solvent (2) is a mixture of ethanol and water, ethanol
15 and water are preferably in an ethanol: water w/w ratio from 99:1 to 10:90, more preferably from 99:1 to 70:30, even more preferably from 99:1 to 90:10, most preferred 95:5.

Preferably, the reaction temperature of step (2) is of from -78 to 150°C , more preferably of from -20 to 70°C , even more preferably of from -2 to 50°C .
20

Preferably, the reaction of step (2) is done at a pressure of from 1 to 10 bar, more preferably of from 1 to 5 bar, even more preferably of from 1 to 2 bar.

Preferably, the reaction time of step (2) is of from 1 min to 20 h, more preferably of from 20 min to 4 h, even more preferably of from 20 min to 2 h.
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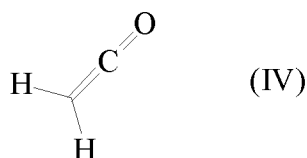
Preferably, the amount of solvent (2) is of from 2 to 100 parts, more preferably of from 5 to 20 parts, even more preferably of from 7 to 13 parts, the parts being a weight factor of the parts by weight of compound of formula (V).
30

Preferably, of from 0.3 to 20, more preferably of from 0.4 to 2, even more preferably of from 0.4 to 1 mol equivalents, of salt (2) are used, the mol equivalents being based on the mol of compound of formula (V).

After the reaction of step (2), the compound of formula (I) is isolated by standard methods such as extraction, concentration, filtration, washing and drying. Concentration is preferably done by distillation of a solvent (2).

- 5 In another embodiment, compound of formula (II) is isolated after step (1) by standard isolation methods known from the skilled person such as extraction, concentration, filtration, washing and drying.

In a preferred embodiment, compound of formula (III) is prepared by a process comprising a
10 step (3) and a step (4);
step (3) comprises the preparation of a compound of formula (V) defined above characterized by cycloaddition of ketene of formula (IV)



- 15 with acetone, in the presence of a solvent (3) and an acid (3);
the solvent (3) being selected from the group consisting of acetone, pentane, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene and mixtures thereof;
20 the acid (3) being an inorganic acid;

- step (4) comprises the preparation of a compound of formula (III) characterized by ring opening of a compound of formula (V) in the presence of a solvent (4) and a salt (4);
the solvent (4) being selected from the group consisting of water, acetonitrile, hexanes,
25 heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene, dioxane, C_{1-4} alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof;
the salt (4) being an inorganic salt;
n being 1 or 2;

- 30 Preferably, the acid (3) is or a Lewis acid such as selected from a group consisting of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{B}(\text{OH})_3$, $\text{BF}_3 \cdot \text{Me}_2\text{O}$, $\text{BF}_3 \cdot \text{THF}$, $\text{BF}_3 \cdot \text{Me}_2\text{S}$, BCl_3 , AlCl_3 , AlBr_3 , FeCl_3 , ZnCl_2 , SnCl_4 ,

Ce(OTf)₃, TiCl₄, GaCl₃, LiCl and mixtures thereof, more preferably BF₃.Et₂O, AlCl₃ or a mixture thereof.

In another preferred embodiment, the acid (3) is an aluminosilicate such as montmorillonite.

5

Preferably, the reaction temperature of step (3) is of from -78 to 50 °C, more preferably of from -40 to 20 °C, even more preferably of from -30 to 5 °C.

Preferably, the reaction of step (3) is done at a pressure of from 1 to 10 bar, more preferably of from 1 to 5 bar, even more preferably of from 1 to 2 bar.

10

Step (3) can be performed in batch mode, semi-continuous mode or continuous mode, preferably in semi-continuous mode or continuous mode, more preferably in continuous mode.

15

Preferably, the reaction time of step (3) performed in batch mode is of from 2 min to 20 h, more preferably of from 15 min to 12 h, even more preferably of from 30 min to 8 h.

20

Preferably, the residence time of step (3) performed in semi-continuous mode or continuous mode is of from 2 min to 10 h, more preferably of from 15 min to 6 h, even more preferably of from 30 min to 4 h.

Preferably, the reaction of step (3) is done in a solvent (3).

25

More preferably, the solvent (3) is selected from the group consisting of acetone, pentane, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene and mixtures thereof,

even more preferably, the solvent (3) is selected from the group consisting of acetone, pentane, hexanes, heptanes, dichloromethane, toluene, xylene, mesitylene and mixtures thereof,

30

in another even more preferred embodiment, the solvent (3) is selected from the group consisting of acetone, pentane, hexanes, heptanes, toluene, xylene, mesitylene and mixtures thereof,

especially, the solvent (3) is selected from the group consisting of acetone, heptanes, dichloromethane and mixtures thereof,

in another especial embodiment, the solvent (3) is selected from the group consisting of acetone, heptanes and mixtures thereof, more especially the solvent (3) is acetone.

- 5 Preferably, the amount of solvent (3) is of from 0 to 100 parts, more preferably of from 1 to 20 parts, even more preferably of from 2 to 5 parts, the parts being a weight factor of the parts by weight of compound of formula (IV).

Preferably, of from 1 to 50, more preferably of from 1.5 to 20, even more preferably of from 1.7 to 5 mol equivalents, of acetone are used in step (3), the mol equivalents being based the mol of compound of formula (IV).

Preferably, of from 0.001 to 10, more preferably of from 0.002 to 1, even more preferably of from 0.003 to 0.012 mol equivalents, of acid (3) are used, the mol equivalents being based the mol of compound of formula (IV).

Preferably the acid (3) of step (3) is quenched with a base (3). Preferably base (3) is selected from the group comprising pyridine, sterically hindered pyridines such as methylpyridine isomers (picoline), dimethylpyridine isomers (lutidine), trimethylpyridine isomers (collidine) and 5-ethyl-2-methylpyridine, DMAP, imidazole, benzimidazole, phosphazenes, urotropine, diamines such as TMEDA, proton sponge, 1,8-bis(hexamethyltriaminophosphazenylnaphthalene, DBU, morpholine, quinuclidine, DABCO, (C₁₋₆ alkyl)₃N such as triethylamine, diisopropylethylamine and trimethylamine, (C₁₋₆ alkyl)₂NH, dicyclohexylamine, didecylmethylamine, ammonia, carbonates such as CaCO₃ and Cs₂CO₃, bicarbonates such as Ca(CO₃)₂, NaH, KH, LiH, C₁₋₆ alkyl-Li such as n-BuLi and hexyllithium, Li-HMDS, K-HMDS, Na-HMDS and mixtures thereof, more preferably, base (3) is selected from the group comprising didecylmethylamine, 5-ethyl-2-methylpyridine, urotropine, proton sponge and mixtures thereof.

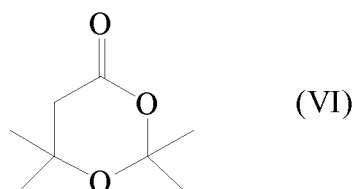
30 Preferably, of from 0.25 to 6, more preferably of from 0.4 to 4, even more preferably of from 0.6 to 2.5 mol equivalents, of base (3) are used, the mol equivalents being based the mol of acid (3).

The base (3) is used either pure or in solution in solvent (3), preferably base (3) is used in a pure form.

Preferably, compound of formula (V) is purified by standard methods known by the skilled person such as extraction, concentration, distillation and chromatography, more preferably by distillation and chromatography, even more preferably by distillation.

Base (3) can be added to acid (3) (normal quench) or acid (3) can be added to base (3) (reverse quench), preferably acid (3) is added to base (3).

In another preferred embodiment, compound of formula (VI)



either pure or as a mixture with compound of formula (V), is prepared in a step (3b). The step (3b) is described for example from ketene of formula (IV) and acetone in WO9834897A1.

Preferably, the acid (3b) is a Lewis acid such as selected from a group consisting of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{B}(\text{OH})_3$, $\text{BF}_3 \cdot \text{Me}_2\text{O}$, $\text{BF}_3 \cdot \text{THF}$, $\text{BF}_3 \cdot \text{Me}_2\text{S}$, BCl_3 , AlCl_3 , AlBr_3 , FeCl_3 , ZnCl_2 , SnCl_4 , $\text{Ce}(\text{OTf})_3$, TiCl_4 , GaCl_3 , LiCl and mixtures thereof, more preferably $\text{BF}_3 \cdot \text{Et}_2\text{O}$, AlCl_3 or a mixture thereof.

In another preferred embodiment, the acid (3b) is an aluminosilicate such as montmorillonite.

Preferably, the reaction temperature of step (3b) is of from -78 to 50°C , more preferably of from -40 to 20°C , even more preferably of from -30 to 5°C .

Preferably, the reaction of step (3b) is done at a pressure of from 1 to 10 bar, more preferably of from 1 to 5 bar, even more preferably of from 1 to 2 bar.

Step (3b) can be performed in batch mode, semi-continuous mode or continuous mode, preferably in semi-continuous mode or continuous mode, more preferably in continuous mode.

- 5 Preferably, the reaction time of step (3b) performed in batch mode is of from 2 min to 35 h, more preferably of from 15 min to 20 h, even more preferably of from 2 min to 10 h.

Preferably, the residence time of step (3b) performed in semi-continuous mode or continuous mode is of from 2 min to 10 h, more preferably of from 15 min to 6 h, even more preferably
10 of from 30 min to 4 h.

Preferably, the reaction of step (3b) is done in a solvent (3b).

More preferably, the solvent (3b) is selected from the group consisting of acetone, pentane, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene,
15 xylene, mesitylene and mixtures thereof,

in another more preferred embodiment, the solvent (3b) is selected from the group consisting of acetone, pentane, hexanes, heptanes, toluene, xylene, mesitylene and mixtures thereof, even more preferably, the solvent (3b) is selected from the group consisting of acetone, heptanes, dichloromethane and mixtures thereof,

20 in another even more preferred embodiment, the solvent (3b) is selected from the group consisting of acetone, heptanes and mixtures thereof, especially, the solvent (3b) is acetone.

Preferably, the amount of solvent (3b) is of from 0 to 100 parts, more preferably of from 1 to
25 20 parts, even more preferably of from 2 to 5 parts, the parts being a weight factor of the parts by weight of compound of formula (IV).

Preferably, of from 1 to 50, more preferably of from 1.5 to 20, even more preferably of from 1.7 to 5 mol equivalents, of acetone are used in step (3b), the mol equivalents being based the
30 mol of compound of formula (IV).

Preferably, of from 0.001 to 10, more preferably of from 0.002 to 1, even more preferably of from 0.003 to 0.012 mol equivalents, of acid (3b) are used, the mol equivalents being based the mol of compound of formula (IV).

Preferably the acid (3b) of step (3b) is quenched with a base (3b). Preferably base (3b) is selected from the group comprising pyridine, sterically hindered pyridines such as methylpyridine isomers (picoline), dimethylpyridine isomers (lutidine), trimethylpyridine isomers (collidine) and 5-ethyl-2-methylpyridine, DMAP, imidazole, benzimidazole, phosphazenes, urotropine, diamines such as TMEDA, proton sponge, 1,8-bis(hexamethyltriaminophosphazeryl)naphthalene, DBU, morpholine, quinuclidine, DABCO, (C₁₋₆ alkyl)₃N such as triethylamine, diisopropylethylamine and trimethylamine, (C₁₋₆ alkyl)₂NH, dicyclohexylamine, didecylmethylamine, ammonia, carbonates such as CaCO₃ and Cs₂CO₃, bicarbonates such as Ca(CO₃)₂, NaH, KH, LiH, C₁₋₆ alkyl-Li such as n-BuLi and hexyllithium, Li-HMDS, K-HMDS, Na-HMDS and mixtures thereof, more preferably, base (3b) is selected from the group comprising didecylmethylamine, 5-ethyl-2-methylpyridine, urotropine, proton sponge and mixtures thereof.

The base (3b) is used either pure or in solution in solvent (3b), preferably base (3b) is used in a pure form.

Preferably, compound of formula (VI) is purified by standard methods known by the skilled person such as extraction, concentration, distillation and chromatography, more preferably by distillation and chromatography, even more preferably by chromatography.

Base (3b) can be added to acid (3b) (normal quench) or acid (3b) can be added to base (3b) (reverse quench), preferably acid (3b) is added to base (3b).

In a preferred embodiment, compound of formula (III) is prepared in a step (4b), characterized by ring opening of a compound of formula (VI), either pure or as a mixture with compound of formula (V), in the presence of a solvent (4b) and a salt (4b); the solvent (4b) being selected from the group consisting of water, acetonitrile, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene, dioxane, C₁₋₄ alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof; preferably, the solvent (4b) is selected from the group consisting of water, acetonitrile, hexanes, heptanes, toluene, xylene, mesitylene, dioxane, C₁₋₄ alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof; the salt (4b) being an inorganic salt;

n being 1 or 2;

In a preferred embodiment, step (4), step (1) and step (2) are performed in one pot.

5 In a preferred embodiment, step (4b), step (1) and step (2) are performed in one pot.

Preferably, the reaction of step (3) and step (3b) are done under inert atmosphere.

10 Preferably, the reactions of step (1), step (2), step (4) and step (4b) are done under normal atmosphere.

In the process of the invention, compound of formula (I) is obtained in the same yield and purity starting from either compound of formula (V), compound of formula (VI) or a mixture thereof.

15

Preferably the salt (4) is selecting from the group consisting of Ni(OH)_2 , Mg(OH)_2 , MgO , ZnO , Ba(OH)_2 , Cu(OH)_2 , Al_2O_3 , Al(OH)_3 , Ag_2O , Ag(OH) , Cs_2CO_3 , $\text{Cs(HCO}_3\text{)}$, FeSO_4 , $\text{Fe}_2(\text{SO}_4)_3$, FeSO_4 , Fe_2O_3 , Fe(OH)_3 , FeO , Fe(OH)_2 , Li(OH) , K(OH) , Na(OH) and mixtures thereof, more preferably the salt (4) is selecting from the group consisting of Li(OH) , K(OH) ,
20 Na(OH) and mixtures thereof, even more preferably the salt (4) is Na(OH) .

Preferably, the reaction temperature of step (4) is of from -78 to 150°C , more preferably of from -20 to 50°C , even more preferably of from -2 to 20°C .

25 Preferably, the reaction of step (4) is done at a pressure of from 1 to 10 bar, more preferably of from 1 to 5 bar, even more preferably of from 1 to 2 bar.

Preferably, the reaction time of step (4) is of from 1 min to 16 h, more preferably of from 10 min to 5 h, even more preferably of from 0.5 to 2 h

30

Preferably, the reaction of step (4) is done in a solvent (4). More preferably, the solvent (4) is the same as solvent (1) defined above. Preferably, all the preferred embodiments of the solvent (1) are applied to the solvent (4).

Preferably, the amount of solvent (4) is of from 0 to 20 parts, more preferably of from 1 to 10 parts, even more preferably of from 3 to 7 parts, the parts being a weight factor of the parts by weight of compound of formula (V).

- 5 Preferably, of from 0.5 to 4, more preferably of from 0.95 to 2, even more preferably of from 1 to 1.4 mol equivalents, of salt (4) are used, the mol equivalents being based the mol of compound of formula (V).

n is 1, 2 or a mixture thereof, preferably n is 1.

10

Preferably the salt (4b) is selecting from the group consisting of Ni(OH)_2 , Mg(OH)_2 , MgO , ZnO , Ba(OH)_2 , Cu(OH)_2 , Al_2O_3 , Al(OH)_3 , Ag_2O , Ag(OH) , Cs_2CO_3 , $\text{Cs(HCO}_3\text{)}$, FeSO_4 , $\text{Fe}_2(\text{SO}_4)_3$, FeSO_4 , Fe_2O_3 , Fe(OH)_3 , FeO , Fe(OH)_2 , Li(OH) , K(OH) , Na(OH) and mixtures thereof, more preferably the salt (4b) is selecting from the group consisting of Li(OH) ,
15 K(OH) , Na(OH) and mixtures thereof, even more preferably the salt (4b) is Na(OH) .

Preferably, the reaction temperature of step (4b) is of from -78 to 150 °C, more preferably of from -20 to 50 °C, even more preferably of from -10 to 10 °C.

- 20 Preferably, the reaction of step (4b) is done at a pressure of from 1 to 10 bar, more preferably of from 1 to 5 bar, even more preferably of from 1 to 2 bar.

Preferably, the reaction time of step (4b) is of from 1 min to 16 h, more preferably of from 10 min to 5 h, even more preferably of from 0.5 to 2 h

25

Preferably, the reaction of step (4b) is done in a solvent (4b). More preferably, the solvent (4b) is the same as solvent (1) defined above. Preferably, all the preferred embodiments of the solvent (1) are applied to the solvent (4b).

- 30 Preferably, the amount of solvent (4b) is of from 0 to 20 parts, more preferably of from 1 to 10 parts, even more preferably of from 3 to 7 parts, the parts being a weight factor of the parts by weight of compound of formula (VI).

Preferably, of from 0.5 to 4, more preferably of from 0.95 to 2, even more preferably of from 1 to 1.4 mol equivalents, of salt (4b) are used, the mol equivalents being based the mol of compound of formula (VI).

5 In another embodiment of the invention, the salt (4) of step (4) is selected from the group consisting of Ca(OH)_2 , CaBr_2 , CaCl_2 , CaO and mixtures thereof, and compound of formula (I), wherein m is 1 or 2, is isolated after step (4) by standard isolation methods known from the skilled person such as extraction, concentration, filtration, washing and drying.

10 In another embodiment of the invention, the salt (4b) of step (4b) is selected from the group consisting of Ca(OH)_2 , CaBr_2 , CaCl_2 , CaO and mixtures thereof, and compound of formula (I), wherein m is 1 or 2, is isolated after step (4b) by standard isolation methods known from the skilled person such as extraction, concentration, filtration, washing and drying.

15 Further subject of the invention is a process for the preparation of a compound of formula (I) and/or a suitable hydrate and/or solvate thereof,
comprising a step (4) and a step (5);
step (4) comprises the preparation of a compound of formula (III) characterized by ring opening of a compound of formula (V), a compound of formula (VI), or a mixture thereof in
20 the presence of a solvent (4) and a salt (4);
the solvent (4) being water;
the salt (4) being NaOH ;
N being Na;
n being 1;

25 step (5) comprises the preparation of a compound of formula (I) characterized by metal exchange of a compound of formula (III) in the presence of a water and a salt (5);
the salt (5) being CaCl_2 , CaBr_2 , CaO , Ca(OH)_2 and mixtures thereof;
m being 1 or 2.

30 Preferably, no organic solvents are used in step (4) and step (5), organic solvents such as solvent (4) described above can be optionally used.

Preferably, NaOH is the salt (4) used in step (4), optionally other alkali bases such as LiOH. KOH and mixtures thereof can be used as salt (4).

m is 1 or 2, preferably m is 2.

5

Preferably, the salt (5) is selected from the group consisting of CaCl_2 , CaBr_2 and a mixture thereof, more preferably the salt (5) is CaCl_2 .

10

Preferably, of from 0.5 to 4, more preferably of from 0.95 to 2, even more preferably of from 1 to 1.4 mol equivalents, of salt (5) are used, the mol equivalents being based the mol of compound of formula (V).

Preferably, the reaction temperature of step (5) is of from -20 to 100 °C, more preferably of from -5 to 70 °C, even more preferably of from -2 to 50 °C.

15

Preferably, the reaction of step (5) is done at a pressure of from 1 to 10 bar, more preferably of from 1 to 5 bar, even more preferably of from 1 to 2 bar.

20

Preferably, the reaction time of step (5) is of from 1 min to 20 h, more preferably of from 20 min to 4 h, even more preferably of from 20 min to 2 h.

25

Preferably, the amount of water is of from 0 to 100 parts, more preferably of from 2 to 20 parts, even more preferably of from 7 to 13 parts, the parts being a weight factor of the parts by weight of compound of formula (V).

Preferably, of from 0.5 to 20, more preferably of from 0.6 to 2, even more preferably of from 0.7 to 1.5 mol equivalents, of salt (5) are used, the mol equivalents being based on the mol of compound of formula (V).

30 In another preferred embodiment, compound of formula (VI), either pure or as a mixture with compound of formula (V), is reacted in step (5) instead of pure compound of formula (V).

The above mentioned preferred embodiments with compound of formula (V) are also applied to compound of formula (VI), either pure or as a mixture with compound of formula (V).

Preferably, no chloroform and no bromoform and no iodoform is present in any step of the process.

Preferably, no halogenated solvent is used in any step of the process.

5

It was found, that the protonation in step (1) is preferably not done at a too low or too high pH, otherwise undesired side products are observed. Furthermore, the protonation should be done in the presence of a solvent, which further proves beneficial for a low content of side products.

10

Examples

Abbreviations:

celite® 545 CAS: 68855-54-9

5 HPLC method used for the determination of the purity:

Column: YMC-Pack ODS-AM, 250×4.6 mm; Temperature: 20°C; Flow: 0.5 mL/min; eluent A: buffered H₂O: pH 2.9 (H₃PO₄/KH₂PO₄); eluent B: acetonitrile/water 4:1 (v/v); gradient: 0-20 min: 100% eluent A, then wash column for 25 min with 100% eluent B; UV Detection: 214 nm.

10 DMA and MoX used as standard were purchased from Aldrich.

Example 1a: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To MTBE (75 mL) was added aqueous NaOH (25% w/w; 45.5 g, 0.29 mol). The reaction
15 mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 25 g, 0.24 mol) in MTBE (50 mL) was added dropwise at 5 °C. After complete addition (ca. 20 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 1.5 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 38.5 g, 0.32 mol) was added dropwise until a pH of 4 was reached
20 (apparent pH of stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (2 × 40 mL). The aqueous phase was discarded. The combined organic phases were cooled to 0 °C and then added dropwise within 30 min to a reaction mixture containing Ca(OH)₂ (9 g, 0.12 mol) in ethanol (150 g). Water (13.5 g) and additional ethanol
25 (100 g) were added at room temperature; then the reaction mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. Stirring was continued at 50 °C until a clear solution was obtained (ca. 10 min). This solution was filtered over celite® 545 and then cooled to 10 °C within 20 min. The precipitated product was filtered off and washed with ethanol (50 g). The product was dried overnight under reduced pressure affording the title
30 compound (26 g, 75%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 5ppm, MoX: 0ppm).

Example 1b: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

Example 1 was repeated with the sole difference, that after cooling of the biphasic solution to 0 °C, the pH was adjusted with aqueous HCl to 2 and not to 4 as in example 1.

The yield of title compound was 49.8 g, 84%. Purity was more than 99.5 area% according to HPLC analysis (DMA: 110 ppm, MoX: 18 ppm).

5

Example 1c: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

Example 1 was repeated with the sole difference, that after cooling of the biphasic solution to 0 °C, the pH was adjusted with aqueous HCl to 3 and not to 4 as in example 1.

10 The yield of title compound was 49.8 g, 84%. Purity was more than 99.5 area% according to HPLC analysis (DMA: 45 ppm, MoX: 12 ppm).

Example 2: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

15 To MTBE (150 mL) was added aqueous NaOH (25% w/w; 87.4 g, 0.55 mol). The reaction mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 50 g, 0.44 mol) in MTBE (50 mL) was added dropwise at 5 °C. After complete addition (ca. 20 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 1 to 2 h. The biphasic solution was cooled to 0 °C and
20 aqueous HCl (30% w/w, 69.8 g, 0.61 mol) was added dropwise until a pH of 4 was reached (apparent pH of stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (2 × 70 mL). The aqueous phase was discarded. The combined organic phases were added dropwise within 30 min to a reaction mixture containing Ca(OH)₂ (16.8 g,
25 0.22 mol) and water (50 g) and MTBE was distilled continuously off. After complete addition and removal of MTBE the reaction mixture was diluted with ethanol (100 mL). The reaction was warmed to 70 °C and filtered over celite® 545. Additional ethanol (400 mL) was added at 55 °C. The solution was then allowed to cool to 0 °C within 4 h. The precipitated product was filtered off and washed with ethanol/water (100 mL; 9:1). The product was dried
30 overnight under reduced pressure affording the title compound (51.5 g, 81%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 8 ppm, MoX: 0 ppm).

Example 3: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

Part 3.1: To MTBE (100 mL) was added aqueous NaOH (25% w/w; 95 g, 0.59 mol). The reaction mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 50 g, 0.24 mol) in MTBE (50 mL) was added dropwise at 5 °C. After complete addition (ca. 25 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 2 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 68.3 g, 0.6 mol) was added dropwise until a pH of 4 was reached (apparent pH of stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (2 × 70 mL). The aqueous phase was discarded. The combined organic phases were divided in two parts 3.2 and 3.3.

Part 3.2: Half of the solution prepared in part 3.1 was added within 30 min to a reaction mixture containing Ca(OH)₂ (9 g, 0.12 mol) in ethanol (150 g) at 20 °C. The reaction mixture was heated up to 45 °C and MTBE was distilled off. Celite® 545 (5 g) was added to the reaction mixture. After filtration, the reaction mixture was cooled to 0 °C within 2 h. The precipitated product was filtered off and washed with ethanol (50 g). The product was dried overnight under reduced pressure affording the title compound (23.5 g, 74%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 10 ppm, MoX: 0 ppm).

Part 3.3: Half of the solution prepared in part 3.1 was added within 30 min to a reaction mixture containing Ca(OH)₂ (9 g, 0.12 mol) in ethanol (150 g) at 40 °C. The reaction mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. Celite® 545 (5 g) was added to the reaction mixture. After filtration, the reaction mixture was cooled to 0 °C within 2 h. The precipitated product was filtered off and washed with ethanol (50 g). The product was dried overnight under reduced pressure affording the title compound (23.9 g, 75%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 12 ppm, MoX: 1 ppm).

Example 4: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

Part 4.1: To MTBE (150 mL) was added aqueous NaOH (25% w/w; 95 g, 0.59 mol). The reaction mixture was cooled to 0 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 50 g, 0.24 mol) in MTBE (100 mL) was added dropwise at 0 to 5 °C. After complete addition (ca. 25 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 2 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 69.5 g, 0.6 mol) was added dropwise until a pH of 4 was reached (apparent pH of stirred mixture). The reaction mixture was allowed to warm to room

temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (2 × 80 mL). The aqueous phase was discarded. The combined organic phases were divided in two parts 4.2 and 4.3.

Part 4.2: Half of the solution (184 g) prepared in part 4.1 was added within 30 min to a reaction mixture containing Ca(OH)₂ (9 g, 0.12 mol), ethanol (250 g) and water (24.4 g) at 0 °C. The reaction mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. The reaction mixture was further diluted with ethanol (100 mL) and then Celite® 545 (5 g) was added to the reaction mixture and stirring was continued for 5 min at this temperature. After filtration, the reaction mixture was cooled to 0 °C within 2 h. The precipitated product was filtered off and washed with ethanol (50 g). The product was dried overnight under reduced pressure affording the title compound (25.8 g, 81%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 5 ppm, MoX: 0 ppm).

Part 4.3: Ethanol (200 g) was added to half of the solution prepared in part 4.1 at 0 °C. To this reaction mixture was then added a mixture of Ca(OH)₂ (9 g, 0.12 mol), ethanol (250 g) and water (24.4 g). The reaction mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. Celite® 545 (5 g) was added to the reaction mixture and stirring was continued for 5 min at this temperature. After filtration, the reaction mixture was cooled to 0 °C within 2 h. The precipitated product was filtered off and washed with ethanol (50 g). The product was dried overnight under reduced pressure affording the title compound (25.1 g, 79%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 35 ppm, MoX: 1 ppm).

Example 5: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To NaOH (25% w/w; 95.9 g, 0.6 mol) was added at 15 °C 4,4-dimethyloxetan-2-one (compound of formula (V); 50 g, 0.48 mol) over 1 h. The reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 1 h. MTBE (160 mL) was added and then the reaction mixture was cooled to 0 °C and aqueous HCl (30% w/w, 69.2 g, 0.57 mol) was added dropwise until a pH of 4 was reached (apparent pH of the stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (3 × 60 mL). The aqueous phase was discarded. To the combined organic phases at room temperature were added Ca(OH)₂ (18.2 g, 0.24 mol) and ethanol (100 g). The reaction mixture was further diluted with water (27 g) and additional ethanol (100 g); then the reaction

mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. Additional ethanol (300 g) was continuously added during the distillation. After complete removal of MTBE (1 h) the hot reaction mixture was filtered over celite® 545 and then cooled to 0 °C within 2 h. The precipitated product was filtered off and washed with ethanol (50 g). The product was dried overnight under reduced pressure affording the title compound (50.6 g, 73%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 24 ppm, MoX: 0 ppm).

Example 6: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To MTBE (100 mL) was added aqueous NaOH (25% w/w; 87.4 g, 0.55 mol). The reaction mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 50 g, 0.24 mol) in MTBE (50 mL) was added dropwise at 5 °C. After complete addition (ca. 20 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 2 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 64.2 g, 0.56 mol) was added dropwise until a pH of 4 was reached (apparent pH of the stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (2 × 70 mL). The aqueous phase was discarded. The combined organic phases were cooled to 0 °C and then added dropwise within 30 min to a reaction mixture containing Ca(OH)₂ (16.7 g, 0.22 mol) in water (60 mL). The reaction mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. After complete removal of MTBE the reaction mixture was cooled to room temperature, then acetone (150 mL) was added and the reaction mixture was heated to 90 °C. Additional acetone (150 mL) was added and the reaction mixture was cooled to 10 °C within 4 h. The precipitated product was filtered off and washed with acetone/water (140 mL, 95:5). The product was dried overnight under reduced pressure affording the title compound (56.9 g, 89%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 67 ppm, MoX: 9 ppm).

Example 7: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To MTBE (50 mL) was added aqueous NaOH (25% w/w; 47.5 g, 0.3 mol). The reaction mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 25 g, 0.12 mol) in MTBE (25 mL) was added dropwise at 5 °C. After complete addition (ca.

20 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 2 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 34 g, 0.28 mol) was added dropwise until a pH of 4 was reached (apparent pH of the stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (2 × 40 mL). The aqueous phase was discarded. The combined organic phases were cooled to 0 °C and then added dropwise within 30 min to a reaction mixture containing Ca(OH)₂ (8.6 g, 0.11 mol) in water (48 mL). The reaction mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. After complete removal of MTBE the reaction mixture was cooled to room temperature, then isopropanol (150 mL) was added and the reaction mixture was heated to 50 °C. Additional isopropanol (100 mL) was added and the reaction mixture was cooled to 20 °C within 4 h. The precipitated product was filtered off. The product was dried overnight under reduced pressure affording the title compound (25.4 g, 73%). Purity was more than 99.5 area% according to HPLC analysis. (DMA: 12 ppm, MoX: 1 ppm).

Example 8a: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To aqueous NaOH (25% w/w; 87.5 g, 0.55 mol) at 0 °C was added 4,4-dimethyloxetan-2-one (compound of formula (V); 50 g, 0.44 mol) within 30 min. The reaction mixture was allowed to warm to room temperature and stirring was continued for further 2 h. This mixture was then added dropwise within 60 min to a reaction mixture containing CaCl₂ (24.8 g, 0.22 mol) and water (100 g). The suspension was then cooled to 0 °C within 1 h and the precipitated product was filtered off. To the mother liquor was added further CaCl₂ (24.8 g, 0.22 mol) and the suspension was cooled to 0 °C. The precipitated product was filtered off and dried overnight under reduced pressure affording the title compound (47 g, 74%). Purity was more than 99 area% according to HPLC analysis (DMA 10 ppm).

Example 8b: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To aqueous NaOH (25% w/w; 87.5 g, 0.55 mol) at 0 °C was added 4,4-dimethyloxetan-2-one (compound of formula (V); 50 g, 0.44 mol) within 30 min. The reaction mixture was allowed to warm to room temperature and stirring was continued for further 2 h. This mixture was

then added dropwise within 60 min to a reaction mixture containing CaCl_2 (96.9 g, 0.88 mol) and water (100 g). The suspension was then cooled to 0 °C within 1 h and the precipitated product was filtered off. To the mother liquor was added further CaCl_2 (24.8 g, 0.22 mol) and the suspension was cooled to 0 °C. The precipitated product was filtered off and dried overnight under reduced pressure affording the title compound (30.5 g, 48%). Purity was more than 99 area% according to HPLC analysis (DMA 48 ppm).

Example 8c: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To aqueous NaOH (25% w/w; 14.4 g, 90 mmol) at 0 °C was added 4,4-dimethyloxetan-2-one (compound of formula (V); 7.5 g, 75 mmol) within 30 min. The reaction mixture was allowed to warm to room temperature and stirring was continued for further 2 h. This mixture was then added dropwise within 60 min to a reaction mixture containing CaCl_2 (24.8 g, 0.45 mol) and water (50 g). The suspension was then cooled to 0 °C within 1 h and the precipitated product was filtered off and dried overnight under reduced pressure affording the title compound (14.6 g, 68%). Purity was more than 99 area% according to HPLC analysis (DMA 168 ppm).

Example 9: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To MTBE (37.5 mL) was added aqueous NaOH (25% w/w; 21.8 g, 136.6 mmol). The reaction mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 12.5 g, 109.2 mmol) in MTBE (12.5 mL) was added dropwise at 5 °C. After complete addition (ca. 10 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 2 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 16.3 g, 0.14 mol) was added dropwise until a pH of 4 was reached (apparent pH of the stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (1 × 18 mL). The aqueous phase was discarded. The combined organic phases were cooled to 0 °C and then added dropwise within 50 min to a reaction mixture containing CaO (3.2 g, 54.6 mmol) in water (3.2 mL) and ethanol (50 mL). The reaction mixture was heated up to 50 °C within ca. 20 min and MTBE was distilled off. After complete removal of MTBE the yellow reaction mixture was heated to 70 °C and stirring was continued for 1 hour. The solution was then filtered over a plug of silica, then

further diluted with ethanol (50 mL) and finally heated to 50 °C. The reaction mixture was cooled to 0 °C within 4 h. The precipitated product was filtered off and washed with ethanol/water (22 mL, 10:1). The product was dried overnight under reduced pressure affording the title compound (11.7 g, 73%). Purity was more than 99.5 area% according to HPLC analysis (DMA: 6 ppm, MoX: 1 ppm).

Example 10: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To a suspension of $\text{Ca}(\text{OH})_2$ (4.1 g, 55.3 mmol) in ethanol/water (4:1; 45 mL) was added dropwise 4,4-dimethyloxetan-2-one (compound of formula (V); 10.9 g, 94.7 mmol) at 0 °C within 4 h keeping the apparent pH of the solution more than 12. After complete addition, the suspension was allowed to warm to room temperature and stirring was continued for further 1 h. The suspension was filtered over a plug of silica (filtration time: ca. 45 min). The filtrate was washed with ethanol/water (1:1 w/w; 3 mL) and dried overnight under reduced pressure affording the title compound (5.9 g, 49%). Purity was more than 97 area% according to HPLC analysis (DMA: 10 ppm, MoX: 1 ppm)

Example 11: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To MTBE (75 mL) was added aqueous NaOH (25% w/w; 43.7 g, 0.27 mol). The reaction mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 25 g, 0.12 mol) in MTBE (25 mL) was added dropwise at 5 °C. After complete addition (ca. 20 min), the reaction mixture was allowed to warm to room temperature within 20 min and stirring was continued for further 2 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 33.6 g, 0.28 mol) was added dropwise until a pH of 4 was reached (apparent pH of the stirred mixture). The reaction mixture was allowed to warm to room temperature within ca. 10 min and then the phases were separated and the aqueous phase was extracted with MTBE (2×35 mL). The aqueous phase was discarded. The combined organic phases were cooled to 0 °C and then added dropwise within 30 min to a reaction mixture containing $\text{Ca}(\text{OH})_2$ (8.4 g, 0.11 mol) in water (5 mL) and 2-methyl-1-propanol (100 mL). The reaction mixture was heated up to 80 °C within ca. 20 min and MTBE was distilled off. After complete removal of MTBE the reaction mixture was filtered over a plug of silica, then further 2-methyl-1-propanol (120 mL) and the reaction mixture was cooled to 5 °C within 4 h. The precipitated product was filtered off. The product was dried overnight under reduced

pressure affording the title compound (16.6 g, 52%). Purity was more than 99.5 area% according to HPLC analysis (DMA 13 ppm, MoX: 2 ppm).

Example 12: Synthesis of calcium 3-hydroxy-3-methylbutyrate (compound of formula (I), m= 1 or/and 2)

To MTBE (40 mL) was added aqueous NaOH (25% w/w; 23 g, 143.7 mmol). The reaction mixture was cooled to 5 °C, then 4,4-dimethyloxetan-2-one (compound of formula (V); 10 g, 94.9 mmol) in MTBE (30 mL) was added dropwise at 5 °C. After complete addition (ca. 20 min), the reaction mixture was allowed to warm to room temperature within 30 min and stirring was continued for further 1 h. The biphasic solution was cooled to 0 °C and aqueous HCl (30% w/w, 19 g, 157 mmol) was added dropwise until a pH of 4 was reached (apparent pH of the stirred mixture). The reaction mixture was allowed to warm to ca. 10°C within ca. 20 min and then the phases were separated and the aqueous phase was extracted with MTBE (2 × 100 mL). The aqueous phase was discarded. The combined organic phases were dried (Na₂SO₄), filtered and 60% of the solvent was distilled off. Then the reaction mixture was cooled to 15 °C and a reaction mixture containing Ca(OH)₂ (3.45 g, 46.6 mmol) in water (1.7 mL) was added. The reaction was further diluted with MTBE (50 mL) then heated up to 50 °C within ca. 20 min. The reaction mixture was cooled to 0 °C within 2 h. The precipitated product was filtered off. The product was washed with MTBE (50 mL), dried overnight under reduced pressure affording the title compound (13.5 g, 99%). Purity was more than 97 area% according to HPLC analysis. (DMA <12 ppm, MoX: <5 ppm)

Example 13: Synthesis of 4,4-dimethyloxetan-2-one (compound of formula (V))

In a continuous stirred tank reactor (CSTR) acetone (135 g) was cooled to -5°C under a nitrogen atmosphere, BF₃.Et₂O (0.81 g/h) and 10 minutes later ketene (39.6 g/h) were added simultaneously with a residence time of 1 h. After 1 h ketene (36.4 g/h), acetone (98.6 g/h) and BF₃.Et₂O (0.81 g/h) were added simultaneously for 5 h so that the reaction temperature did not exceed -5°C. The reaction mixture was stirred for 1 h and then completely transferred to a second reactor containing urotropin (10.2 g) cooled at -10°C. The solution contained 44 % w/w of compound (V) according to ¹H-NMR, which corresponds to a yield of approx. 76.3% based on ketene, and 4.8 % w/w of compound (VI) which corresponds to a yield of approx. 5.3% yield based on ketene.

Example 14: Purification of 4,4-dimethyloxetan-2-one (compound of formula (V))

The solution of example 13 containing 4,4-dimethyloxetan-2-one was distilled at 50 mbar and 50 to 60°C using a falling film evaporator system to remove the majority of the volatile components. The 4,4-dimethyloxetan-2-one was further purified using a wiped film evaporator system under 10 to 20 mbar at 100°C (jacket temperature 105 to 115°C). The
5 purified 4,4-dimethyloxetan-2-one was more than 97wt-% assay as determined by gas chromatography after derivatisation with piperidine. The 4,4-Dimethyloxetan-2-one (compound of formula (V)) was stored at 0 to -10°C until being used in examples 1 to 12.

Example 15 - Repetition of the example of CN1417190A

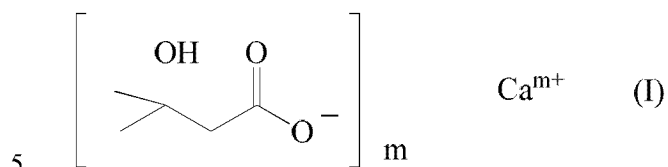
10 NaOH (50 g, 1.25 mol) dissolved in water (200 mL) are cooled to 0 °C in an ice-salt bath, and bromine (96 g, 0.6 mol) was added thereto dropwise under agitation while controlling the temperature between 0 to 5 °C, thereby obtaining a NaOBr solution after the addition is completed, which solution is preserved at 0 to 5°C. The obtained solution is added dropwise
15 to a solution of 4-hydroxy-4-methylpentan-2-one (diacetone alcohol, 23.2 g, 0.2 mol) and water (60 mL), and the reaction is conducted for 6 h; then NaHSO₃ (4 g, 0.19 mol) is added to fade the colour of the solution after the reaction is completed, followed by separating the bottom layer of bromoform, adjusting the top water layer to a pH of 2 to 3 with about HCl solution (2M, 60 g), extracting with isobutanol (3 to 4 times 75 g), and finally combining the isobutanol layer. To the obtained isobutanol layer is added successively water (60 g) and
20 Ca(OH)₂ (7.4 g), then further stirred at room temperature for 2 h, followed by filtering off the insoluble substance, standing and stratifying to separate the water layer, and evaporating the water under reduced pressure to obtain a brown solid (9.32 g) containing HMB-Ca (11%).
Yield: 3.6% (DMA: 497 ppm).

Example 16 - Repetition of example 15

Example 15 was repeated with the same result.

Claims

1. A process for the preparation of a compound of formula

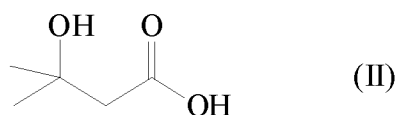


and/or a suitable hydrate and/or solvate thereof;

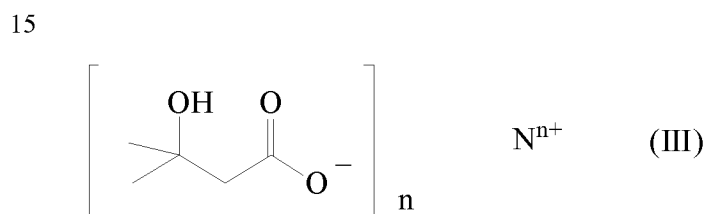
wherein m is 1 or 2;

said process comprising a step (1) and a step (2);

10 step (1) comprising the preparation of a compound of formula (II)



by protonation of a compound of formula (III);



wherein N is Na, Li, K, Ag, Cu, Ni, Mg or a mixture thereof;

n is 1, 2 or a mixture thereof;

20 in the presence of a solvent (1) and an acid (1);

said solvent (1) being selected from the group consisting of water, acetonitrile, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene, dioxane, C₁₋₄ alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof;

25 said acid (1) being selected from the group consisting of polymeric sulfonic acid resin, aqueous HCl, HCl gas, HBr, HI, HF, HCN, H₂SO₄, HNO₃, HNO₂, MsOH, TsOH, TfOH, BzOH, trifluoroacetic acid, ammonium chloride, phosphoric acid and mixtures thereof; and

said step (2) comprising the preparation of a compound of formula (I) characterized by deprotonation of a compound of formula (II) in the presence of a solvent (2) and a salt (2);

5 said solvent (2) being selected from the group consisting of water, acetonitrile, ethanol, 2-methyl-1-propanol, isopropanol, MTBE, THF, acetone, methanol and mixtures thereof; and

said salt (2) being selected from the group consisting of CaCO_3 , $\text{Ca}(\text{HCO}_3)_2$, $\text{Ca}(\text{OTf})_2$, $\text{Ca}(\text{OMs})_2$, $\text{Ca}(\text{OTs})_2$, $\text{Ca}(\text{OBz})_2$, CaBr_2 , CaF_2 , CaI_2 , CaNO_3 , CaSO_4 , $\text{Ca}(\text{HSO}_4)_2$,
 10 $\text{Ca}(\text{OAc})_2$, $\text{Ca}(\text{O-aryl})_2$, $\text{Ca}(\text{O-C}_{1-6} \text{ alkyl})$, CaS , $\text{Ca}(\text{SH}_2)$, $\text{Ca}_3(\text{PO}_4)_2$, $\text{Ca}(\text{HPO}_4)$, $\text{Ca}(\text{H}_2\text{PO}_4)_2$, CaCl_2 , CaO , $\text{Ca}(\text{OH})_2$ and mixtures thereof;

with the proviso, that compound of formula (III) is not prepared by a haloform reaction from diacetone alcohol.

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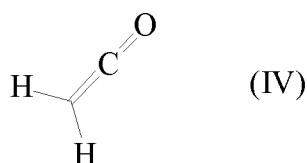
2. The process of claim 1, wherein the compound of formula (III)

wherein N is Na, Li, K, Ag, Cu, Ni, Mg or a mixture thereof;

n is 1, 2 or a mixture thereof;

has been prepared by a process comprising a step (3) and a step (4);

20 said step (3) comprising cycloaddition of ketene of formula (IV)



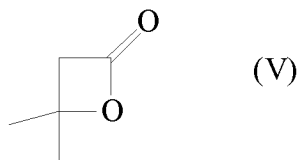
and acetone in the presence of a solvent (3) and an acid (3);

25 said solvent (3) being selected from the group consisting of acetone, pentane, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene and mixtures thereof;

the acid (3) being a Lewis acid selected from the group consisting of montmorillonite,

$\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{BF}_3 \cdot \text{Me}_2\text{O}$, $\text{B}(\text{OH})_3$, $\text{BF}_3 \cdot \text{THF}$, $\text{BF}_3 \cdot \text{Me}_2\text{S}$, BCl_3 , AlCl_3 , AlBr_3 , FeCl_3 , ZnCl_2 ,
 30 SnCl_4 , $\text{Ce}(\text{OTf})_3$, TiCl_4 , GaCl_3 , LiCl and mixtures thereof;

to obtain a compound of formula (V),



and a step (4) comprising ring opening of the compound of formula (V) in the presence of a solvent (4) and a salt (4);

said solvent (4) being selected from the group consisting of water, acetonitrile, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene, dioxane, C₁₋₄ alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof; and

said salt (4) being selected from the group consisting of Mg(OH)₂, Ni(OH)₂, Cu(OH)₂, Ag(OH), Li(OH), K(OH), Na(OH) and mixtures thereof.

3. The process of claim 1, wherein the salt (2) in step (2) is selected from the group consisting of Ca(OH)₂, CaO and CaCl₂.

4. The process of claim 2, wherein the solvent (4) in step (4) is water.

5. The process of claim 2, wherein the solvent (4) in step (4) is a mixture of water and MTBE.

6. The process of any of the preceding claims, wherein step (4), step (1) and step (2) are performed in one pot.

7. The process of claim 2, wherein the solvent (1) in step (1) is the same as the solvent (4) in step (4).

8. The process of any of the preceding claims, wherein the acid (1) in step (1) is aqueous HCl, H₂SO₄, or a mixture thereof.

9. The process of any of the preceding claims, wherein the salt (4) in step (4) is NaOH.

10. The process of any of the preceding claims, wherein the solvent (2) in step (2) is selected from the group consisting of water, ethanol, 2-methyl-1-propanol,

isopropanol, acetone, methanol and mixtures thereof.

11. The process of any of the claims 1 to 10, wherein the solvent (2) in step (2) is ethanol.

5 12. The process of any of the claims 1 to 10, wherein the solvent (2) in step (2) is a mixture of ethanol and water.

13. The process of claim 12, wherein the mixture of ethanol and water in an ethanol: water w/w ratio from 99:1 to 90:10.

10

14. The process of any of claims 1 to 10, wherein the solvent (2) is a mixture of water and acetone.

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15. The process of any of claims 1 to 10, wherein the solvent (2) is a mixture of water and isopropanol.

16. The process of any of claims 1 to 10, wherein the solvent (2) is water.

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17. The process of any of the preceding claims, wherein the reaction temperature of step (2) is of from -5 to 55 °C.

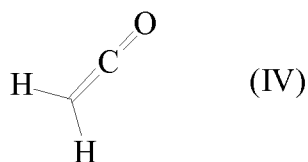
18. The process of claim 1, wherein the compound of formula (III)

wherein N is Na, Li, K, Ag, Ni, Mg or a mixture thereof;

n is 1, 2 or a mixture thereof;

25 has been prepared by a process comprising a step (3b) and a step (4b);

said step (3b) comprising cycloaddition of ketene of formula (IV)

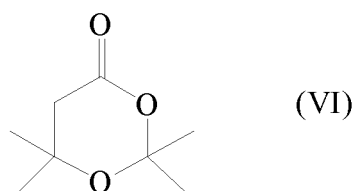


30 and acetone in the presence of a solvent (3b) and an acid (3b);

said solvent (3b) being selected from the group consisting of acetone, pentane, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene and mixtures thereof;

the acid (3b) being a Lewis acid selected from the group consisting of montmorillonite, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, $\text{BF}_3 \cdot \text{Me}_2\text{O}$, $\text{B}(\text{OH})_3$, $\text{BF}_3 \cdot \text{THF}$, $\text{BF}_3 \cdot \text{Me}_2\text{S}$, BCl_3 , AlCl_3 , AlBr_3 , FeCl_3 , ZnCl_2 , SnCl_4 , $\text{Ce}(\text{OTf})_3$, TiCl_4 , GaCl_3 , LiCl and mixtures thereof;

to obtain a compound of formula (VI)



and a step (4b) comprising ring opening of the compound of formula (VI) in the presence of a solvent (4b) and a salt (4b);

said solvent (4b) being selected from the group consisting of water, acetonitrile, hexanes, heptanes, dichloromethane, dichloroethane, carbon tetrachloride, toluene, xylene, mesitylene, dioxane, C_{1-4} alkyl ether, THF, 2-methyltetrahydrofuran and mixtures thereof; and

said salt (4b) being selected from the group consisting of $\text{Mg}(\text{OH})_2$, $\text{Ni}(\text{OH})_2$, $\text{Ag}(\text{OH})$, $\text{Li}(\text{OH})$, $\text{K}(\text{OH})$, $\text{Na}(\text{OH})$ and mixtures thereof.

19. The process of claim 18, wherein the solvent (4b) in step (4b) is water.

20. The process of claim 18, wherein the solvent (4b) in step (4b) is a mixture of water and MTBE.

21. The process of claims 18 to 20, wherein step (4b), step (1) and step (2) are performed in one pot.

22. The process of claim 18, wherein the solvent (1) in step (1) is the same as the solvent (4b) in step (4b).

23. The process of claims 18 to 22, wherein the salt (4b) in step (4b) is NaOH.

24. A process for the preparation of a compound of formula (I) and/or a suitable hydrate and/or solvate thereof;
comprising a step (4) and a step (5);
5 said step (4) comprising ring opening of compound of formula (V) in the presence of a solvent (4) and a salt (4);
said solvent (4) being water; and
said salt (4) being Na(OH);
to obtain compound of formula (III),
10 wherein n is 1,
N is Na;
and step (5) for the preparation of a compound of formula (I) characterized by metal exchange of a compound of formula (III) in the presence of a water and a salt (5);
the salt (5) being CaCl₂, CaBr₂, CaO, Ca(OH)₂ and mixtures thereof;
15 m being 1 or 2.

25. A process for the preparation of a compound of formula (I) and/or a suitable hydrate and/or solvate thereof;
comprising a step (4) and a step (5);
20 said step (4) comprising ring opening of compound of formula (VI) in the presence of a solvent (4) and a salt (4);
said solvent (4) being water; and
said salt (4) being Na(OH);
to obtain compound of formula (III),
25 wherein n is 1,
N is Na;
and step (5) for the preparation of a compound of formula (I) characterized by metal exchange of a compound of formula (III) in the presence of a water and a salt (5);
the salt (5) being CaCl₂, CaBr₂, CaO, Ca(OH)₂ and mixtures thereof;
30 m being 1 or 2.

26. The process of any of the claims 24 and 25, wherein the salt (5) is CaCl₂.

27. The process of any of the claims 1, 24 and 25, wherein the compound of formula (I) is a

monohydrate.

28. Process according to one or more of claims 1 to 27, characterized that in step (1) no chloroform and no bromoform and no iodoform is present.

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29. Process according to one or more of claims 1 to 28, characterized that in step (2) no chloroform and no bromoform and no iodoform is present.

30. Process according to one or more of claims 1 to 28, characterized that the protonation of
10 step (1) is done at a pH of from 3.5 to 6.2.

31. Process according to 30, characterized that the protonation of step (1) is done at a pH is of
from 3.6 to 6.1.

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