

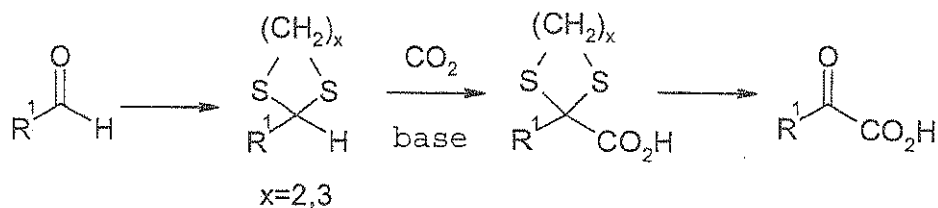
Method for the production of ketoacids and their derivatives

- 5 The present invention relates to a novel process for preparing α -keto acids, especially α -ketomethionine, and derivatives thereof.

α -Keto acids are important products and are used,
10 inter alia, for the supplementation of amino acids in the treatment of chronic kidney failure (Jungers et al., Blood Purification 1988, 6, 299-314 and Clasen et al., Med. Klin. 1978, 73, 1403-1408).

- 15 The synthesis of α -keto acids has been described in various ways in the literature, including by the reaction of a Grignard reagent with a dialkyl oxalate and subsequent hydrolysis of the resulting ester to the free acid (Rambaud et al., Synthesis 1988, 564 and
20 Macritchie et al., Tetrahedron: Asymmetry 1997, 8, 3895). The acidic catalyzed hydrolysis of acyl cyanides likewise affords α -keto acids (Nozaki et al., Tetrahedron: Asymmetry 1993, 4, 2179). Billek reports the preparation of a series of α -keto acids. In this
25 preparation, alkylidenesulfonylureas are hydrolyzed under basic reaction conditions (Billek, Monatsh. Chem. 1961, 92, 343-352).

- α -Keto acids can also be prepared from the
30 corresponding aldehyde and carbon dioxide by an umpolung reaction. One means of subjecting the aldehyde to umpolung is the formation of a cyclic dithiane, from which a carbanion can be formed by deprotonation with a strong base. This carbanion can subsequently be reacted
35 with carbon dioxide. The cyclic dithiane is finally split under oxidative conditions, for example with mercury salts, to give the desired α -keto acid.



According to studies by Corey and Seebach [Corey et al., Angew. Chem. 1965, 77, 1134-1136 and Seebach et al., J. Org. Chem. 1975, 40, 231-237], dithiols are typically used in order to synthesize cyclic dithioacetals (dithianes). This succeeds particularly readily since the formation of cyclic dithianes proceeds preferentially owing to the high thermodynamic stability of the five- or six-membered ring formed. The cyclization with dithiols is additionally preferred kinetically. Precisely this high stability, however, is a serious disadvantage, since it complicates the cleavage of the dithiane ring to an extreme degree, and hence the release of the desired α -keto acid succeeds only under chemically severe conditions. The cleavage of the dithiane is normally brought about by an oxidation process [Seebach, Synthesis 1969, 17-36]. Removal and reuse of the dithiol are thus no longer possible, since the sulfur, for the removal, is oxidized and then precipitated as a sparingly soluble salt with mercury salts. Further disadvantages of this process are the high costs of suitable dithiols, for example, 1,2-ethanedithiol or 1,3-propanedithiol, and the small amounts which would be available for industrial scale use. These problems make the industrial use of the above-described umpolung method very unattractive.

The literature describes several examples for the reaction of short-chain thiols, for example, methyl mercaptan, with aldehydes to give the corresponding thioacetals [Trofimov et al., J. Org. Chem. USSR 1972,

8, 2036 and Rothstein et al., J. Chem. Soc. 1940, 1563]. In addition, the use of these dithioacetals in umpolung reactions with various electrophiles is known. However, there is only a single literature example
5 where an aromatic thioacetal has been reacted successfully with CO₂ in an umpolung reaction [Micetich et al., Heterocycles 1985, 23, 585-592].

α -Ketomethionine constitutes an exceptional α -keto
10 acid, since it is formed as an intermediate in the organism in the course of conversion of D-methionine to L-methionine. α -Ketomethionine is obtainable by numerous synthesis routes and has been described in the literature. In addition, several salts and other
15 derivatives, for example, ketomethionine esters, are known from the literature. The processes for preparing α -ketomethionine in principle can be divided into chemical and biochemical processes:

20 a) Biochemical syntheses:

Meister obtained the sodium salt of α -ketomethionine in a yield of 77% by the oxidation, catalyzed by L-aminooxidases, of methionine (Meister, J. Biol. Chem.
25 1952, 197, 309). Before that, Waelsch et al., showed that the aminooxidases present in the liver can convert methionine to α -ketomethionine (Waelsch et al., J. Am. Chem. Soc. 1938, 61, 2252).

30 Mosbach et al. likewise describe the preparation of α -ketomethionine by the oxidation, catalyzed by L-amino-oxidases, of methionine. In this preparation, immobilized *Providencia* sp. PCM 1298 cells are used (Mosbach et al. Enzyme Microb. Technol. 1982, 4, 409).

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The disadvantages of the preparation of α -ketomethionine or derivatives thereof with the aid of biological systems, either using purified enzymes or

whole cells, are usually the relatively low space-time yields and the technically complicated isolation and product purification. An additional factor in the case of use of high-purity enzymes is that the development, production and purification of the enzymes is very expensive and complicated, and the reuse of already used enzymes is usually not possible.

b) Chemical syntheses:

10

In 1957, Sakurai et al. published a first chemical synthesis route for preparing α -ketomethionine. As the key step, methyl α -methoxalyl- γ -methylmercapto-propionate was hydrolyzed with dilute hydrochloric acid to α -ketomethionine (Sakurai et al., J. Biochem. 1957, 44, 9, 557).

Almost at the same time, Yamada et al. published the same synthesis route after first attempts to prepare α -ketomethionine via an α -oximo ester which had been formed as an intermediate afforded only relatively low yields (Chibata et al., Bull. Agr. Chem. Soc. Japan 1957, 21, 336).

The process disclosed by Sakurai and Yamada has the great disadvantage that considerable amounts of salt are formed, which make industrial scale implementation impossible. In addition, the synthesis route is not atom-economic, since some of the molecule is eliminated as carbon dioxide in a synthesis step and is thus lost. An industrial scale implementation of this synthesis route would therefore be too expensive and uneconomic.

In the patent application WO 06-72711 preparation of α -ketomethionine proceeding from butadiene was recently published. In this preparation, butadiene is oxidized selectively to the unsaturated monoepoxide and then converted to the corresponding 1,2-diol by an acid-

catalyzed ring opening with water. The subsequent oxidation of the 1,2-diol to the α,β -unsaturated α -keto acid and the subsequent 1,4 addition of MeSH leads to α -ketomethionine.

5

This process has the disadvantage that expensive butadiene is required as the reactant. It is probable that the price of butadiene will again rise significantly in the years to come depending on the price of crude oil. A further disadvantage of the process described in WO 06-727211 is the fact that none of the existing plants would be usable for methionine or MHA production, and therefore new production plants for every individual process step described would have to be built. The synthesis route described in WO 06-72711 always leads to the free α -ketomethionine, which is unstable and very difficult to isolate.

α -Ketomethionine and its derivatives, for example, its salts or esters, are particularly important compounds, since they constitute alternatives to methionine and to methionine hydroxy analog (MHA) as animal feed additives.

In 1942, Rudolph et al. reported that the sodium salt of α -ketomethionine can be used as a replacement for D,L-methionine, and that it accelerates the growth of young rats (Rudolph et al., J. Biol. Chem. 1942, 145, 210).

30

It has been shown several times that α -ketomethionine can provide the sulfur required for the biosynthesis of L-methionine and L-cysteine (Sizer et al., Poultry Sci. 1964, 44, 673; Baker et al., Poultry Sci. 1975, 54, 584 and Baker, J. Nutr. 1976, 106, 1376).

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In addition, Baker and Harter were able to show that the calcium salt of α -ketomethionine has a relative

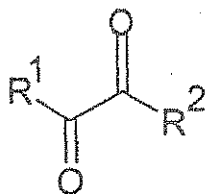
biological value with regard to the growth of chickens of 83% compared to L-methionine (100%) and MHA (53%) (Baker and Harter, Proceedings of the Society for Experimental Biology and Medicine 1977, 156, 201). The relative biological value of various methionine derivatives, including α -ketomethionine (90% compared to L-methionine), was published by Baker in "Utilization of Precursors for L-Amino Acids" on page 39.

The use of α -ketomethionine and of its salts and esters and amides as an animal feed additive is described in WO 06-72711.

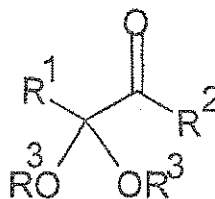
Against a background of the disadvantages of the prior art, it is an object of the present invention to provide an improved, more environmentally friendly, process realizable on an industrial scale for preparing keto acids, especially α -ketomethionine and its derivatives, as alternatives to methionine or MHA as animal feed additives.

This object is achieved by the process according to the invention.

The invention provides a process for preparing α -keto acids and derivatives thereof of the general formula (I) or (II)



(I)



(II)

in which

5 R^1 is a branched or straight-chain C_1 - C_{18} -alkyl, C_5 - C_8 -cycloalkyl, vinyl, allyl, C_6 - C_{10} -aryl- C_1 - C_4 -alkylene, preferably benzyl, or C_4 - C_9 -heteroaryl- C_1 - C_4 -alkylene group, preferably 4-imidazolylmethylene or 3-indolylmethylene, where R^1 is optionally substituted,

10 R^2 is $-OR'''$ or $-NR'R''$, in which R' and R'' may be the same or different and are each a hydrogen atom or a branched or straight-chain C_1 - C_6 -alkyl group, and R''' is a hydrogen atom, a branched or straight-chain C_1 - C_8 -alkyl, C_5 - C_8 -cycloalkyl, allyl or a benzyl group, where
15 alkyl in R' , R'' and/or R''' is optionally substituted, or R''' is an alkaline metal ion, alkaline earth metal ion or a mono- or divalent transition metal ion,

R^3 is the same or different and is a hydrogen atom, a
20 branched or straight-chain C_1 - C_8 -alkyl, allyl or a benzyl group, where alkyl and/or benzyl is optionally substituted, or the two R^3 radicals together are C_2 - C_8 -alkanediyl and together form a ring, or the two R^3 and R''' radicals together are part of a C_3 - C_8 -
25 alkanetriyl group of the general formula $-R^3(CH-)R'''$ and together form a bicyclic group,

wherein

30 a) an aldehyde R^1CHO is reacted with two identical or different thiols of the formula R^4-SH , in which R^4 is a branched or straight-chain, optionally substituted C_1 - C_6 -alkyl, C_5 - C_8 -cycloalkyl, allyl or benzyl group to give the corresponding
35 dithioacetal,

b) the dithioacetal formed reacts with carbonyl-containing electrophiles such as carbon dioxide,

phosgene, chloroformic esters, orthoformic esters or dialkyl carbonate in the presence of a strong base and after hydrolysis to give the α,α -(dithio)carboxylic acid or derivatives thereof of the formula (III)



(III)

in which R^5 may be a hydrogen atom or a branched or straight-chain C_1 - C_6 -alkyl group and the R^4 and R^1 radicals are each as defined above, and

c) the α,α -(dithio)carboxylic acid or derivatives thereof of the formula (III) are converted by acid-catalyzed solvolysis in the presence of at least 1 molar equivalent of water with release of thiols of the formula R^4SH to give the α -keto acid or derivatives thereof of the general formula (I) or (II).

The radicals mentioned under R^1 may optionally be substituted by $-\text{SH}$, $-\text{SCH}_3$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{CHO}$, guanidyl, $-\text{OH}$, $-\text{NR}'\text{R}''$ or $-\text{SS}-\text{CH}_2-\text{C}(\text{H})\text{NH}_2-\text{CO}_2\text{H}$, where R' and R'' are each as defined above.

R^1 is preferably vinyl or a branched or straight-chain, optionally substituted C_1 - C_8 -alkyl, preferably vinyl, or a branched or straight-chain, optionally substituted C_1 - C_4 -alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl and tert-butyl.

R^1 is most preferably vinyl, n-propyl or 2-(methylthio)ethyl, especially 2-(methylthio)ethyl.

R^2 is preferably $-OR'''$, in which R''' is a hydrogen atom or a branched or straight-chain C_1 - C_4 -alkyl group.

5 R^3 is independently preferably a hydrogen atom or a branched or straight-chain, optionally substituted C_1 - C_4 -alkyl group, especially *i*-propyl or *i*-butyl, or the two R^3 radicals together are C_2 - C_4 -alkanediyl and together form a ring, or the two R^3 and R''' radicals
10 together are part of a C_3 - C_6 -alkanetriyl group of the general formula $-R_3(CH-)R'''$ and together form a bicyclic group.

R^4 is preferably methyl or ethyl, especially methyl.

15

In the process according to the invention, a noncyclic dithioacetal is initially formed (step a)).

The dithioacetal obtained in a) is then converted by an
20 umpolung reaction with a carbonyl-containing electrophile, for example, carbon dioxide, phosgene, chloroformic esters, orthoformic esters or dialkyl carbonate (step b)) in the presence of a base to an α,α -(dithio)carboxylic acid or derivatives thereof. The
25 electrophile used is preferably carbon dioxide, which can be used in the form of a gas, solid (e.g. dry ice) or liquid (in supercritical form or as a solvent).

For the deprotonation which is effected first in b),
30 bases whose corresponding acid has a pK_a value of > 20 are particularly suitable. Preferred bases here are alkyllithium compounds, especially *n*-butyllithium and *tert*-butyllithium, and also metal amides and hydrides, especially sodium amide and sodium hydride, and also
35 metal hydroxides or carbonates alone or in combination with chelating ligands, for example, crown ethers, preferably potassium hydroxide or potassium carbonate with 18-crown-6.

The deprotonation in b) with the aforementioned bases is preferably performed in aprotic organic solvents or in liquid supercritical carbon dioxide or in liquid ammonia. Particular preference is given to ethers such as tetrahydrofuran, alkyl sulfoxides, such as DMSO, aromatic compounds such as toluene, aliphatic and cyclic alkanes such as n-hexane and cyclohexane, and alkylamides such as DMF.

10

A temperature of -80°C to 100°C, preferably of -30°C to 25°C, is advantageous for the reaction.

The hydrolysis is effected preferably in aqueous solutions in the pH range of 1-14, preferably in the range of pH 1-4 or pH 9-13.

In general, the hydrolysis takes place at temperatures of -20°C to 100°C, preferably of 0 to 30°C.

20

Thereafter, in step c), the acid-catalyzed solvolysis of the α,α -(dithio)carboxylic acid or derivatives thereof formed in b) is effected with release of thiols or salts thereof, and the product, depending in each case on the solvent used, may, for example, be the free α -keto acid and salts thereof, an α -keto ester, an α -keto amide, a ketal derivative of the α -keto acid or a ketal derivative of the α -keto ester (see also scheme).

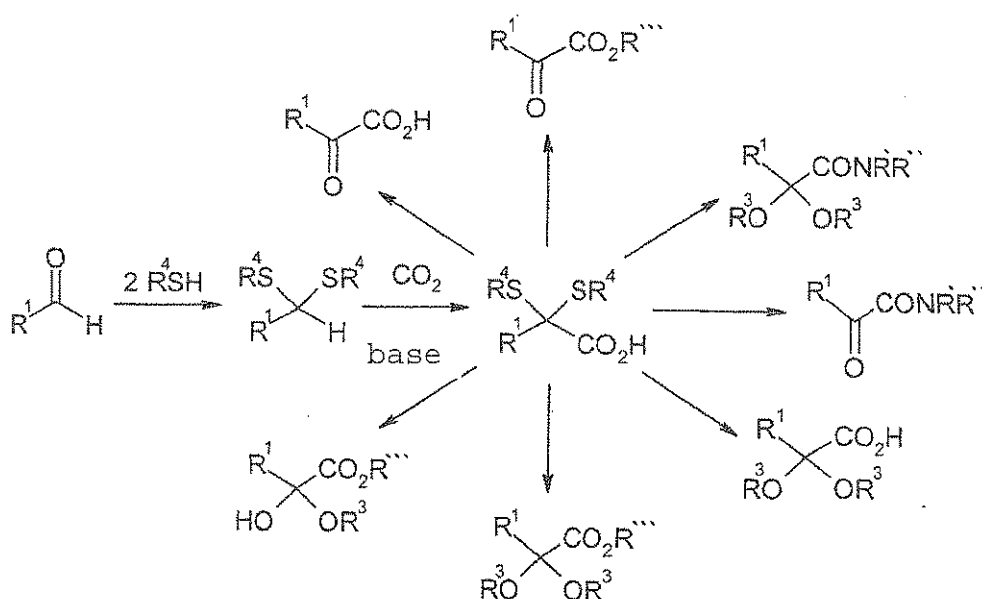
Solvolysis is understood to mean the reaction of the α,α -(dithio)carboxylic acid with the solvent, for example, hydrolysis (with water).

The solvolysis is effected generally at temperatures of 20°C - 200°C, preferably at 50-150°C, under acidic catalysis. Preferred catalysts are, for example, para-toluenesulfonic acid, $\text{CF}_3\text{SO}_3\text{H}$, and also mineral acids such as HCl or H_2SO_4 , or strong organic acids which are

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non-nucleophilic.

The thiols of the formula R^4SH formed may be removed from the reaction mixture by a vacuum, by introducing 5 inert gas or by another suitable separation process, for example, phase separation, crystallization, complex formation or precipitation, and recycled, and hence subsequently reused in the umpolung reaction.



10

In one embodiment, water is used as the solvent in the acid-catalyzed solvolysis in c), in which case the free α -keto acid of the formula (I) in which $R^2 = OR'''$,
15 R''' is a hydrogen atom and R^1 is as defined above, is formed.

In an alternative embodiment, in the acid-catalyzed solvolysis in c), an alcohol R'''OH in which R''' is a
20 branched or straight-chain C₁-C₈-alkyl, C₅-C₈-cycloalkyl, allyl or benzyl group, and alkyl is optionally substituted is used as the solvent; in which case the α -keto ester of the formula (I) in which R² = OR''' and R''' is as defined hereinabove and R¹ as
25 specified above is formed.

In a further alternative embodiment, in the acid-catalyzed solvolysis in c), a diol $\text{HO-R}^3\text{-OH}$ where R^3 is a branched or straight-chain, optionally substituted
5 $\text{C}_2\text{-C}_8\text{-alkanediyl}$ group is used as the solvent, in which case a cyclic ketal of the formula (II) in which $\text{R}^2 = \text{OR}'''$ where $\text{R}''' = \text{H}$, R^3 is as defined hereinabove and R^1 as specified above is formed.

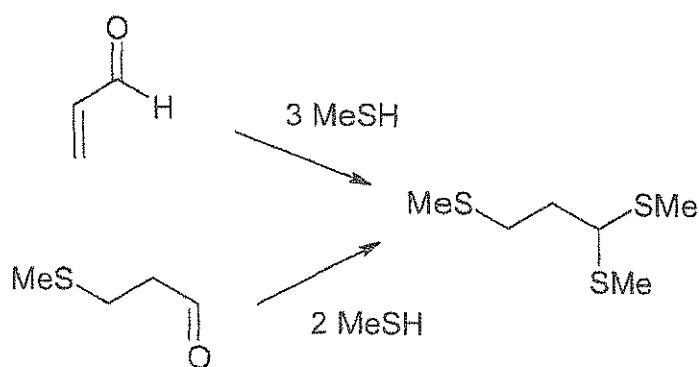
10 In a further alternative embodiment, in the acid-catalyzed solvolysis in c) a triol of the formula $\text{HOR(CHOH)R}''' \text{OH}$ in which the R^3 and R''' radicals together are part of a branched or straight-chain, optionally substituted $\text{C}_3\text{-C}_8\text{-alkanetriyl}$ group of the
15 general formula $-\text{R}^3(\text{CH-})\text{R}'''$, is used as the solvent, in which case a bicyclic ketal ester of the formula (II), in which $\text{R}^2 = \text{OR}'''$, R''' and R^3 are each as defined hereinabove and R^1 are specified above is formed.

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In a further alternative embodiment, in the acid-catalyzed solvolysis in c), an amine HNR'R'' , in which R' and R'' may be the same or different and are each a hydrogen atom or a branched or straight-chain
25 $\text{C}_1\text{-C}_6\text{-alkyl}$ group, where R' and R'' cannot both be a hydrogen atom, is used as the solvent. In this case, an amide of the formula (I), in which $\text{R}^2 = \text{NR'R''}$ and R' and R'' are each as defined hereinabove is formed.

30 In the process according to the invention for preparing α -keto acids and derivatives thereof, the dithioacetal formed in a) also functions as a protecting group which, after the addition of carbon dioxide (b)), can be removed again in the presence of an acid by
35 solvolysis (c)) under reduced pressure or by introducing an inert gas, for example nitrogen. It is advantageous that the thiol released can then be recycled and reused by means of a circulation process.

In the case of α -ketomethionine, it may be advantageous to prepare the dithioacetal in a) either by reacting 3-(methylthio)propanal (= 3-methylmercaptopropionaldehyde (MMP)) with methylthiol (MeSH) or directly from acrolein by the triple addition of methylthiol.



10 Me = methyl-

Compared to the prior art, the process according to the invention allows the preparation of α -keto acids or derivatives thereof in a higher yield, which constitutes a great economic advantage.

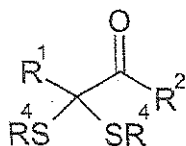
In addition, it is possible in the process according to the invention to continue to use the existing plants for preparing 3-(methylthio)propanal, i.e. the plants for preparing acrolein and methylthiol, in contrast to the process disclosed in WO 06-72711.

The process according to the invention is additionally environmentally friendly, since preference is given to using carbon dioxide as a C-1 unit, and hence contributes to climate protection (Kyoto Protocol).

In contrast to the process described in WO 06-72711 for preparing α -ketomethionine proceeding from butadiene, the process according to the invention has a high

flexibility, since both the α -keto acid itself and also all derivatives, for example esters, ketals, etc. can be prepared directly.

- 5 The invention further provides the intermediate of the formula (IV),



(IV)

- 10 in which

R^1 is a branched or straight-chain C_1 - C_{18} -alkyl, C_5 - C_8 -cycloalkyl, vinyl, allyl, C_6 - C_{10} -aryl- C_1 - C_4 -alkylene, preferably benzyl, or C_4 - C_9 -heteroaryl- C_1 - C_4 -alkylene group, preferably 4-imidazolylmethylene or 3-indolylmethylene, where R^1 is optionally substituted,

R^2 is $-OR'''$ or $-NR'R''$, in which R' and R'' may be the same or different and are each a hydrogen atom or a branched or straight-chain C_1 - C_6 -alkyl group, and R''' is a hydrogen atom, a branched or straight-chain C_1 - C_8 -alkyl, C_5 - C_8 -cycloalkyl, allyl or a benzyl group, where alkyl in R' , R'' and/or R''' is optionally substituted, or R''' is an alkaline metal ion, alkaline earth metal ion or a mono- or divalent transition metal ion,

and R^4 is the same or different and may be a branched or straight-chain, optionally substituted C_1 - C_6 -alkyl, C_5 - C_8 -cycloalkyl, allyl or benzyl group.

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Preference is given to inventive intermediates of the formula (IV), in which R^1 is optionally substituted

C₁-C₄-alkyl, especially CH₃SCH₂CH₂.

The invention further provides for the use of a thiol of the formula R⁴-S-H, where R⁴ is a branched or straight-chain, optionally substituted C₁-C₆-alkyl, C₅-C₈-cycloalkyl, allyl or benzyl group for umpolung of aliphatic and/or aromatic aldehydes.

Examples

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Example 1:

Preparation of 1,1,3-tris(methylthio)propane (2) from 3-(methylthio)propanal (1)

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Me = methyl

3-(methylthio)propanal (1) (1.44 mol, 150 g) was saturated at 0°C with HCl (g) and then added dropwise directly to MeSH (6.25 mol, 300 g) at 0°C over a period of 30 minutes. The reaction mixture was heated to 20°C and stirred at 20°C for 24 h. After the excess MeSH had been removed under reduced pressure, GC analysis showed the following product distribution: 91% thioacetal (2) and 8% 3-(methylthio)propanal (1). For further purification, this mixture was dissolved in diethyl ether and washed with a 30% aqueous sodium pyrosulfite (Na₂S₂O₅) solution. After phase separation, the organic phase was dried over MgSO₄. After the solvent had been

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removed, the thioacetal (2) was obtained as a pale-yellow colored oil (168 g, yield = 64%, GC purity = 98%).

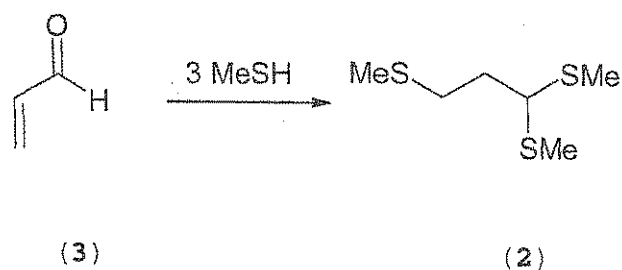
5 ^1H NMR of 1,1,3-tris(methylthio)propane (2) (500 MHz, CDCl_3): δ = 2.01-2.05 (m, 2H, CH_2), 2.11 (s, 9H, 3 $\times$ SCH_3), 2.71 (t, 3J = 7.3 Hz, 2H, CH_2), 3.83 (t, 3J = 7.3 Hz, 1H, CH)

10 ^{13}C NMR of 1,1,3-tris(methylthio)propane (2) (125.8 MHz, CDCl_3): δ = 12.6 (2 $\times$ SCH_3), 15.5 (SCH_3), 32.0 (CH_2), 33.9 (CH_2), 53.0 ($\text{C}(\text{SCH}_3)_2$)

Example 2:

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Preparation of 1,1,3-tris(methylthio)propane (2) from acrolein (3)



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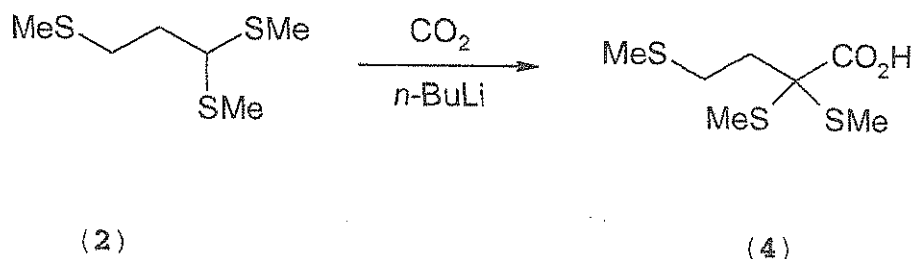
Acrolein (3) (89 mmol, 5.0 g) was added dropwise at -78°C with stirring to MeSH (358 mmol, 17.2 g), which had been saturated with HCl gas at 0°C , over a period of 15 minutes. This mixture was heated slowly to 20°C and then stirred further at 20°C for 24 h. After removal of the excess MeSH under reduced pressure, this mixture was dissolved in diethyl ether and washed with a 30% aqueous sodium pyrosulfite solution. After phase separation, the organic phase was dried over MgSO_4 .

25 After distillation (88°C at 1.2 mbar), the pure thioacetal (2) was obtained as a pale-yellow colored oil (11.4 g, yield = 70%, GC purity = 98%). The NMR

characterization gave the same data as in Example 1.

Example 3:

- 5 Preparation of 2,2,4-tris(methylthio)butanoic acid (4) by umpolung reaction of 1,1,3-tris(methylthio)propane (2) with dry ice (CO₂)



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In a three-neck flask under a protective gas atmosphere, 1,1,3-tris(methylthio)propane (2) (3.65 g, 20 mmol) was dissolved in 50 ml of abs. THF. Subsequently, at -20°C, a butyllithium solution in
15 n-hexane (14 ml, 1.6 M) was slowly added dropwise with stirring. In the course of this, the solution turned bright yellow. After stirring had been continued at this temperature for a further 2 h, anhydrous dry ice (CO₂, 10 g) which had been washed beforehand in
20 abs. THF was added in portions at -70°C. The reaction solution was thawed slowly to 20°C and a 10% aqueous KOH solution (80 ml) was added. After phase separation, the organic phase was washed with 10% aqueous KOH solution (2 × 50 ml). The combined KOH phases were
25 washed with diethyl ether (3 × 30 ml) and then adjusted cautiously to pH 1 with conc. HCl while cooling. The product was extracted with diethyl ether (3 × 50 ml). The combined ether phases were subsequently dried over Na₂SO₄ and, after filtration, concentrated on a rotary
30 evaporator. 2,2,4-tris(methylthio)butanoic acid (4) was obtained as a yellowish oil (4.3 g, yield = 95%), which crystallized slowly when left to stand.

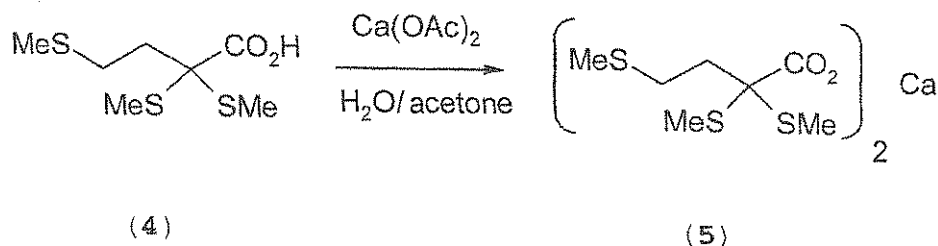
¹H NMR of 2,2,4-tris(methylthio)butanoic acid (4)
 (500 MHz, CDCl₃): δ = 2.12 (s, 6H, 2 × SCH₃), 2.14 (s,
 3H, SCH₃), 2.22-2.26 (m, 2H, CH₂), 2.67-2.70 (m, 2H,
 5 CH₂)

¹³C NMR of 2,2,4-tris(methylthio)butanoic acid (4)
 (125.8 MHz, CDCl₃): δ = 12.5 (2 × SCH₃), 15.6 (C-5),
 29.7 (C-3), 34.6 (C-4), 63.5 (C-2), 175.3 (CO₂H)

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Example 4:

Preparation of calcium 2,2,4-tris(methylthio)butanoate
 (5) from the corresponding α,α-(dialkylthio)carboxylic
 15 acids (4)



16.6 g of 2,2,4-tris(methylthio)butanoic acid (4)
 20 (73.3 mmol) were dissolved in a mixture of 140 ml of
 H₂O and 35 ml of acetone. Subsequently, a solution of
 6.2 g of calcium acetate (93%) and 22 ml of H₂O was
 slowly added dropwise at 20°C with vigorous stirring.
 After a short time a white solid precipitated out which
 25 was filtered off after 30 minutes. The resulting white
 solid was washed twice with 200 ml of H₂O each time,
 then with 200 ml of acetone and 200 ml of diethyl
 ether, and dried in a drying cabinet. A total of 17.7 g
 of calcium 2,2,4-tris(methylthio)butanoate (5)
 30 (M = 490.8 g/mol, yield = 98%) were isolated.

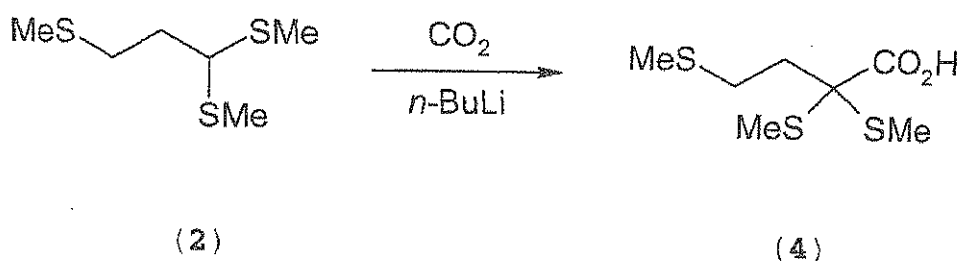
¹H NMR of calcium 2,2,4-tris(methylthio)butanoate (5)

(500 MHz, DMSO- D_6): δ = 1.93 (s, 6H, 2 SCH₃), 1.95-1.99 (m, 2H, CH₂), 2.05 (s, 3H, SCH₃), 2.52-2.55 (m, 2H, CH₂)

Example 5:

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Preparation of 2,2,4-tris(methylthio)butanoic acid (4) by umpolung reaction of 1,1,3-tris(methylthio)propane (2) with gaseous CO₂



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In a three-neck flask under a protective gas atmosphere, 1,1,3-tris(methylthio)propane (2) (3.65 g, 20 mmol) was dissolved in 50 ml of abs. THF. Subsequently, at -20°C, a butyllithium solution in n-hexane (14 ml, 1.6 M) was slowly added dropwise with stirring. In the course of this, the solution turned bright yellow. After stirring had been continued at this temperature for 2 h, gaseous dry CO₂ was passed through via a frit at -70°C over a period of 30 minutes. The reaction solution was thawed slowly until a temperature of 20°C was attained, at which a 10% aqueous KOH solution (80 ml) was added. After phase separation, the organic phase was washed with 10% aqueous KOH solution (2 × 50 ml). The combined KOH phases were washed with diethyl ether (3 × 30 ml) and then adjusted cautiously to pH 1 with conc. HCl while cooling. The product was extracted with diethyl ether (3 × 50 ml). The combined ether phases were subsequently dried over Na₂SO₄ and, after filtration, concentrated on a rotary evaporator. 2,2,4-tris(methylthio)butanoic acid (4) was obtained as

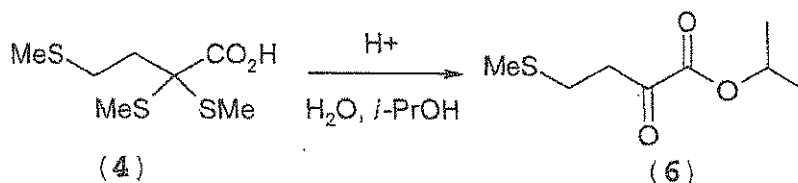
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a yellowish oil (4.1 g, yield = 90%), which crystallized slowly when left to stand. The NMR characterization gave the same data as in Example 3.

5 Example 6:

Preparation of ketomethionine isopropyl ester (6) by removal of the thiol from 2,2,4-tris(methylthio)-butanoic acid (4) in the presence of isopropanol

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0.1 mol of 2,2,4-tris(methylthio)butanoic acid (4) (22.6 g) was dissolved in a mixture of 200 ml of
15 toluene and 200 ml of isopropanol. Subsequently, 2.0 eq of H₂O (3.6 ml) and one spatula-tip of p-toluenesulfonic acid monohydrate were added. The overall mixture was then heated to boiling temperature and stirred under reflux for 3 h. After cooling, 150 ml
20 of water were added and the mixture was extracted three times with 100 ml each time of diethyl ether. The combined ether phases were subsequently washed to neutrality with a dilute sodium hydrogencarbonate solution, and dried over magnesium sulfate. After
25 filtration, all of the solvent was drawn off with a rotary evaporator. Ketomethionine isopropyl ester (6) (14.5 g, yield = 76%) was obtained as a pale yellowish oil.

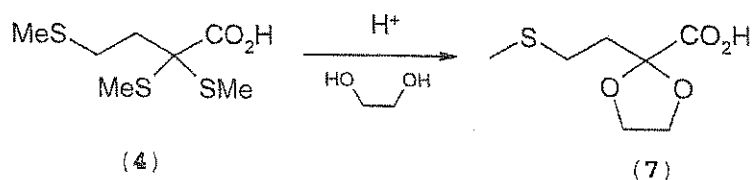
30 ¹H NMR of ketomethionine isopropyl ester (6) (500 MHz, CDCl₃): δ = 1.35 (d, ³J = 6.3 Hz, 6H, 2 CH₃), 2.14 (s, 3H, SCH₃), 2.79 (t, ³J = 7.2 Hz, 2H, CH₂), 3.15 (t, ³J = 7.2 Hz, 2H, CH₂), 5.15 (quint, ³J = 6.3 Hz, 1H, CH)

Elemental analysis for $C_8H_{14}O_3S$ (6) ($M = 190.26$ g/mol):
C 50.50; H 7.43; S 16.85 found: C 50.66; H 7.57;
S 16.52

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Example 7:

Direct preparation of ketomethionine ethylene glycol
ketal (7) by removing the thiol from 2,2,4-
10 tris(methylthio)butanoic acid (4) in the presence of
ethylene glycol



15 0.1 mol of 2,2,4-tris(methylthio)butanoic acid (4)
(22.6 g) was dissolved in 200 ml of ethylene glycol
(1,2-ethanediol). Subsequently, 1.1 eq of H₂O (1.8 ml)
and a spatula-tip of p-toluenesulfonic acid monohydrate
were added. The overall mixture was then heated to 50°C
20 and a constant nitrogen stream was passed through the
solution via a frit. After 4 h, the reaction mixture
was added to 300 ml of water and extracted three times
with 100 ml each time of diethyl ether. The combined
ether phases were dried over MgSO₄. After filtration,
25 the ether was drawn off with a rotary evaporator.
Subsequently, 100 ml of methanol and 100 ml of 2 M NaOH
solution were added to the ester, protected as the
ketal, and the mixture was stirred at 20°C for 2 h.
Thereafter, the solution was acidified to pH = 1 with
30 conc. HCl and extracted three times with 100 ml each
time of diethyl ether. The combined ether phases were
subsequently dried over MgSO₄. After filtration, the
ether was drawn off and the crude product was crystal-
lized from a mixture of methylene chloride and

n-hexane. 13.0 g of a white crystalline solid (7) were obtained. (Yield = 68%, M = 192.23 g/mol, melting point: 74°C (crystallized from methylene chloride/n-hexane)).

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¹H NMR of 2-(2-(methylthio)ethyl)-1,3-dioxolane-2-carboxylic acid (7) (500 MHz, CDCl₃): δ = 2.11 (s, 3H, SCH₃), 2.24-2.28 (m, 2H, CH₂), 2.58-2.61 (m, 2H, CH₂), 4.07-4.14 (m, 4H, OCH₂CH₂O)

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¹³C NMR of 2-(2-(methylthio)ethyl)-1,3-dioxolane-2-carboxylic acid (7) (125.8 MHz, CDCl₃): δ = 15.5 (SCH₃), 27.1 (CH₂), 34.9 (CH₂), 66.1 (2 OCH₂), 105.9 (C), 174.1 (COO)

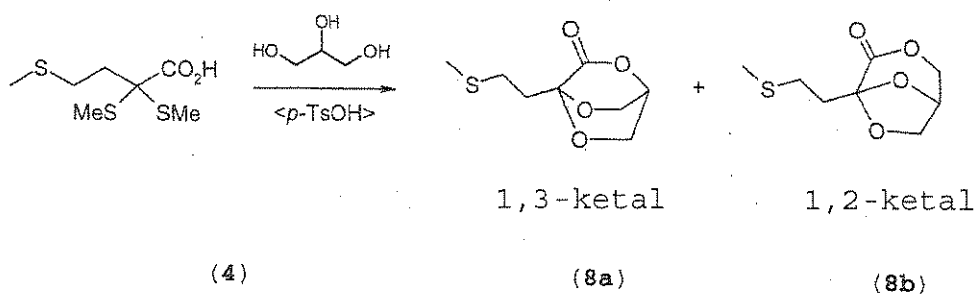
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Elemental analysis for C₇H₁₂O₄S (7) (M = 192.24 g/mol): C 43.74; H 6.29; S 16.68 found: C 43.80; H 6.25; S 16.61

20 Example 8:

Direct preparation of ketomethionine ketal ester (8a)/(8b) by removal of the thiol from the α,α-(dialkylthio)carboxylic acid (4) in the presence of glycerol

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0.1 mol of 2,2,4-tris(methylthio)butanoic acid (4) (22.6 g) was dissolved in 100 ml of glycerol (1,2,3-propanetriol). Subsequently, 1.1 eq of H₂O (1.8 ml) and a spatula-tip of p-toluenesulfonic acid monohydrate

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were added. The overall mixture was then heated to 70°C and a vacuum of 750 mbar was applied. After 5.5 h, the reaction mixture was added to 300 ml of water and extracted three times with 100 ml each time of diethyl ether. The combined ether phases were dried over MgSO₄. After filtration, the ether was removed on a rotary evaporator and the oily crude product ((8a):(8b) ratio = 70:30) was crystallized from a mixture of methylene chloride/n-hexane. The main product (8a) crystallized out in the form of colorless needles (9.2 g, yield = 45%, M = 204.25 g/mol, melting point = 39.5°C (recrystallized from methylene chloride/n-hexane)).

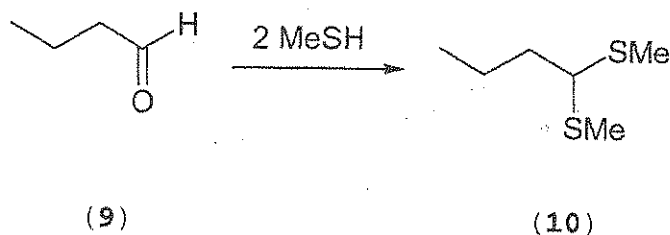
¹H NMR of 4-(2-(methylthio)ethyl)-2,5,8-trioxabicyclo [2.2.2]octan-3-one (8a) (500 MHz, CDCl₃): δ = 2.13 (s, 3H, SCH₃), 2.17-2.20 (m, 2H, CH₂), 2.65-2.68 (m, 2H, CH₂), 4.12-4.13 (m, 4H, 2 CH₂), 4.76 (s, 1H, CH)

¹³C NMR of 4-(2-(methylthio)ethyl)-2,5,8-trioxabicyclo [2.2.2]octan-3-one (8a) (125.8 MHz, CDCl₃): δ = 15.4 (SCH₃), 26.9 (CH₂), 33.2 (CH₂), 66.5 (2 OCH₂), 70.9 (CH), 92.9 (C), 166.2 (COO)

Elemental analysis for C₈H₁₂O₄S (8a) (M = 204.25 g/mol): C 47.04; H 5.92; S 15.70 found: C 47.21; H 5.93; S 15.69

Example 9:

Preparation of 1,1-bis(methylthio)butane (10)



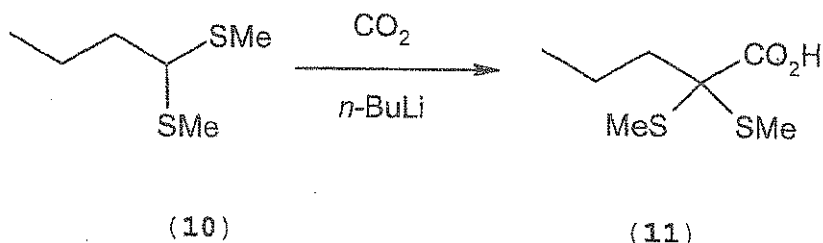
10.0 g of butanal (9) (139 mmol) were saturated with HCl (g) at 0°C and then added dropwise directly to MeSH (624 mmol, 30.0 g) at 0°C over a period of 25 minutes.

5 The reaction mixture was heated to 20°C and stirred at 20°C for 17 h. For further purification, this mixture was dissolved in diethyl ether and washed with a 30% aqueous sodium pyrosulfite solution. After phase separation, the organic phase was dried over Na₂SO₄.
10 After the solvent had been removed, the thioacetal (10) was obtained as a clear colorless oil (17.3 g, yield = 83%; GC purity 98%). The NMR data agree with those from the literature.

15 Example 10

Preparation of 1,1-bis(methylthio)pentanoic acid (11) by umpolung reaction of 1,1-bis(methylthio)butane (10) with dry ice (CO₂)

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10 mmol of 1,1-bis(methylthio)butane (10) (1.26 g) were initially charged in 25 ml of dry THF under a nitrogen atmosphere and cooled to -20°C. Subsequently, 11 mmol
25 of 1.6 M n-BuLi solution in n-hexane (7.0 ml) were added dropwise at -20°C over a period of 5 minutes, and the mixture was stirred for 2 h. The clear, pale yellow reaction solution was added dropwise to 15 g of dry ice
30 at -78°C and stirred for 36 h, in the course of which the temperature rose to 20°C overnight. Subsequently, the reaction mixture was admixed with 40 ml of 10% KOH

- 25 -

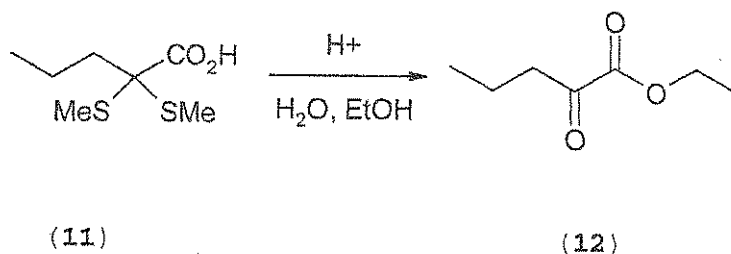
solution and the phases were separated. The organic phase was washed twice with 25 ml each time of 10% KOH solution, and the combined KOH phases were washed three times with 25 ml each time of methyl tert-butyl ether (MTBE). The KOH phase was then acidified (pH 1) with conc. HCl (aq) and extracted four times with 25 ml each time of MTBE. The combined organic phases were dried over MgSO₄ and concentrated with a rotary evaporator. The 2,2-(dimethylthio)pentanoic acid (**11**) was obtained as a white solid (1.0 g, yield = 51.5%, melting point = 85°C (recrystallized from a mixture of chloroform, methanol and acetic acid)).

¹H NMR of 2,2-(dimethylthio)pentanoic acid (**11**) (500 MHz, CDCl₃): δ = 0.96 (t, ³J = 7.4 Hz, 3H, C⁵H₃), 1.50-1.60 (m, 2H, C⁴H₂), 1.88-1.94 (m, 2H, C³H₂), 2.10 (s, 6H, 2 × SCH₃), 11.5 (bs, 1H, C¹OOH)

¹³C NMR of 2,2-(dimethylthio)pentanoic acid (**11**) (125.8 MHz, CDCl₃): δ = 12.5 (2 × SCH₃), 14.0 (C-5), 15.1 (C-4), 36.9 (C-3), 64.6 (C-2), 176.3 (C-1)

Example 11:

Preparation of ethyl 2-oxovalerate (**12**) by removing the thiol from 2,2-(dimethylthio)pentanoic acid (**11**) in the presence of water and ethanol



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0.1 mol of 2,2-(dimethylthio)pentanoic acid (**11**) (19.4 g) was dissolved in 150 ml of toluene and admixed

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with 2.0 eq of H_2O (3.6 ml) and a spatula-tip of p-toluenesulfonic acid monohydrate. Subsequently, the mixture was heated to boiling point and a nitrogen stream was passed through the solution via a frit.

5 After 3 h under reflux, the reaction mixture was cooled to 80°C and admixed with 200 ml of ethanol and a further spatula-tip of p-toluenesulfonic acid monohydrate. After a further 3 h under reflux, the mixture was cooled to 20°C , 200 ml of water were added

10 and the mixture was extracted three times with 100 ml each time of diethyl ether. The combined ether phases were subsequently washed to neutrality with a dilute sodium hydrogencarbonate solution and dried over magnesium sulfate. After filtration, all of the solvent

15 was drawn off with a rotary evaporator. The ethyl 2-oxovalerate (**12**) (10.2 g, yield = 71%) was obtained as a pale yellowish oil.

^1H NMR of ethyl 2-oxovalerate (**12**) (500 MHz, CDCl_3):

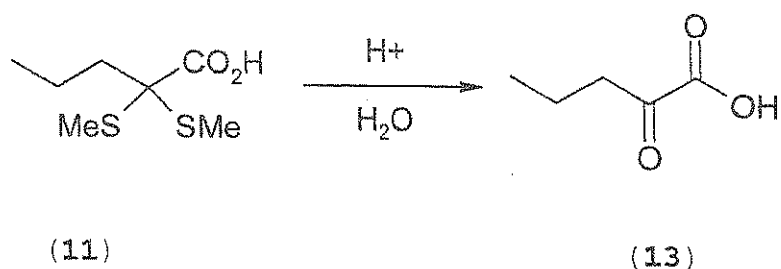
20 $\delta = 0.97$ (t, $^3J = 7.3$ Hz, 3H, C^5H_3), 1.37 (t, $^3J = 7.3$ Hz, 3H, OCH_2CH_3), 1.67 (sext, $^3J = 7.3$ Hz, 2H, C^4H_2), 2.81 (t, $^3J = 7.3$ Hz, 2H, C^3H_2), 4.32 (q, $^3J = 7.3$ Hz, 2H, OCH_2CH_3)

25 ^{13}C NMR of ethyl 2-oxovalerate (**12**) (125.8 MHz, CDCl_3): $\delta = 13.5$ (OCH_2CH_3), 14.0 (C-5), 16.6 (C-4), 41.2 (C-3), 62.3 (OCH_2CH_3), 161.4 (C-1), 194.7 (C-2)

Example 12:

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Preparation of 2-oxovaleric acid (**13**) by removing the thiol from 2,2-(dimethylthio)pentanoic acid (**11**) in the presence of water



10.0 mmol of 2,2-(dimethylthio)pentanoic acid (11) (1.94 g) were suspended in 30 ml of fuming hydrochloric acid (37%) and admixed with a spatula-tip of p-toluenesulfonic acid monohydrate. Subsequently, the mixture was heated to boiling temperature and stirred for 5 h. A vacuum of 750 mbar was applied. After the reaction, the mixture was diluted with 100 ml of water and extracted three times with 80 ml each time of diethyl ether. The combined organic phases were washed three times with 100 ml each time of sodium hydrogencarbonate solution. The combined aqueous phases were subsequently acidified to pH = 1 with concentrated hydrochloric acid and extracted three times with 100 ml each time of diethyl ether. The combined ether phases were dried over MgSO_4 and filtered, and the filtrate was concentrated to dryness under reduced pressure at room temperature. 2-oxovaleric acid (13) was obtained as a colorless oil (0.72 g, yield = 62%).

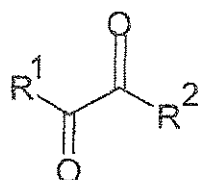
^1H NMR of 2-oxovaleric acid (13) (500 MHz, $\text{DMSO}-d_6$): δ = 0.88 (t, 3J = 7.4 Hz, 3H, C^5H_3), 1.53 (sext, 3J = 7.4 Hz, 2H, C^4H_2), 1.96 (t, 3J = 7.4 Hz, 2H, C^3H_2), 13.5 (bs, 1H, COOH)

^{13}C NMR of 2-oxovaleric acid (13) (125.8 MHz, $\text{DMSO}-d_6$): δ = 13.64 (C-5), 16.37 (C-4), 40.56 (C-3), 163.28 (C-1), 196.93 (C-2)

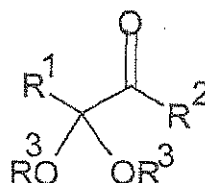
Claims

1. Process for preparing α -keto acids and derivatives thereof of the general formula (I) or (II)

5



(I)



(II)

in which

10 R^1 is a branched or straight-chain C_1 - C_{18} -alkyl, C_5 - C_8 -cycloalkyl, vinyl, allyl, C_6 - C_{10} -aryl- C_1 - C_4 -alkylene or C_4 - C_9 -heteroaryl- C_1 - C_4 -alkylene group, where R^1 is optionally substituted,

15 R^2 is $-OR'''$ or $-NR'R''$, in which R' and R'' are the same or different and are each a hydrogen atom or a branched or straight-chain C_1 - C_6 -alkyl group, and R''' is a hydrogen atom, a branched or straight-chain C_1 - C_8 -alkyl, C_5 - C_8 -cycloalkyl, allyl or a benzyl group, where alkyl in R' , R'' and/or R''' is optionally substituted, or R''' is an
20 alkaline metal ion, alkaline earth metal ion or a mono- or divalent transition metal ion,

25 R^3 is the same or different and is a hydrogen atom, a branched or straight-chain C_1 - C_8 -alkyl, allyl or a benzyl group, where alkyl and/or benzyl is optionally substituted, or the two R^3 radicals together are C_2 - C_8 -alkanediyl and together form a ring, or the two R^3 and R''' radicals together are
30 part of a C_3 - C_8 -alkanetriyl group of the general formula $-R^3(CH-)R'''$ and together form a bicyclic

group,

wherein

- 5 a) an aldehyde R^1CHO is reacted with identical or different thiols of the formula R^4-S-H , in which R^4 is a branched or straight-chain, optionally substituted C_1-C_6 -alkyl, C_5-C_8 -cycloalkyl, allyl or benzyl group to
- 10 give the corresponding dithioacetal,
- b) the dithioacetal formed reacts with a carbonyl-containing electrophile in the presence of a strong base and after
- 15 hydrolysis to give the α,α -(dithio)carboxylic acid or derivatives thereof of the formula (III)



(III)

20

in which R^5 is a hydrogen atom or a branched or straight-chain C_1-C_6 -alkyl group and the R^4 and R^1 radicals are each as defined above, and

25

- c) the α,α -(dithio)carboxylic acid or derivatives thereof of the formula (III) are converted by acid-catalyzed solvolysis in the presence of at least 1 molar equivalent of
- 30 water with release of thiols of the formula R^4SH to give the α -keto acid or derivatives thereof of the general formula (I) or (II).

2. Process according to Claim 1, characterized in that the strong base used for deprotonation in b), measured on its corresponding acid, has a pK_a value of > 20 .
5
3. Process according to Claim 1 or 2, characterized in that the deprotonation in b) is performed in aprotic organic solvents or in liquid supercritical carbon dioxide or in liquid ammonia.
10
4. Process according to one or more of Claims 1-3, characterized in that process step b) is effected at a temperature of -80°C to 100°C .
15
5. Process according to one or more of Claims 1-4, characterized in that the thiol of the formula R^4SH released in c) is removed from the reaction mixture, then recycled and reused in a).
20
6. Process according to Claim 5, characterized in that the thiol of the formula R^4SH is a C_1 - C_6 -alkylthiol which is removed from the reaction mixture by a vacuum or by passing inert gas through.
25
7. Process according to one or more of Claims 1-6, characterized in that the thiol used in a) is methylthiol.
30
8. Process according to one or more of Claims 1-7, characterized in that the acid-catalyzed solvolysis in c) is effected with water as the solvent.
35
9. Process according to one or more of Claims 1-7, characterized in that the acid-catalyzed solvolysis in c) is effected with an alcohol

R'''OH as the solvent, in which R''' is a branched or straight-chain C₁-C₈-alkyl, C₅-C₈-cycloalkyl, allyl or a benzyl group, and alkyl is optionally substituted.

5

10. Process according to one or more of Claims 1-7, characterized in that the acid-catalyzed solvolysis in c) is effected with a diol HO-R³-OH as the solvent, where R³ is a branched or
10 straight-chain, optionally substituted C₂-C₈-alkanediyl group.

11. Process according to one or more of Claims 1-7, characterized in that the acid-catalyzed
15 solvolysis in c) is effected with a triol HOR³(CHOH)R'''OH as the solvent where the R³ and R''' radicals together are part of a branched or straight-chain, optionally substituted C₃-C₈-alkanetriyl group of the general formula
20 -R³(CH-)R'''.

12. Process according to one or more of Claims 1-7, characterized in that the acid-catalyzed solvolysis in c) is effected with an amine HNR'R'' as the solvent, in which R' and R'' may be the
25 same or different and are each a hydrogen atom or a branched or straight-chain C₁-C₆-alkyl group, but R' and R'' cannot both be a hydrogen atom.

30 13. Process according to one or more of Claims 1-12, characterized in that an aldehyde R¹CHO in which R¹ is vinyl or CH₃SCH₂CH₂- is used in a).

14. Process according to one or more of Claims 1-13,
35 characterized in that the α-keto acid of the general formula (I) is α-ketomethionine and derivatives thereof, where R¹ is CH₃SCH₂CH₂, and an aldehyde R¹CHO in which R¹ = CH₃SCH₂CH₂- is reacted

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with methylthiol in step a).

15. Process according to one or more of Claims 1-13, characterized in that the α -keto acid of the general formula (I) is α -ketomethionine and derivatives thereof, where R^1 is vinyl, and the triple addition of methylthiol to acrolein takes place in step a).
16. Intermediate of the formula (IV)



(IV)

in which

- R^1 is a branched or straight-chain C_1 - C_{18} -alkyl, C_5 - C_8 -cycloalkyl, vinyl, allyl, C_6 - C_{10} -aryl- C_1 - C_4 -alkylene or C_4 - C_9 -heteroaryl- C_1 - C_4 -alkylene group, where R^1 is optionally substituted,
- R^2 is $-OR'''$ or $-NR'R''$, in which R' and R'' are the same or different and are each a hydrogen atom or a branched or straight-chain C_1 - C_6 -alkyl group, and R''' is a hydrogen atom, a branched or straight-chain C_1 - C_8 -alkyl, C_5 - C_8 -cycloalkyl, allyl or a benzyl group, where alkyl in R' , R'' and/or R''' is optionally substituted, or R''' is an alkaline metal ion, alkaline earth metal ion or a mono- or divalent transition metal ion,
- and R^4 is the same or different and is a branched or straight-chain, optionally substituted C_1 - C_6 -alkyl, C_5 - C_8 -cycloalkyl, allyl or benzyl group.

17. Use of a thiol of the formula R^4-S-H , where R^4 is a
branched or straight-chain, optionally substituted
 C_1-C_6 -alkyl, C_5-C_8 -cycloalkyl, allyl or benzyl
5 group for umpolung of aliphatic and/or aromatic
aldehydes.