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(54) Titre : PROCEDE DE PRODUCTION DE METHIONINE A PARTIR D'HOMOSERINE
(54) Title: METHOD FOR PRODUCING METHIONINE FROM HOMOSERINE

(57) **Abrégé/Abstract:**

Method for producing L-methionine, D-methionine and/or any mixture of L-methionine and D-homoserine, by chemical conversion of L-homoserine or D-homoserine or corresponding mixtures of L-homoserine and D-homoserine, without going through any of the intermediate stages N-carbamoyl homoserine, 4-(2-methyl bromide)hydantoin and 4-(2-methylthioethyl)hydantoin.



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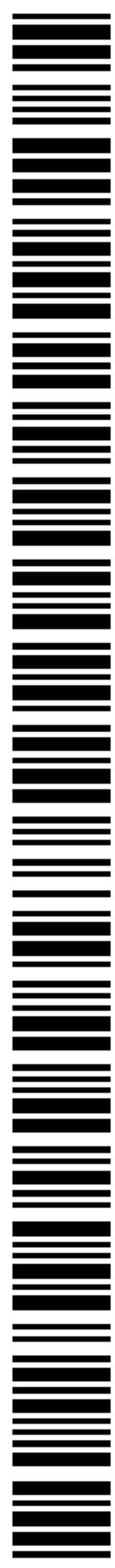
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(54) Title: METHOD FOR PRODUCING METHIONINE FROM HOMOSERINE

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON METHIONIN AUS HOMOSERIN

(57) Abstract: Method for producing L-methionine, D-methionine and/or any mixture of L-methionine and D-homoserine, by chemical conversion of L-homoserine or D-homoserine or corresponding mixtures of L-homoserine and D-homoserine, without going through any of the intermediate stages N-carbamoylhomoserine, 4-(2-methyl bromide)hydantoin and 4-(2-methylthioethyl)hydantoin.

(57) Zusammenfassung: Gegenstand der Erfindung ist ein Verfahren zur Herstellung von L-Methionin, D-Methionin oder einer beliebigen Mischung von L- und D-Methionin durch chemische Umwandlung von L- oder D-Homoserin oder entsprechenden Mischungen von L- und D-Homoserin, wobei keine der Zwischenstufen N-Carbamoylhomoserin, 4-(2-Brommethyl)hydantoin und 4-(2-Methylthioethyl)hydantoin durchlaufen werden.



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"Method for producing methionine from homoserine"

The present invention relates to the production of methionine by combination of biotechnological and
5 chemical steps.

In particular, the present invention relates to the production of L-homoserine by fermentation and subsequent chemical conversion to L-methionine in one or
10 more steps.

The amino acid methionine is currently produced industrially in large amounts worldwide and is of considerable commercial importance.

15

Methionine is employed in many fields such as, for example, pharmaceutical, health and fitness products. In particular, however, methionine is used as feed additive in many feeds for various farm animals, both
20 the racemic form and also the enantiomerically pure form of methionine being able to be used.

On an industrial scale, methionine is produced chemically via the Bucherer-Bergs reaction, which is a
25 variant of Strecker synthesis. In this method the starting substances methylmercaptopropionaldehyde (produced from acrolein and methylmercaptan), prussic acid, ammonia and carbon dioxide are reacted to form 5-(2-methylmercaptoethyl)hydantoin (methioninehydantoin),
30 this is subsequently hydrolysed under alkaline conditions to give alkali metal methioninate and then the methionine is liberated by neutralization with acid, for example sulphuric acid or carbonic acid. Various other methods can also be used for producing
35 methionine, such as, for example the amidocarbonylation reaction, the hydrolysis of proteins or fermentation.

Since methionine is produced industrially on a large scale, it is desirable to have an economic but also

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environmentally friendly process available.

Both Strecker synthesis and the Bucherer-Bergs reaction have the disadvantage that the poisonous precursors prussic acid and acrolein are used as C₁- and C₃-building blocks, respectively. Prussic acid is produced from methane and ammonia at high temperatures. Acrolein is produced by partial oxidation of propene which in turn is produced from petroleum. The methionine process is described in more detail, for example, in EP 1256571. The process for producing acrolein is described in more detail, for example, in EP 417723. Both processes are associated with high equipment usage and high energy requirement.

Owing to the price increase of petroleum in recent years, acrolein is also becoming increasingly more expensive and thus as a building block has become less and less attractive economically. Furthermore, not only prussic acid but also acrolein, because of their toxicity and physical properties with respect to safety and environmental protection, give rise to corresponding expenditure in the handling of large amounts.

Methionine is produced in chemical synthesis as a racemic mixture of D and L enantiomers. This racemate can be used directly as feed additive, since under in vivo conditions, there is a conversion mechanism which converts the unnatural D enantiomer into the natural L enantiomer. However, this conversion is associated with a loss of methionine and thus also a loss of bioefficiency compared with the same amount of pure L enantiomer. Therefore, more racemic D,L-methionine is required compared with L-methionine, to achieve the same effect.

It was therefore desirable to provide a process for production of methionine which is as far as possible of greater economic interest and more environmentally

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friendly and safer. In particular, it was desirable to provide a process for production of enantiomerically enriched L-methionine, very particularly preferably of as far as possible enantiomerically pure L-methionine, which should be able to be carried out on an industrial scale.

Previous processes which are based on the production of L-methionine using microorganisms as described, for example in WO04/024933, have the disadvantage that comparatively small yields are achieved. This has its origin, in particular, in the problems with the strictly organized regulatory network of microbial L-methionine biosynthesis, with the excretion of methionine from the cell into the fermentation broth, and also with the energy-intensive eight-electron step in the reduction of sulphate to hydrogen sulphide. Secondly, the limited solubility of methionine in water or in aqueous fermentation broths has the effect that methionine precipitates out at high biosynthesis performance in the fermentation and thus makes purification difficult. The complex purification leads as a result to the fact that considerable waste streams are produced, the removal of which is associated with high costs.

Although in WO05/059155 a method is described for the improved isolation of L-methionine from fermentation broths, the improvement is achieved, however, by a comparatively complicated sequence of steps which comprises, heating and dissolving the L-methionine in the fermentation broth, filtering off the biomass at a defined temperature and post-treating the methionine-containing biomass which was filtered off, concentrating the mother liquor by evaporation, cooling, crystallizing, filtering off, washing and drying the L-methionine from the mother liquor and recycling mother liquors, and by the fact that two different product streams are produced, namely a low concentra-

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tion and a high-concentration L-methionine product. The forced production of two different methionine quality grades means, however, again increased expenditure and is moreover undesirable from the marketing point of view.

The said problems ultimately lead to a lower overall yield for a purely fermentative L-methionine method compared with the fermentative production methods of, for example, L-lysine, which have already been used for many years in industry and/or to a corresponding additional expenditure in the production of L-methionine by fermentation.

Against the background of the disadvantages of the prior art, it was, in particular, the object to provide a method for methionine which overcomes the above disadvantages described in more detail of the method of the prior art. This method should, as far as possible proceeding from another available precursor and producible by fermentation, lead in the simplest possible manner and without the use of the abovementioned hazardous chemicals to L-, D- or D,L-methionine, but preferably to L-methionine and in so doing overcome in particular the disadvantages of the conventional chemical methods and also of the direct biotechnological production methods for methionine.

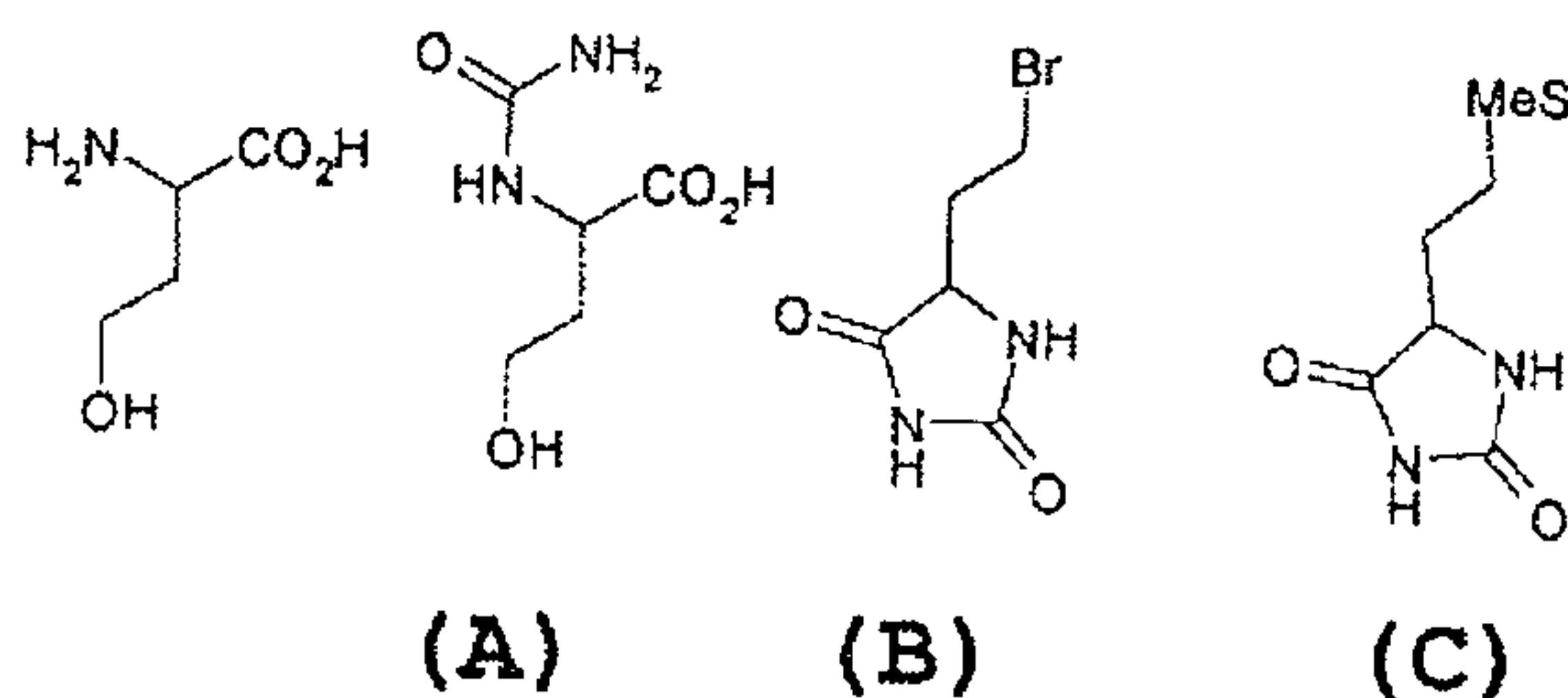
It was a further object to provide a production method which can be carried out at least in part starting from natural or renewable raw materials.

A third object was to provide a method which can be carried out technically without problem, which makes L-methionine accessible in suitable amounts and purities.

These objects and also further objects which are not

mentioned explicitly, but which can be derived or concluded from the context discussed herein without problem, are **achieved** in that another amino acid which is available and producible better by fermentation is used as starting material, which is then converted via a suitable chemical transformation without using the abovementioned hazardous chemicals to L-, D- or D,L-methionine, but in particular to L-methionine. By this means, not only the disadvantages of the conventional chemical production processes for methionine are overcome, but also those of the conventional production processes for L-methionine by direct fermentation. The amino acid homoserine has proved suitable according to the invention, which, in contrast to methionine, has a high water solubility and which is also accessible via fermentative methods.

The pathway described by Livak, Britton, VanderWeele and Murray ("Synthesis of dl-methionine", Journal of the American Chemical Society, (1945), 67, 2218-20) in which D,L-homoserine occurs as synthesis intermediate, proceeds first from D,L-2-amino-4-butyrolactone which leads via D,L-homoserine, N-carbamoylhomoserine, 4-(2-bromomethyl)hydantoin and 4-(2-methylthioethyl)-hydantoin, finally to D,L-methionine:



The deuterated homoserine derivatives $\text{HO-CHD-CH}_2\text{-CH(HNCOOtBu)COOtBu}$ or $\text{H}_3\text{CC}_6\text{H}_4\text{SO}_2\text{O-CHD-CH}_2\text{-CH(HNCOOtBu)COOtBu}$ (tBu = tert-butyl) were used according to Son and Woodard ("Stereochemical mechanism of iodoacetic acid mediated decomposition of L-methionine to L-homoserine lactone", Journal of the American Chemical Society (1989), 111(4), 1363-7) as precursors

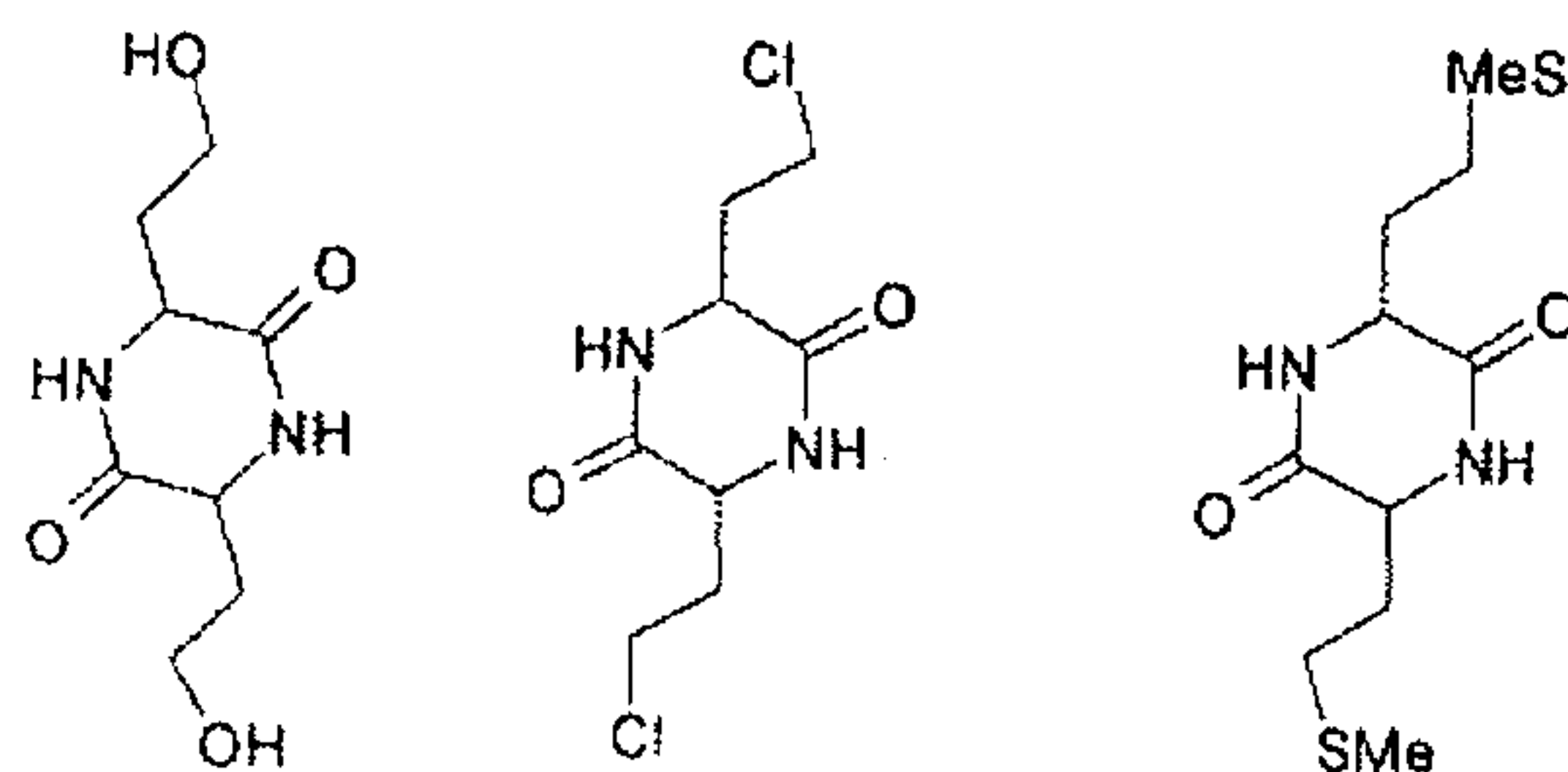
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of L-homoserine correspondingly deuterated in the 4 position. The corresponding non-deuterated compounds $\text{HO-CH}_2\text{-CH}_2\text{-CH(HNCOOtBu)COOtBu}$ or $\text{H}_3\text{CC}_6\text{H}_4\text{SO}_2\text{O-CH}_2\text{-CH}_2\text{-CH(HNCOOtBu)COOtBu}$ have not been described on the pathway to homoserine.

The subsequently schematized compounds 3,6-di(2-hydroxyethyl)-2,5-diketopiperazine, 3,6-di(2-chloroethyl)-2,5-diketopiperazine or 3,6-di(2-methylthioethyl)-2,5-diketopiperazine are chemical intermediates through which the pathway to D,L-methionine passes according to US2,397,628, however, starting not from homoserine, but starting from 2-acetyl-4-butyrolactone:



15

In addition there are further production methods for D,L-methionine which likewise do not start from homoserine, but start, for example, from 2-acetyl-4-butyrolactone via 2-amino-4-butyrolactone or appropriately protected 2-amino-4-butyrolactone, according to Snyder, Andreen, John, Cannon and Peters ("Convenient synthesis of dl-methionine", Journal of the American Chemical Society (1942), 64, 2082-4).

25

The synthesis according to Plieninger starts from 2-amino-4-butyrolactone ("Die Aufspaltung des γ -Butyrolactons und α -Amino- γ -butyrolactons mit Natriummethylmercaptid bzw. -selenid. Eine Synthese des Methionins" [The Cleavage of γ -Butyrolactone and α -Amino- γ -butyrolactone using Sodium Methyl Mercaptide or Selenide. A Synthesis of Methionine], Chemische Berichte (1950), 83, 265-8).

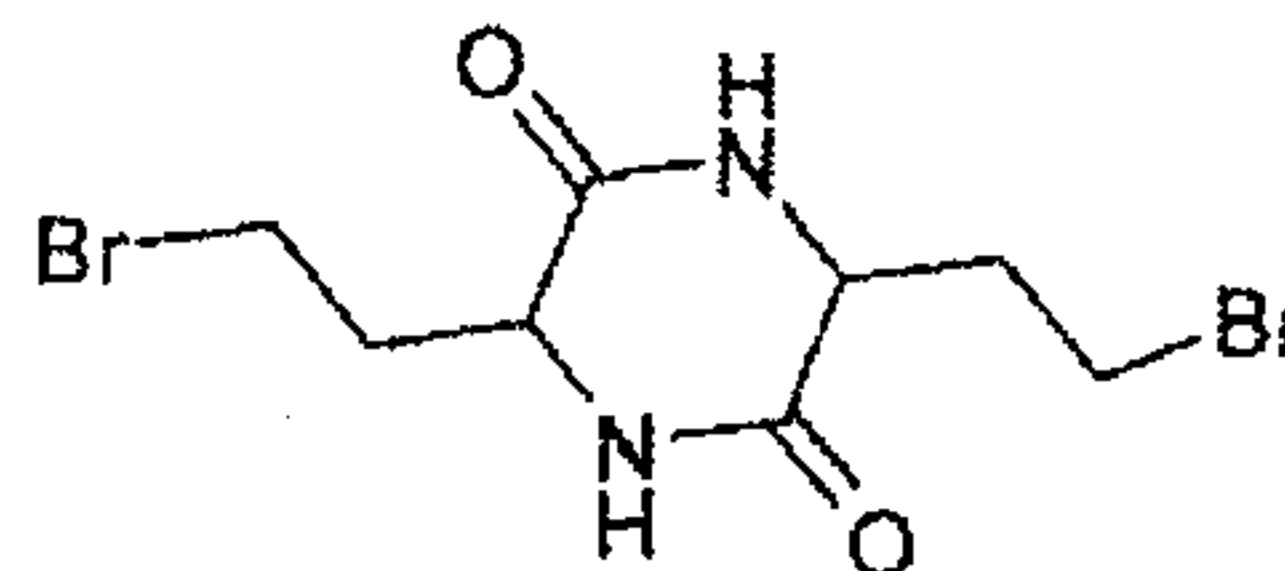
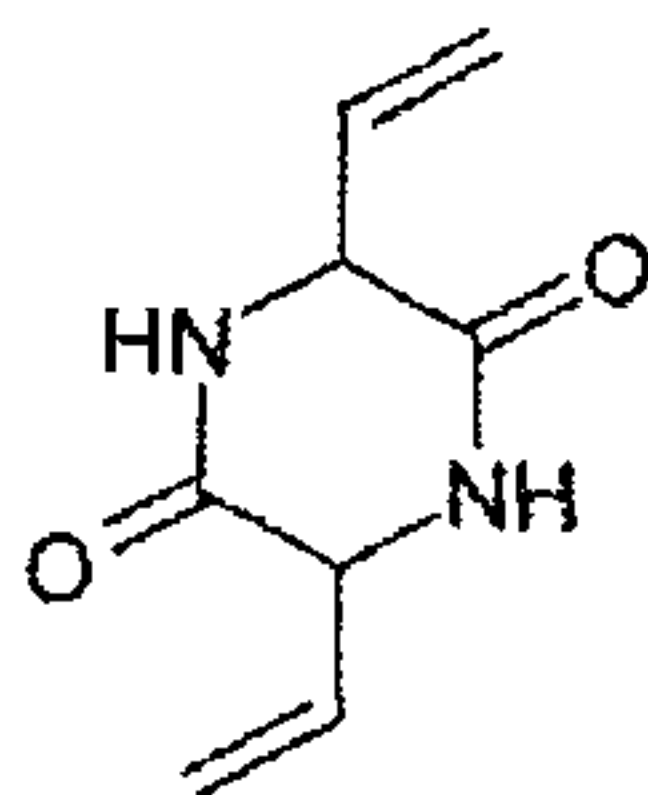
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The subsequently schematized compounds, 3,6-di-(2-vinyl)-2,5-diketopiperazine and 3,6-di(2-bromoethyl)-2,5-diketopiperazine are likewise chemical precursors

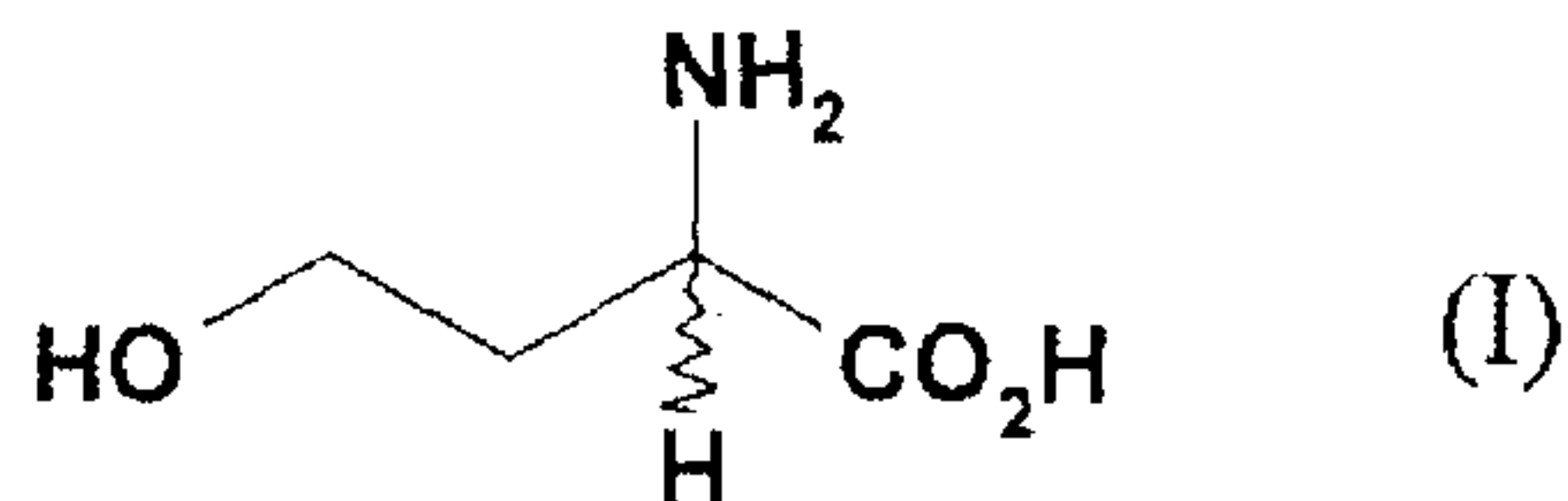


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through which, according to Snyder and Chiddix ("Non-Markovnikov addition in reactions of 3,6-divinyl-2,5-diketopiperazine", Journal of the American Chemical Society (1944), 66, 1002-4) the pathway to D,L-methionine passes. However, here also homoserine is not used.

In particular, the abovementioned objects are achieved by a method according to Claim 1. Expedient forms and modifications of the inventive method are brought under protection in the subclaims referred back to Claim 1.

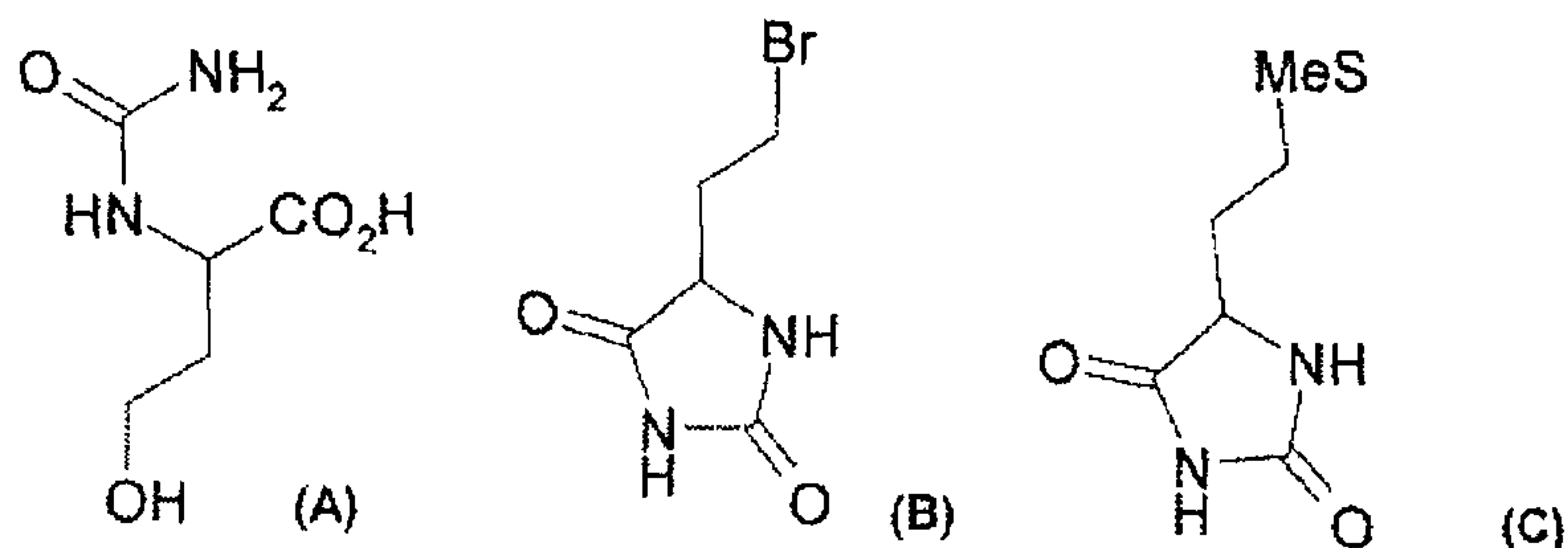
By the means that a method is used for production of L-methionine, D-methionine or any desired mixtures of L- and D-methionine which starts from homoserine and in which L-homoserine, D-homoserine or corresponding mixtures of L- and D-homoserine of the formula I below



25

are converted to methionine by chemical transformation, without passing through any of the intermediates N-carbamoylhomoserine, 4-(2-bromoethyl)hydantoin and 4-(2-methylthioethyl)hydantoin (formulae A-C),

30



the disadvantages of the said purely chemical or direct biotechnological methods are successfully overcome.

5

These disadvantages are overcome, in particular, when the L-homoserine used has been produced via fermentation. It is already known that L-homoserine can be produced by fermentation of microorganisms, in particular bacteria of the family Enterobacteriaceae or coryneform bacteria, with carbon sources such as, for example, sucrose, glucose, fructose and glycerol or mixtures thereof and customary nitrogen sources such as, for example, ammonia being used.

15

Examples of the microbial production of L-homoserine in which Enterobacteriaceae, in particular *Escherichia coli*, are used, can be found in US 6,303,348, US 6,887,691 or US 6,960,455 or EP 1217076 A1.

20

Examples of the microbial production of L-homoserine in which coryneform bacteria, in particular *Corynebacterium glutamicum*, are used, can be found in US 3,189,526 or US 3,598,701.

25

By using L-homoserine obtained by fermentation, the said relatively hazardous raw materials acrolein and prussic acid are successfully avoided.

30

However, it can also be advantageous to mix L-homoserine obtained by fermentation with racemic D,L-homoserine produced classically by the chemical route and to use a resulting mixture of D- and L-homoserine for the chemical transformation, from which at the end then

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corresponding mixtures of D- and L-methionine result. This can be advantageous, especially, when D-/L-homoserine is to be utilized as residue of chemical production processes of D-/L-homoserine production.

5 Pure D-homoserine can also be used. This can be advantageous, in particular, when D-homoserine is to be utilized as residue from the separation of D-/L-homoserine racemate. The use of pure D-homoserine, however, is generally only advantageous when

10 D-methionine is to be produced specifically.

By use of L-homoserine obtained by fermentation, it is possible, in contrast, to arrive directly at L-methionine and in fact with the use according to the

15 invention of chemical method steps which do not impair the L configuration. In the case of exclusive use of L-homoserine, ultimately a pure L-methionine is produced which can be used directly for pharmaceutical and food uses and is distinguished in animal nutrition

20 by higher bioefficiency compared with conventional D,L-methionine. This aspect of the method of the invention is generally of greatest benefit.

In a preferred method, use is made of an L-homoserine-

25 containing solid product which was produced from an L-homoserine-containing fermentation broth by removal of water. This has the advantage that byproducts of fermentation can first be separated off in the L-methionine stage in the last purification step, and

30 thus purification expenditure can be saved. If appropriate, byproducts and/or accompanying substances of fermentation can also remain in the end product if they do not interfere with the subsequent reaction or are even desired in the end product. This is the case,

35 in particular, if they themselves have nutritious properties and L-methionine is used for feed production. Such nutritionally active compounds can be, for example, further amino acids or proteins.

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Accordingly, the invention also relates to a mixed product of L-methionine and byproducts and/or accompanying substances of the production of L-homoserine by fermentation.

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The L-homoserine-containing fermentation broth is expediently produced by culturing an L-homoserine-excreting microorganism in a suitable nutrient medium.

10 As microorganism, use is preferably made of bacteria, in particular bacteria of the genus *Corynebacterium* or *Escherichia*.

It has furthermore proved to be advantageous when the
15 concentration of the L-homoserine in the fermentation broth is at least 1 g/l.

Surprisingly, it has been found that the chemical transformation of L- and/or D-homoserine can be carried
20 out directly using methylmercaptan (MeSH) if appropriate in the presence of an acid catalyst. This has the great advantage that a single chemical step leads directly to the end product L-methionine. Methylmercaptan can be used here in great excesses and
25 unconsumed methylmercaptan can subsequently readily be separated off and recycled, since, in contrast to the amino acid, it is a compound gaseous at room temperature.

30 Here, it has proved advantageous to use 1 to 100 mol equivalents, preferably 1 to 50 mol equivalents, of MeSH.

To accelerate the reaction and to increase the yield,
35 it has also proved advantageous when use is made of an acid catalyst selected from the group consisting of Brönstedt acids having a pK_a of ≤ 3 .

Such acids are, for example, HCl, HBr, HI, H_2SO_4 , alkali

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metal HSO_4 , H_3PO_4 , alkali metal H_2PO_4 , where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C_1 - C_{12} -alkylsulphonic acid, C_6 - C_{10} -arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion). Nafion as solid catalyst has the advantage, in particular, that it can readily be separated off from the reaction mixture after the reaction and be recycled.

It can likewise be advantageous when use is made of a **Lewis acid catalyst**. Here, mention may be made of, in particular, Lewis acid catalysts having at least one low-molecular-weight Lewis acid selected from the group AlCl_3 , ZnCl_2 , $\text{BF}_3 \cdot \text{OEt}_2$, SnCl_2 , FeCl_3 .

Also, **strongly acidic ion-exchange resins** which likewise can be recovered particularly readily, have proved advantageous here, in particular an optionally substituted, for example by divinylbenzene, crosslinked polystyrenesulphonic acid resin.

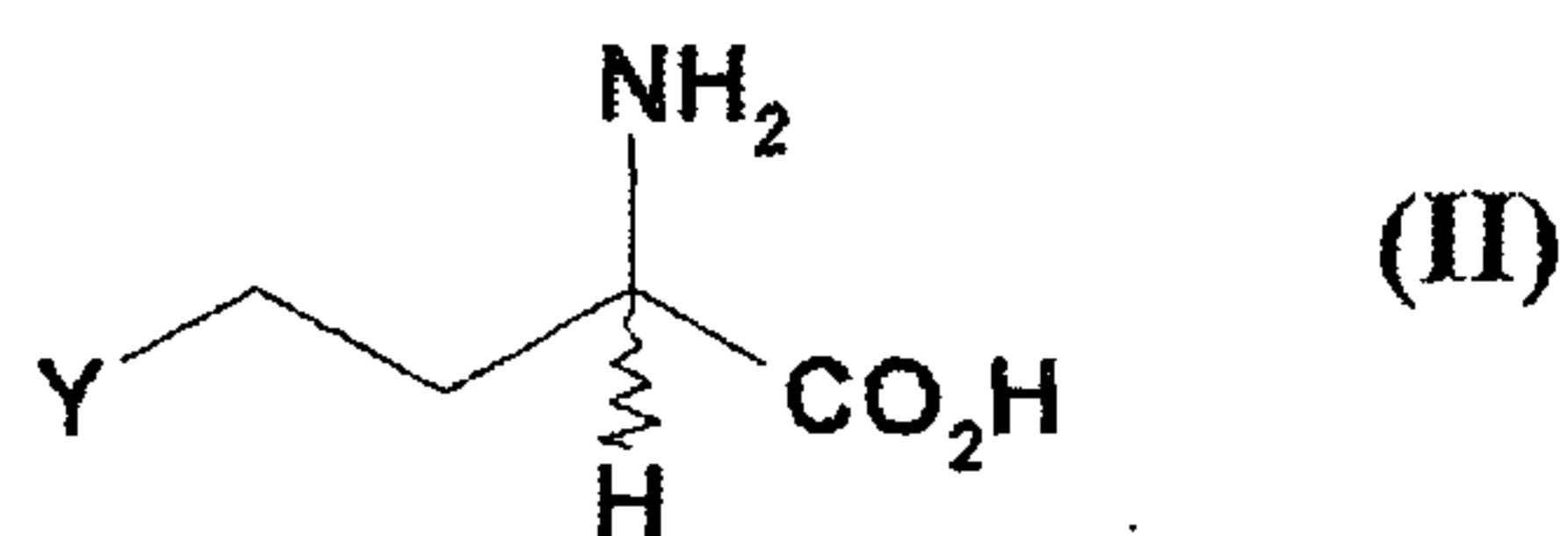
However, **heterogeneous acid catalysts** from the group zeolite, montmorillonite and (WO_3 - and Cs_2O)-containing aluminium oxide can also be used according to the invention. Among the said aluminium oxides, preference is given to those having 5-15% WO_3 and 5-15% Cs_2O content.

Expediently, the reaction is carried out in **solution and/or in suspension** in the presence of water and/or an organic solvent. If the reaction is carried out in the presence of water, it can be expedient to proceed directly from an L-homoserine-containing aqueous fermentation solution, which is optionally freed from solid fractions, since in this manner advantageously, further work-up steps can be omitted. However, an aqueous crude L-homoserine can also be correspondingly

advantageously used.

For instance, according to the invention, use can be made of water and/or at least one low-molecular-weight organic solvent selected from the group consisting of C₃ to C₆ ketones, preferably methyl isobutyl ketone (MIBK) or acetone, straight-chain or branched C₁ to C₄ alcohols, C₄ to C₁₀ carboxylic esters, preferably ethyl or butyl acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate, propylene carbonate, butylene carbonate. However, methylmercaptan, used in corresponding excesses, can also act as solvent or at least as cosolvent.

According to another preferred embodiment of the invention, a method for the chemical transformation of L- and/or D-homoserine to methionine can also be carried out in such a manner that, in a first step, by introduction of a **leaving group Y on the C₄ atom** of homoserine, a compound of the formula II



is produced, where Y is halogen (= chlorine, bromine or iodine), sulphonyloxy (= p-toluenesulphonyloxy [pTsO], C₆H₅SO₃, H₃CSO₃, H₅C₂SO₃ or CF₃SO₂), sulphate (OSO₃H) or phosphate (OPO₃H), and compound II is then reacted in a second step with **MeSH** to give L-methionine, D-methionine or a corresponding mixture of L- and D-methionine.

Introduction of the leaving group Y proceeds advantageously, when Y = halogen, in the first step correspondingly by reaction of the homoserine with PCl₅, PCl₃, BBr₃, PJ₃, POCl₃, SOCl₂ or SOBr₂.

When Y = sulphonyloxy, introduction of the leaving group Y in the first step proceeds correspondingly and advantageously by reaction with p-toluenesulphonyl chloride (p-TsCl), C₆H₅SO₂Cl, H₃CSO₂Cl, H₅C₂SO₂Cl or CF₃SO₂Cl.

When, in contrast, Y = sulphate, for introduction of the leaving group Y, in the first step typically use is correspondingly made of SO₃, H₂SO₄ or oleum, and when Y = phosphate, preferably use is made of polyphosphoric acid to introduce Y.

After activation of the homoserine by introducing the corresponding leaving group Y in the 4 position, in a next step, the Me-S group may be particularly readily introduced by substitution of Y.

This substitution is advantageously carried out by reacting the compound of the formula II with **MeSH** in the presence of a basic or acid catalyst.

Suitable basic catalysts are, in particular, NaOH, KOH, pyridine, trimethylamine, triethylamine or an acetate, carbonate or hydrogencarbonate of the alkali metals or alkaline earth metals, alkali metal being lithium, sodium, potassium, rubidium or caesium and alkaline earth metal being magnesium, calcium or barium.

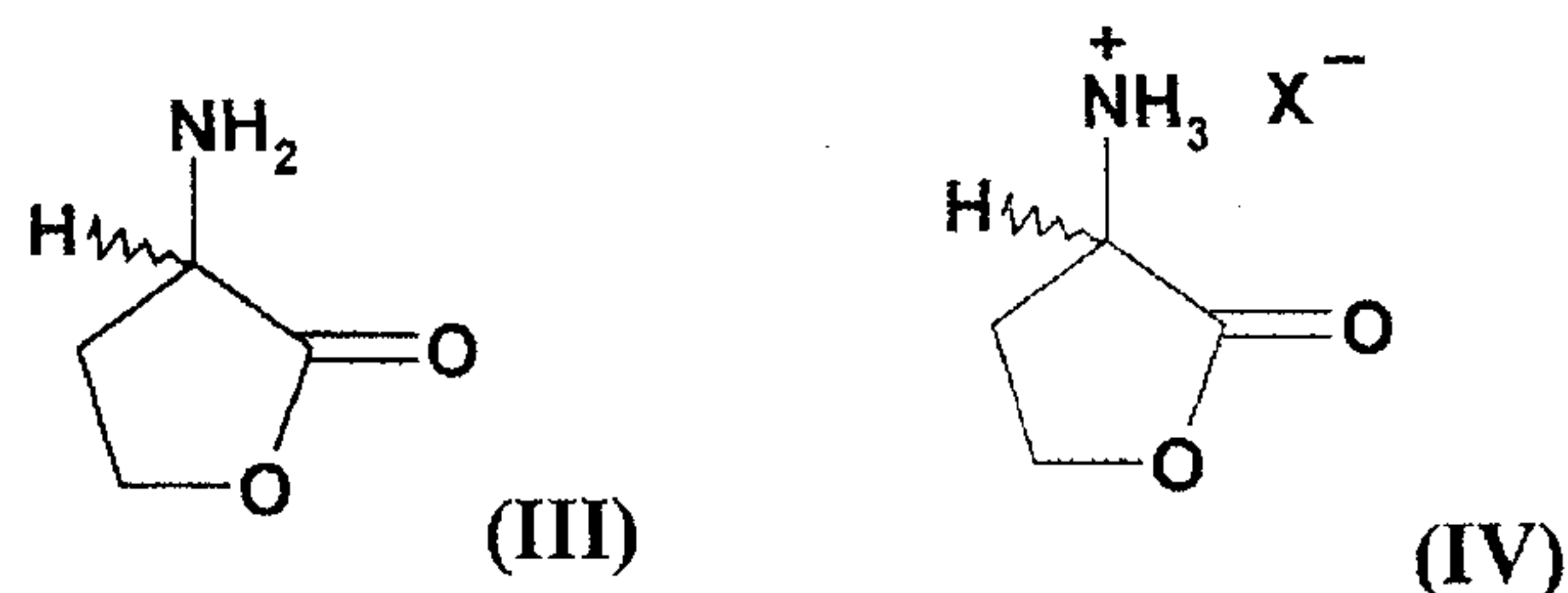
Suitable acid catalysts are, in particular, HCl, HBr, HI, H₂SO₄, alkali metal HSO₄, H₃PO₄, alkali metal H₂PO₄, where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion) is used.

The reaction is preferably carried out in the presence

of an organic solvent and/or water.

As organic solvent, use is preferably made of a low-molecular-weight organic solvent selected from the group consisting of C₃ to C₆ ketones, preferably methyl isobutyl ketone (MIBK) or acetone, straight-chain or branched C₁ to C₄ alcohols, C₄ to C₁₀ carboxylic esters, preferably ethyl or butyl acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate, propylene carbonate or butylene carbonate.

According to a further preferred embodiment of the invention, a method for the chemical transformation of L- and/or D-homoserine to methionine can also be carried out in such a manner that, in a first step, by **acid-catalysed cyclization**, the corresponding 2-amino-4-butyrolactone of the formula III or salt thereof (formula IV)



is produced, where X is Cl, Br, I, HSO₄, (SO₄)_{1/2}, H₂PO₄, (HPO₄)_{1/2}, (PO₄)_{1/3} or R'-SO₃ (where R' = methyl, ethyl, phenyl, tosyl), which is then reacted in a second step with **MeSH** to give L-methionine, D-methionine or a corresponding mixture of L- and D-methionine. In particular, the salt is a stable intermediate which can be temporarily stored or else transported, which is a not inconsiderable advantage.

Suitable **acid catalysts** are acids selected from the group consisting of Brönstedt acids having a pK_a of ≤ 3.

Preferably, as acid catalyst, use is made here of HCl, HBr, HI, H₂SO₄, alkali metal HSO₄, H₃PO₄, alkali metal H₂PO₄, where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

10

Likewise, **strongly acidic ion-exchange resins** are suitable as acid catalyst and in this case in particular optionally substituted, preferably by divinylbenzene, crosslinked polystyrenesulphonic acid resins.

15

Use can also be made of **heterogeneous acid catalysts** from the group (WO₃- and Cs₂O)-containing aluminium oxide, zeolite and montmorillonite according to the invention. Among the said aluminium oxides, preference is given to those having 5-15% WO₃ content and 5-15% Cs₂O content.

20

Likewise, use can be made of **Lewis acid catalysts** and, in particular, **low-molecular-weight Lewis acids** selected from the group AlCl₃, ZnCl₂, BF₃·OEt₂, SnCl₂, FeCl₃, which are available and inexpensive.

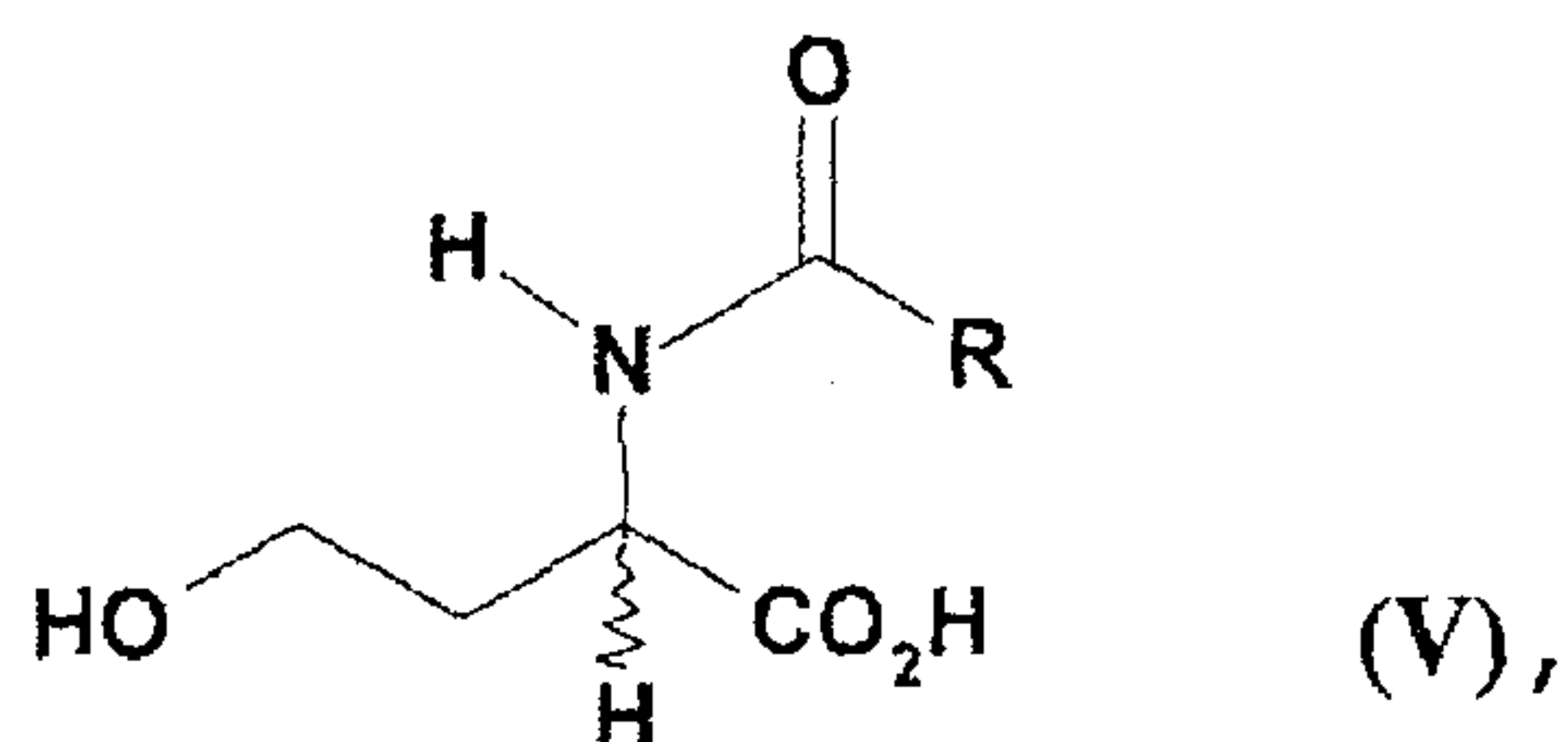
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According to a further preferred embodiment of the invention, a method for the chemical transformation of homoserine to methionine can also be designed in such a manner that the following steps are carried out:

30

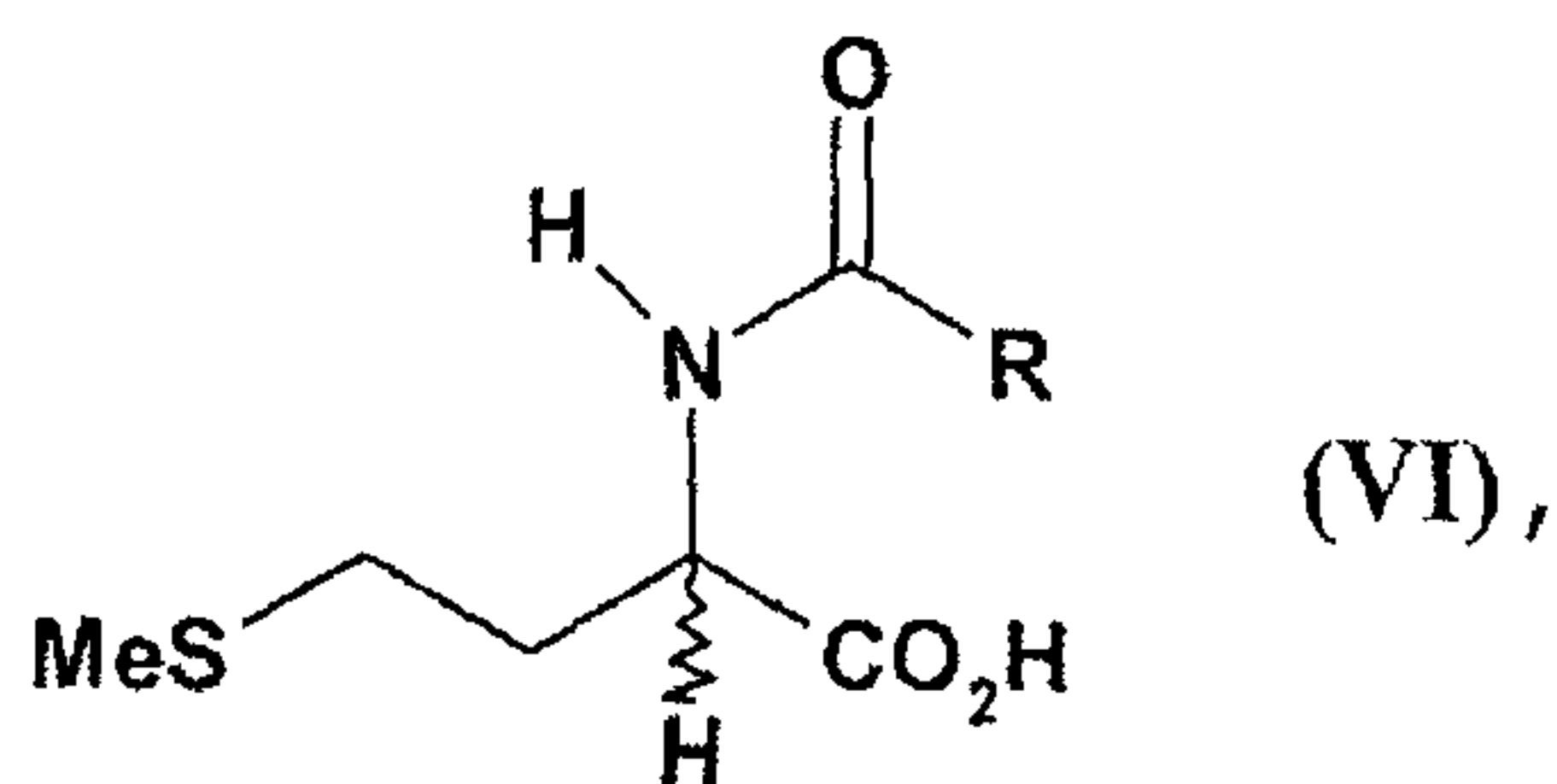
a) **N-acylation** of L- and/or D-homoserine using an acylating agent to give N-acyl-L- and/or D-homoserine of the formula V,

35



where R = hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where halogen = F or Cl, preferably CF₃ or CCl₃, benzyloxycarbonyl or C₁- to C₄-alkyloxycarbonyl, preferably tert-butyl-oxycarbonyl, or methyloxycarbonyl,

- 10 b) reaction of the N-acylhomoserine V obtained in step a) with **MeSH** in the presence of a basic or acid catalyst to give N-acylmethionine of the formula VI



- 15 c) **hydrolysis** of the N-acyl-L- and/or D-methionine obtained in step b) to give the corresponding methionine.

20

Depending on the exact choice of reaction conditions, in step a) either the corresponding O-acylhomoserine is primarily formed which is subsequently rearranged to form the N-acylhomoserine V, or V is formed directly in one stage.

25

For the acylation in step a), preferably use is made of an acylating agent of the general formula R-CO-X¹, where X¹ can be R¹COO, OR² (R² = methyl or ethyl), Cl, Br, and

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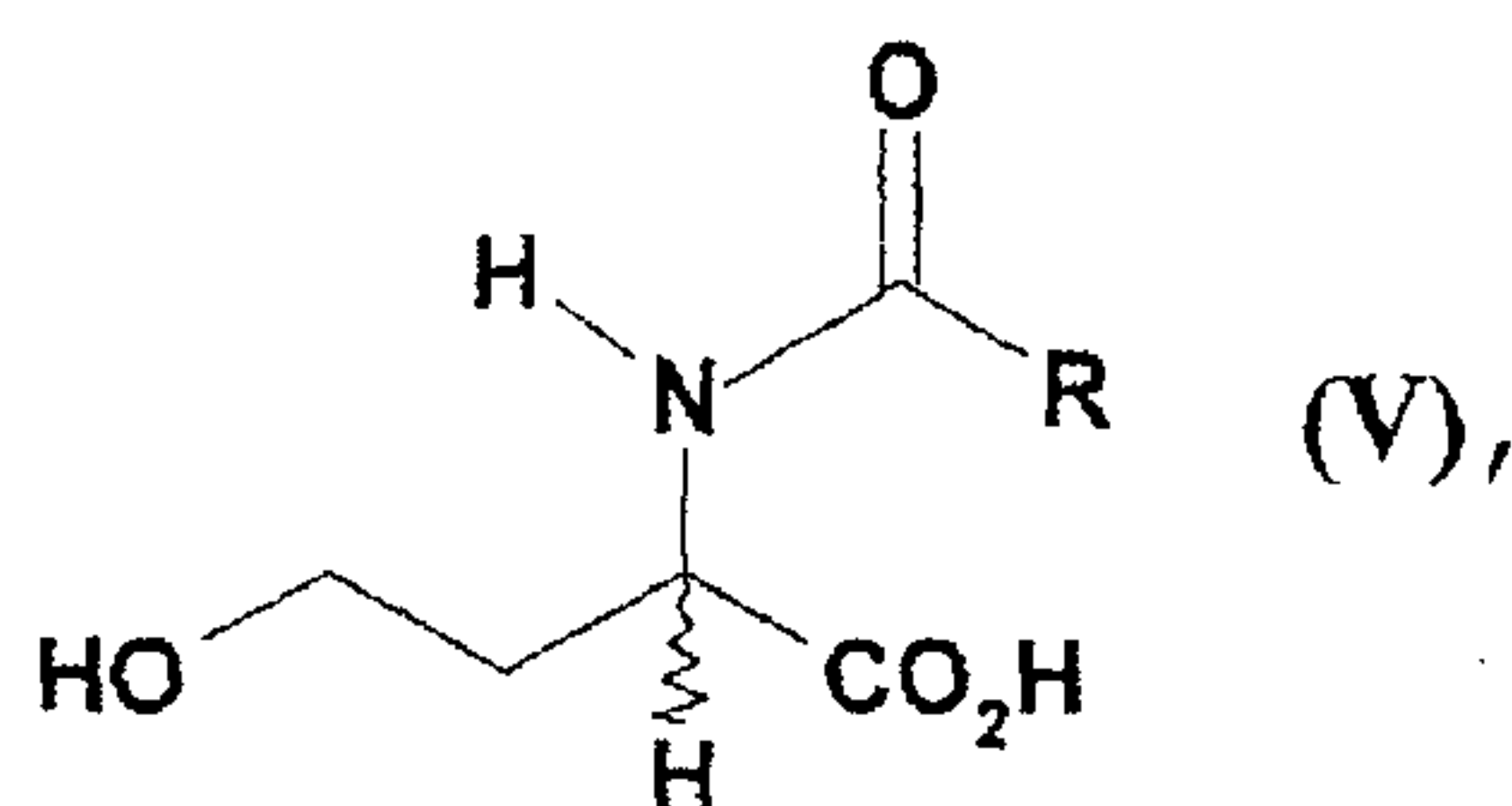
R and R¹ can be identical or different and are hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where halogen = F or Cl, preferably CF₃ or CCl₃,
 5 benzyloxycarbonyl, or C₁- to C₄-alkyloxycarbonyl, preferably tert-butyloxycarbonyl, or methyloxycarbonyl.

As basic catalyst in step b), use can be made of NaOH, KOH, pyridine, trimethylamine, triethylamine, or an
 10 acetate, carbonate or hydrogencarbonate of the alkali metals or alkaline earth metals, where alkali metal is lithium, sodium, potassium, rubidium or caesium, and alkaline earth metal is magnesium, calcium or barium.

15 Suitable acid catalysts for step b) are, in particular, HCl, HBr, HI, H₂SO₄, alkali metal HSO₄, H₃PO₄, alkali metal H₂PO₄, where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-arylsulphonic acid,
 20 trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

According to a further preferred embodiment of the
 25 invention, a method for the chemical transformation of homoserine to methionine can also be designed in such a manner that the following steps are carried out:

a) **N-acylation** of the L- and/or D-homoserine using an
 30 acylating agent to give the N-acyl-L- and/or D-homoserine of the formula V



35 where R is hydrogen, methyl, ethyl, n-propyl,

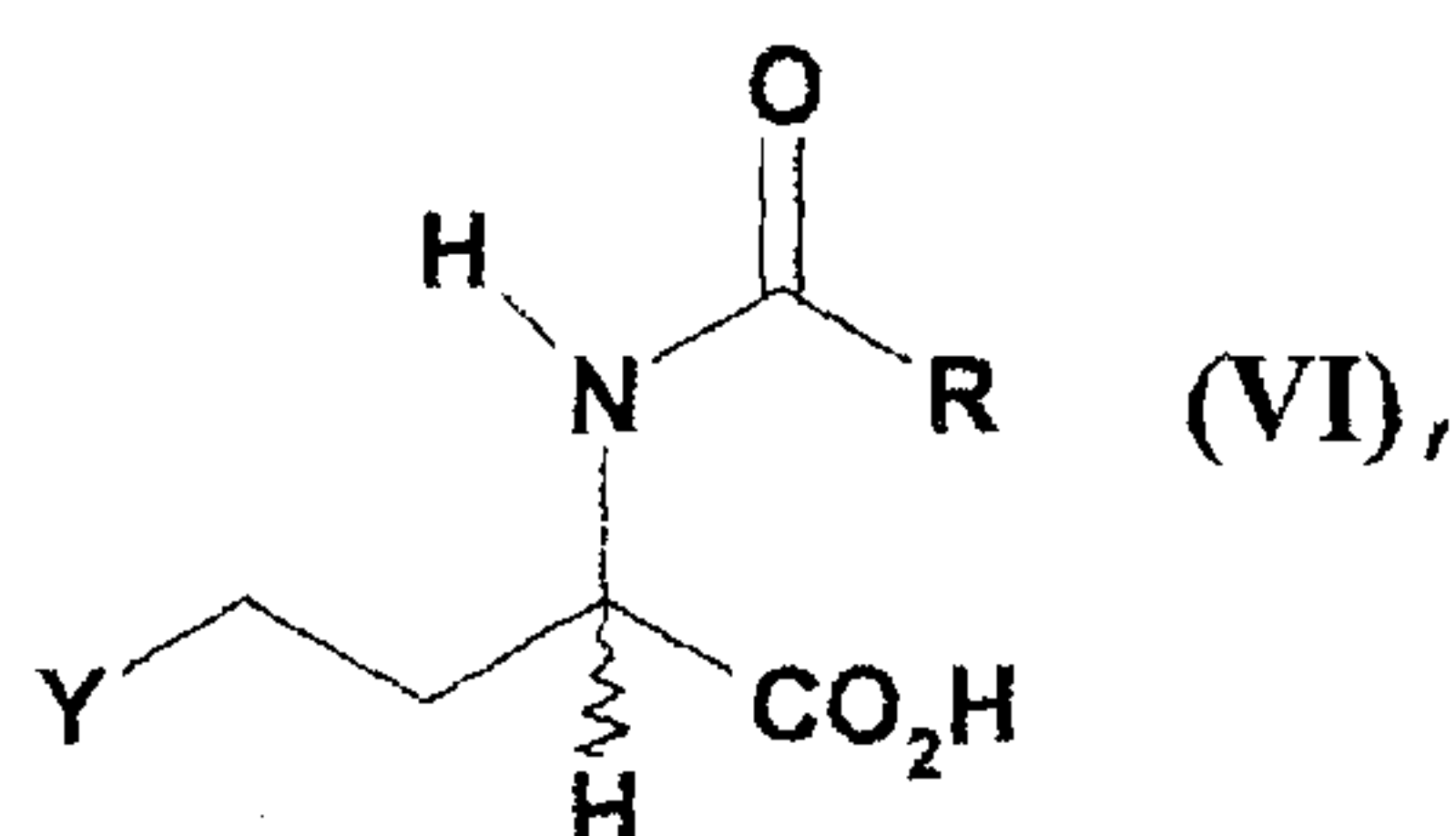
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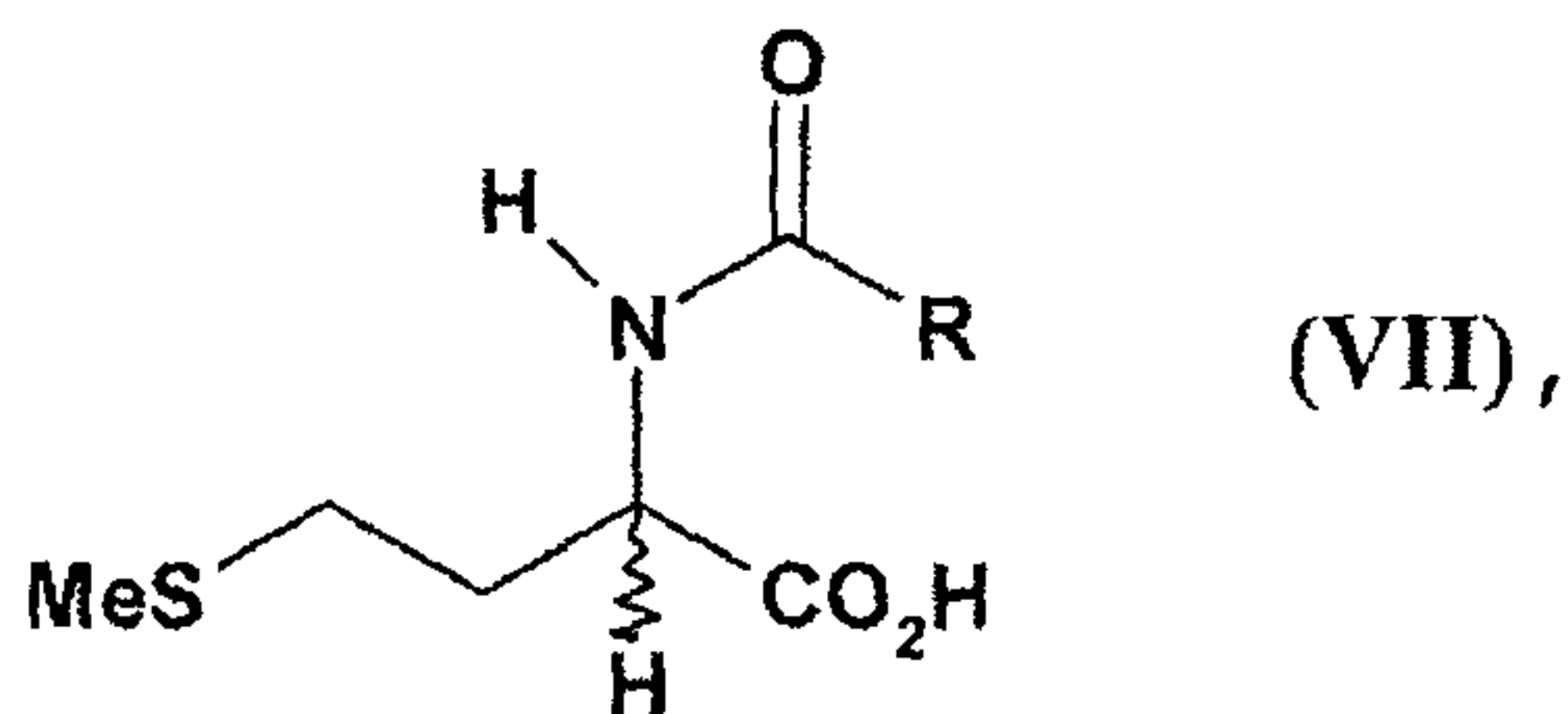
isopropyl, n-butyl, sec-butyl, tert-butyl,
phenyl, mono-, di- or trihaloalkyl, where
halogen = F or Cl, preferably CF₃ or CCl₃,
benzyloxycarbonyl or C₁- to C₄-alkyloxycarbonyl,
preferably tert-butyloxycarbonyl, or
methyloxycarbonyl,

- b) conversion of the compound V obtained in step
a) by introduction of a **leaving group Y on the**
C4 atom into a compound of the formula VI



where Y is halogen (= chlorine, bromine or
iodine), sulphonyloxy (= pTsO, C₆H₅SO₃, H₃CSO₃ or
H₅C₂SO₃), sulphate (OSO₃H) or phosphate (OPO₃H),

- c) reaction of the compound VI obtained in step b)
with MeSH in the presence of a basic or acid
catalyst to give N-acyl-L-methionine, N-acyl-D-
methionine or a corresponding mixture of
N-acyl-L- and/or D-methionine of the formula
VII



- d) **hydrolysis** of the N-acyl-L- and/or D-methionine
VII obtained in step c) to give L- and/or
D-methionine.

The compound V is formed, depending on exact choice of

the reaction conditions, either by rearrangement of the O-acylhomoserine primarily formed to give N-acylhomoserine, or by a combination of in-situ lactonization and acylation with subsequent ring opening.

5

For the acylation in step a), use is preferably made of an acylating agent of the general formula $R-CO-X^1$, where $X^1 = R^1COO$, OR^2 ($R^2 = \text{methyl or ethyl}$), Cl or Br and R and R^1 can be identical or different and are hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where halogen = F or Cl , preferably CF_3 or CCl_3 , benzyloxycarbonyl or C_1 - to C_4 -alkyloxycarbonyl, preferably tert-butyloxycarbonyl, or methyloxycarbonyl.

15

The introduction of the leaving group Y proceeds advantageously, when $Y = \text{halogen}$, in the first step correspondingly by reaction of the homoserine with PCl_3 , BBr_3 , PI_3 , $SOCl_2$ or $SOBr_2$.

20

When $Y = \text{sulphonyloxy}$, the introduction of the leaving group Y in the first step proceeds correspondingly and advantageously by reaction with p-toluenesulphonyl chloride ($p-TsCl$), $C_6H_5SO_2Cl$, H_3CSO_2Cl , $H_5C_2SO_2Cl$ or CF_3SO_2Cl . When, in contrast, $Y = \text{sulphate}$, for the introduction of the leaving group Y , in the first step typically use is correspondingly made of SO_3 , H_2SO_4 or oleum. When $Y = \text{phosphate}$ (OPO_3H), for the introduction of the leaving group Y , use is made in the first step typically of polyphosphoric acid.

30

After activation of the N-acylhomoserine by introduction of the corresponding leaving group Y in the 4 position, it is possible to introduce the Me-S group particularly readily in a next step via substitution of Y .

35

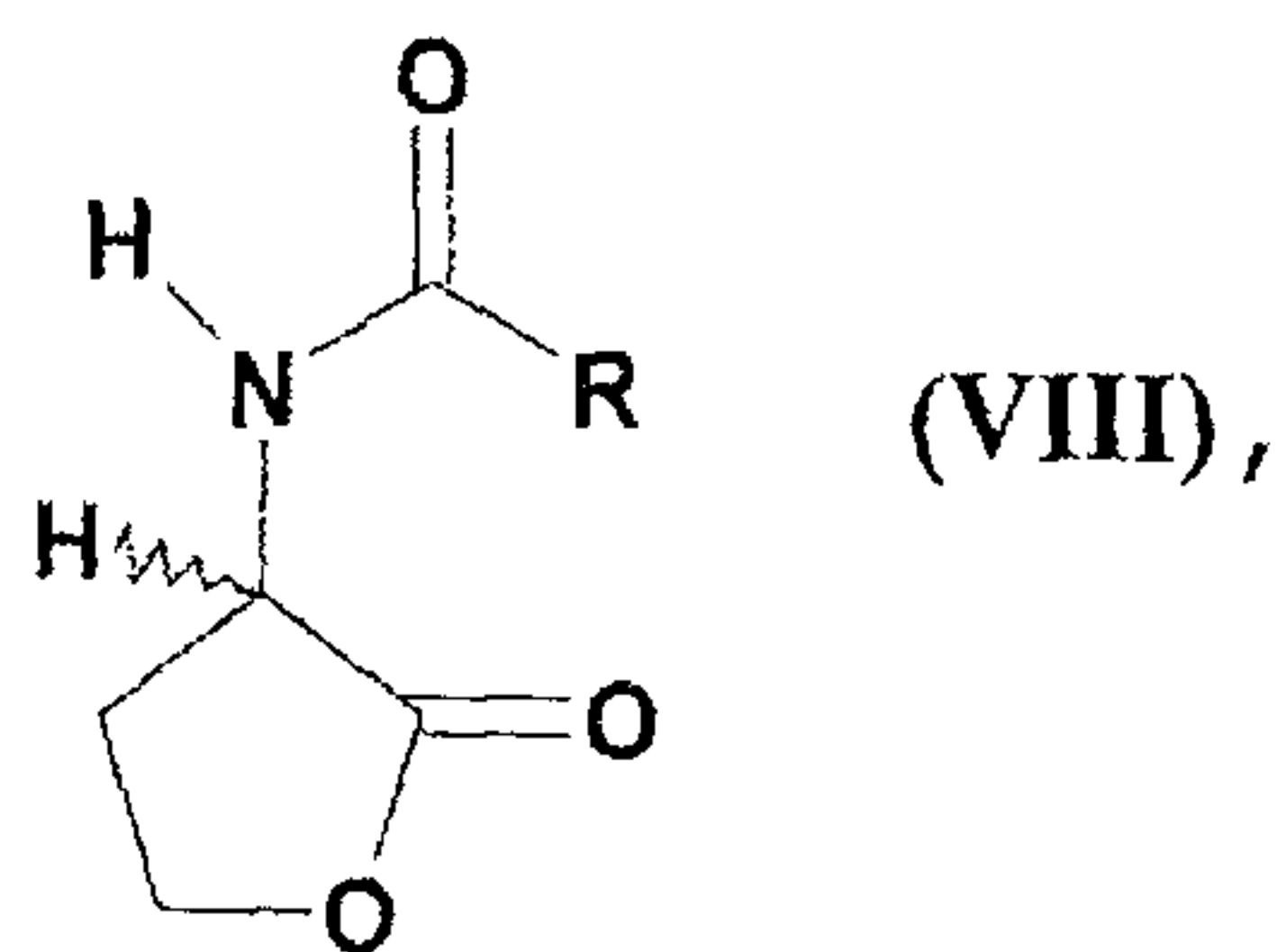
Suitable basic catalysts in step c) are, in particular, $NaOH$, KOH , pyridine, trimethylamine, triethylamine, or

an acetate, carbonate or hydrogencarbonate of the alkali metals or alkaline earth metals, where alkali metal is lithium, sodium, potassium, rubidium or caesium and alkaline earth metal is magnesium, calcium or barium.

Suitable acid catalysts in step c) are, in particular, HCl, HBr, HI, H₂SO₄, alkali metal HSO₄, H₃PO₄, alkali metal H₂PO₄, where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

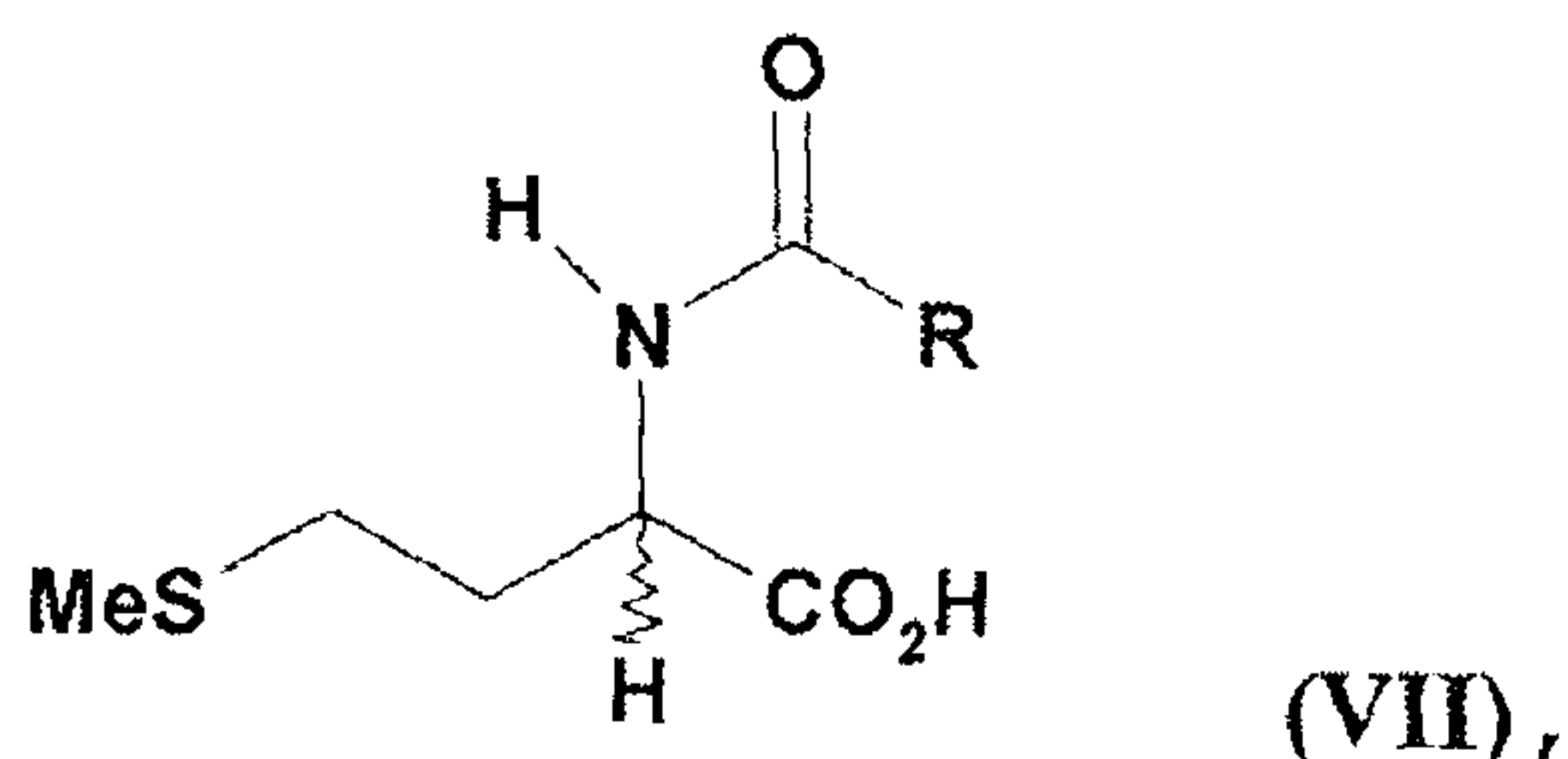
According to a further preferred embodiment of the invention, a method for the chemical transformation of L- and/or D-homoserine to methionine can also be designed in such a manner that the following steps are carried out:

a) **N-acylation and cyclization** of the L- and/or D-homoserine using an acylating agent to give the N-acyl-L- and/or D-homoserine lactone of the formula VIII



where R is hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where halogen = F or Cl, preferably CF₃ or CCl₃, benzyloxycarbonyl or C₁- to C₄-alkyloxycarbonyl, preferably tert-butyl-oxycarbonyl, or methyloxycarbonyl,

- b) reaction of the N-acylhomoserine lactone obtained in step a) with MeSH in the presence of a basic or acid catalyst to give the corresponding N-acyl-methionine of the formula VII



- c) **hydrolysis** of the N-acyl-L- and/or D-methionine obtained in step b) to give the corresponding methionine at temperatures of $> 95^{\circ}\text{C}$.

For the acylation in step a), preferably use is made of an **acylating agent** of the general formula R-CO-X^1 , where $\text{X}^1 = \text{R}^1\text{COO}, \text{OR}^2$ ($\text{R}^2 = \text{methyl or ethyl}$), Cl or Br, and R and R^1 can be identical or different and are hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where halogen = F or Cl, preferably CF_3 or CCl_3 , benzyloxycarbonyl or C_1 - to C_4 -alkyloxycarbonyl, preferably tert-butyloxycarbonyl or methyloxycarbonyl. The N-acetylation in step a) proceeds either by rearrangement of O-acylhomoserine primarily formed to give the N-acylhomoserine with subsequent ring closure, or by a combination of in-situ lactonization and direct N-acylation.

Furthermore, in the acylation in step a), as **solvent**, preferably use is made of a carboxylic acid RCOOH or R^1COOH , where R or R^1 have the meaning given above, if appropriate in the presence of a further cosolvent from the group consisting of C_3 to C_6 ketones, preferably MIBK or acetone, C_4 to C_{10} carboxylic esters, preferably ethyl or butyl acetate, C_3 to C_6 carboxamides,

preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate, propylene carbonate or butylene carbonate.

5

As basic catalysts in step a), use is preferably made of **pyridine derivatives**, preferably dimethylamino-pyridine (DMAP), or carbonyldiimidazole.

10 **Step a) is carried out preferably at temperatures** of 20 to 100°C, in particular at 50 to 90°C.

As **basic catalyst in step b)**, preferably use is made of a catalyst which is selected from the group consisting
15 of tetraalkylammonium hydroxides having a maximum of 48 carbon atoms, hydroxides, carbonates, hydrogen-carbonates, acetates of alkali metals or alkaline earth metals, where alkali metal is lithium, sodium, potassium, rubidium or caesium and alkaline earth metal
20 is magnesium, calcium or barium, tertiary amines having a maximum of 36 carbon atoms and 1 to 4 nitrogen atoms, tetra(C₁-C₄-alkyl)guanidine, bicyclic amines, preferably DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), pyridine and
25 strongly alkaline ion-exchange resins.

Other preferably used **basic catalysts in step b) are** trialkylamines of the general formula NR³R⁴R⁵, where R³, R⁴ and R⁵ can be identical or different and are a linear
30 or branched C₁- to C₁₂-alkyl radical, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl or sec-butyl.

Very particularly preferred basic catalysts are N(methyl)₃, N(methyl)₂(ethyl), N(methyl)(ethyl)₂,
35 N(ethyl)₃, N(n-propyl)₃, N(ethyl)(isopropyl)₂ or N(n-butyl)₃, but also diazabicyclooctane (DABCO), DBU, TBD, hexamethylenetetramine, tetramethylethylenediamine or tetramethylguanidine.

Likewise, particularly preferably, as basic catalysts, use is made of $R^3R^4R^5R^6N$ -hydroxide, Li-, Na-, K-, Rb-, Cs-hydroxide, Mg-, Ca-, Ba-hydroxide, where R^3 , R^4 , R^5 and R^6 can be identical or different and are a linear or
5 branched C_1 - to C_{12} -alkyl radical, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl or sec-butyl.

As particularly preferred basic catalysts, use is also made of $R^7R^8NR^9$ -substituted crosslinked polystyrene
10 resins, where R^7 , R^8 and R^9 can be identical or different and are a linear or optionally branched C_1 - to C_4 - alkyl radical, preferably methyl, ethyl, n-propyl, n-butyl.

15 To achieve a rapid and as complete as possible sequence of the reaction in step b), use is made of 1 to 20 mol equivalents of base, calculated as hydroxide or N equivalent, preferably 1 to 10 mol equivalents of base.

20 If in **step b)**, however, an **acid catalyst** is used, then it is advantageous to make use of an acid catalyst selected from the group consisting of Brönstedt acids having a pK_a of < 3 , or Lewis acids.

25 Preferably, as acid catalysts, use is made of HCl, HBr, HI, H_2SO_4 , alkali metal HSO_4 , H_3PO_4 , alkali metal H_2PO_4 , where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C_1 - C_{12} -alkylsulphonic acid, C_6 - C_{10} -arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid or a
30 copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

However, as acid catalysts, use can also be made of
35 **strongly acidic ion-exchange resins** which can readily be separated off after reaction is complete.

In this case use is preferably made of optionally substituted, preferably by divinylbenzene, crosslinked

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polystyrenesulphonic acid resins.

Use can also be made of **heterogeneous acid catalysts** from the group (WO_3 - and Cs_2O)-containing aluminium
5 oxide, zeolite and montmorillonite. Among the said aluminium oxides, those having 5 - 15% WO_3 and 5 - 15% Cs_2O content are preferred.

Also, use is advantageously made of **Lewis acid**
10 **catalysts**.

As Lewis acid, use is preferably made of a **low-molecular-weight Lewis acid** selected from the group AlCl_3 , ZnCl_2 , $\text{BF}_3 \cdot \text{OEt}_2$, SnCl_2 , FeCl_3 .
15

It is also advantageous if the reaction in step b) is carried out in **solution and/or in suspension** in an organic solvent.

20 As solvent, use can be made of water and/or at least one low-molecular-weight organic solvent selected from the group consisting of C_3 to C_6 ketones, preferably MIBK or acetone, straight-chain or branched C_1 to C_4 alcohols, C_4 to C_{10} carboxylic esters, preferably ethyl
25 or butyl acetate, C_3 to C_6 carboxamides, preferably DMF or dimethylacetamide, C_6 to C_{10} aromatics, preferably toluene, and C_3 to C_7 cyclic carbonates, preferably ethylene carbonate, propylene carbonate or butylene carbonate.

30

The hydrolysis **in step c)** can be carried out in aqueous **solution and/or suspension**.

In addition, however, it can also be advantageous if
35 use is made additionally of at least one low-molecular-weight organic solvent which is selected from the group consisting of C_3 to C_6 ketones, preferably MIBK or acetone, straight-chain or branched C_1 to C_4 alcohols, C_4 to C_{10} carboxylic esters, preferably ethyl or butyl

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acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate, propylene carbonate or butylene carbonate.

The reaction in step c) is generally carried out at a **temperature** of 90 to 180°C, preferably at 100 to 160°C, in particular at 120 to 150°C, very particularly preferably at 130 to 140°C.

To accelerate the hydrolysis reaction in step c), the procedure can be carried out in addition in the presence of an acid, basic or Lewis acid catalyst, or a combination of acid and Lewis acid catalyst.

A methionine process which comprises an inventive combination of biotechnological and chemical steps has in total more advantages compared with a conventional process, in particular with respect to the mentioned requirement for a more economic, more reliable process which in addition should supply L-methionine.

Firstly, the use of sugar instead of propene (or acrolein) makes it possible to design the methionine production more economically, firstly from the point of view of current raw material costs, and secondly owing to the independence on continuously increasing costs for crude oil achieved.

Secondly, the sugar being used is a renewable raw material, so that here a valuable contribution to conservation of resources is achieved. In addition, sugar is far less dangerous than the industrial intermediates acrolein and prussic acid, so that substitution of sugar for these raw materials as starting material significantly reduces the risk potential of a production process and thus increases safety.

Thirdly, the combination of a fermentation step which makes possible the enantiospecific production of L-homoserine, makes possible, using suitable
5 comparatively mild chemical method steps, the conversion of L-homoserine to L-methionine without racemization and in this manner leads to enantiomerically pure L-methionine. As mentioned, L-methionine has a higher bioavailability compared with
10 currently produced D,L-methionine.

Fourthly, the production of enantiomerically pure L-methionine using a combined production process of the type described above permits the problems mentioned at
15 the outset to be overcome elegantly, which problems are associated with production of L-methionine in a purely biotechnological way.

The inventive examples hereinafter serve for more
20 detailed explanation of the invention without restricting the invention in any way, however.

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Direct reaction of L-homoserine to give L-methionine**Example 1**

- 5 Reaction with a heterogeneous catalyst (7-10% WO₃/7-10% Cs₂O on Al₂O₃ support - manufacturer - Degussa).

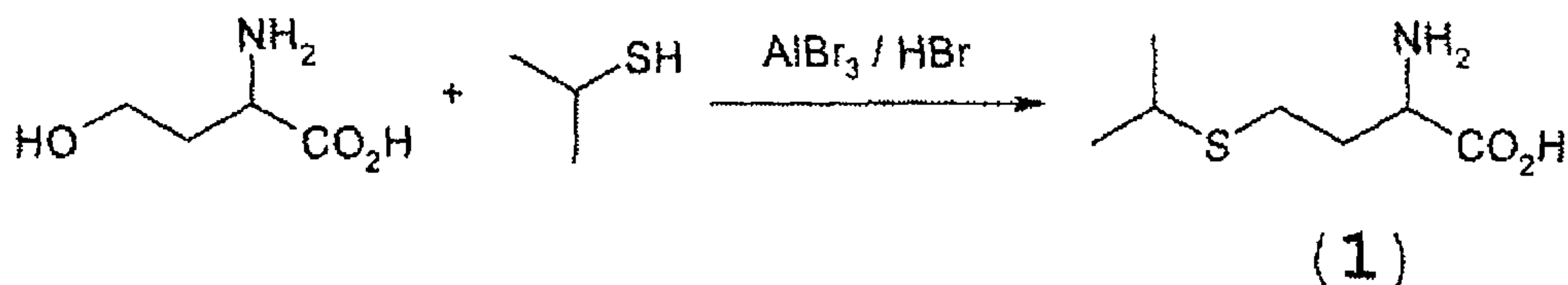


- L-Homoserine (biotechnologically produced) and the
 10 finely ground heterogeneous catalyst were charged into the autoclave and MeSH was added as liquid. The autoclave was subsequently heated to 140°C over 2.5 h. After expansion and removal of MeSH, the system was flushed with a 20% aqueous NaOH solution. The
 15 subsequent filtration and HPLC analysis gave a yield of 3% of theory of L-methionine.

In comparison: A similar attempt using a pure Al₂O₃ support gave only traces of methionine.

20

Example 2 - Reaction with isopropylthiol (iPrSH) and acid/Lewis acid (does not come under the claims)



25

- iPrSH (20 ml) was treated slowly with gaseous HBr. Subsequently L-homoserine (10 mmol) was added and the mixture was stirred for 10 minutes. Thereafter, AlCl₃ (40 mmol) was added and the reaction mixture was
 30 stirred for 4 h at room temperature. The reaction mixture was quenched using H₂O/HCl and then made basic

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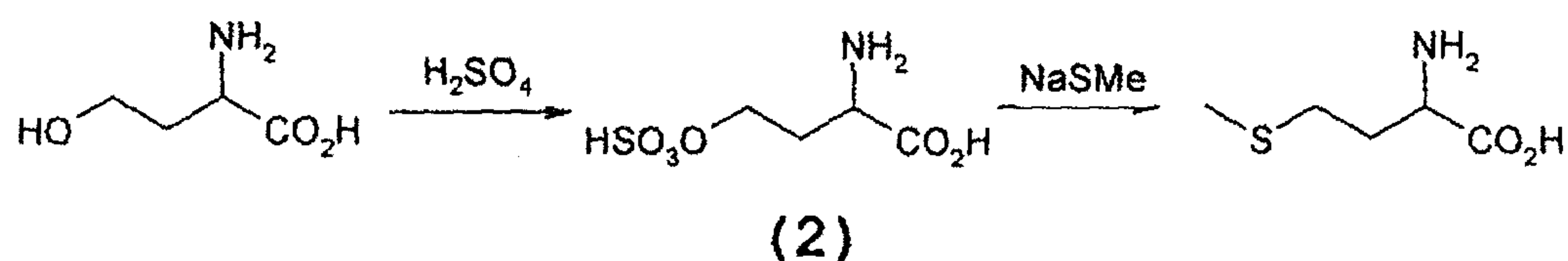
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with NaOH. After filtering off $\text{Al}(\text{OH})_3$ by suction the filtrate solution was concentrated to dryness and analysed by HPLC. Yield of (1) = 8.2%.

5 **Activation of L-homoserine at the C-4 atom and reaction to give L-methionine**

Example 3 - Activation by sulphate with subsequent nucleophilic substitution by NaSMe:

10



L-Homoserine (19.4 mmol) was admixed with concentrated H_2SO_4 (10 ml) with cooling. The resultant reaction mixture was stirred in the course of 30 minutes until the homoserine was dissolved. Subsequently the solution was allowed to stand for 3 hours at room temperature. Thereafter the reaction solution was added to 800 ml of diethyl ether cooled to -78°C , stirred well and the supernatant solution was decanted off. The solid was washed 3 times each time with 200 ml of diethyl ether at -78°C . After filtering off the whitish-yellow solid by suction, it was dried for 2 hours in an oil-pump vacuum. Yield of sulphate ester (2): 88.0%.

25

The sulphate ester (19 mmol) was dissolved in DMSO (20 ml) and admixed with NaSMe (50 mmol). This reaction solution was stirred at 80°C and analysed after 90 minutes by HPLC - L-methionine yield: 19.6%. Repetition of the experiment in N-methylpyrrolidone (NMP) as solvent gave 33.6% L-methionine after 10 minutes.

30

Cyclization of L-homoserine and further reaction to give L-methionine

35

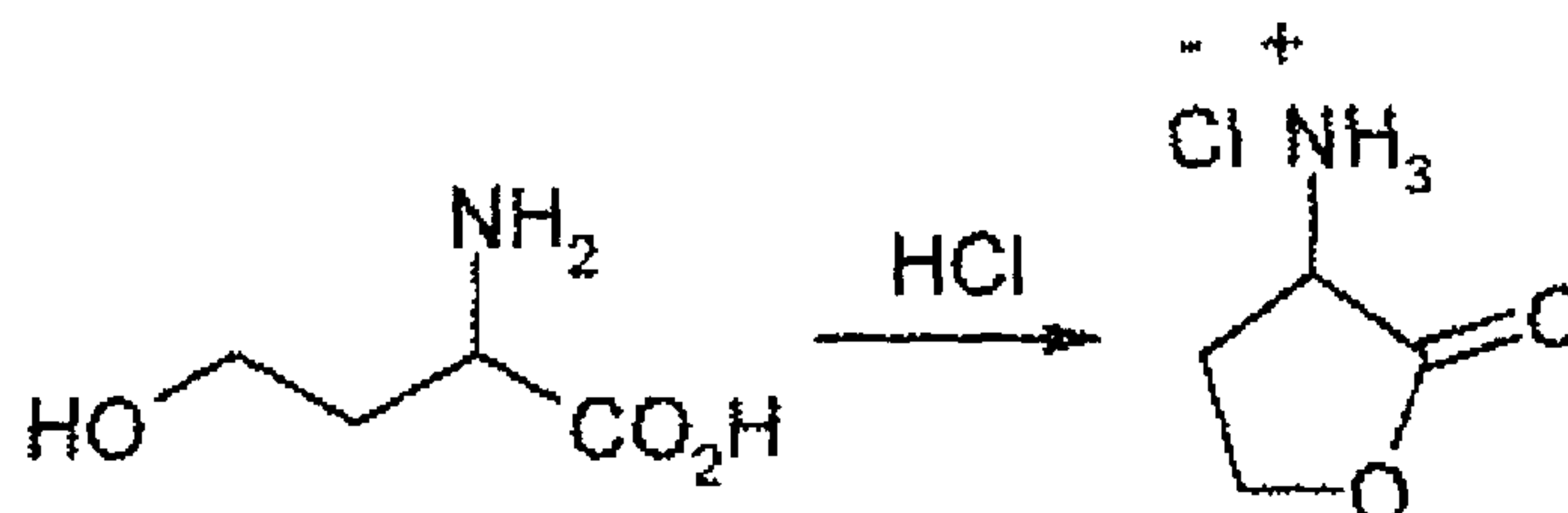
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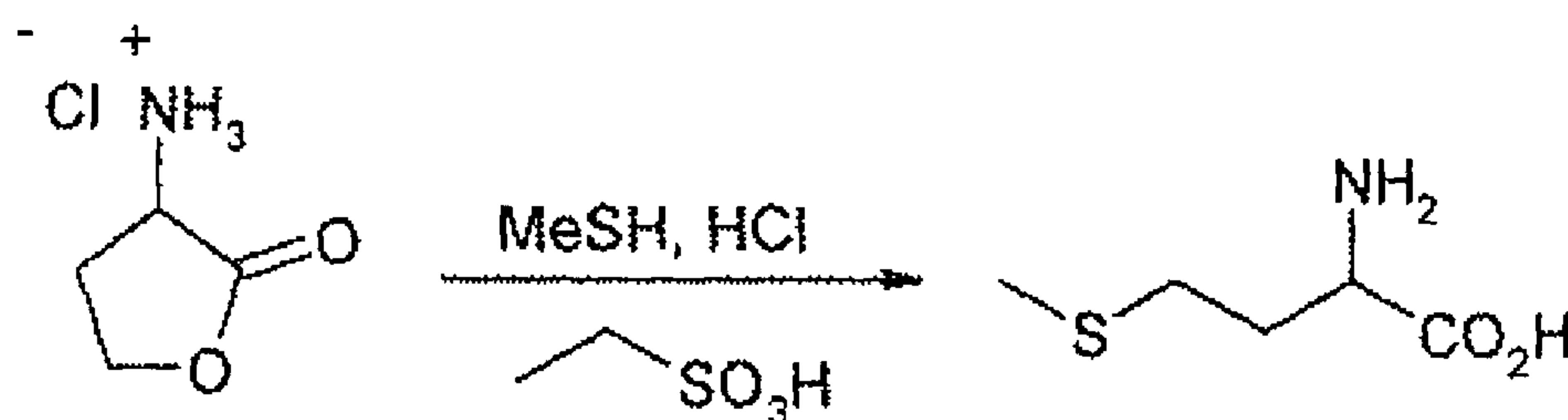
Example 4 - Production of 2-amino-4-butyrolactone hydrochloride salt

Activation by lactone formation with subsequent
5 nucleophilic substitution by MeSH



L-Homoserine (0.84 mol) was admixed with 600 ml of concentrated HCl (6.1 mol). The solution was stirred
10 for about 15 minutes until everything had dissolved, and subsequently the water was removed under vacuum over the course of 1.5 hours. The residue was dried. Yield: 99% of 2-amino-4-butyrolactone hydrochloride salt.

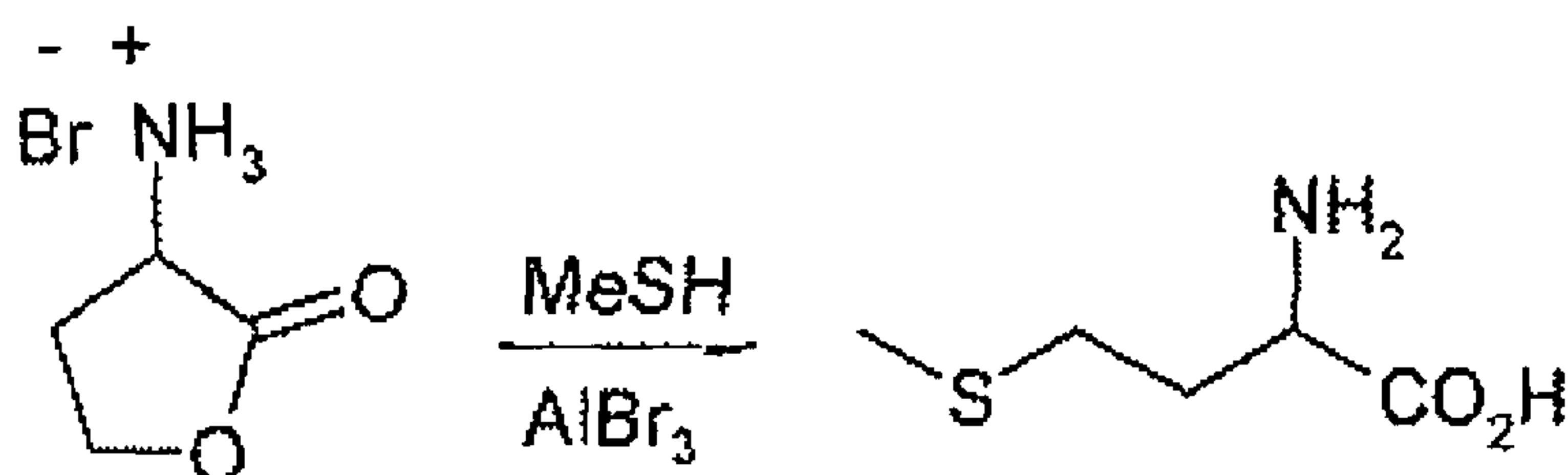
15

Example 5 - Reaction of 2-amino-4-butyrolactone hydrochloride salt to give L-methionine

The 2-amino-4-butyrolactone hydrochloride salt
20 (22 mmol) was charged into the autoclave in HCl-saturated ethanesulphonic acid (0.2 mol) and MeSH (0.83 mol) was added to this mixture in liquid form. Subsequently the autoclave was sealed and heated for 5 hours at 70°C. After expansion and cooling, the
25 reaction solution was analysed by HPLC. The L-methionine yield was 21%.

Example 6 - Reaction of 2-amino-4-butyrolactone

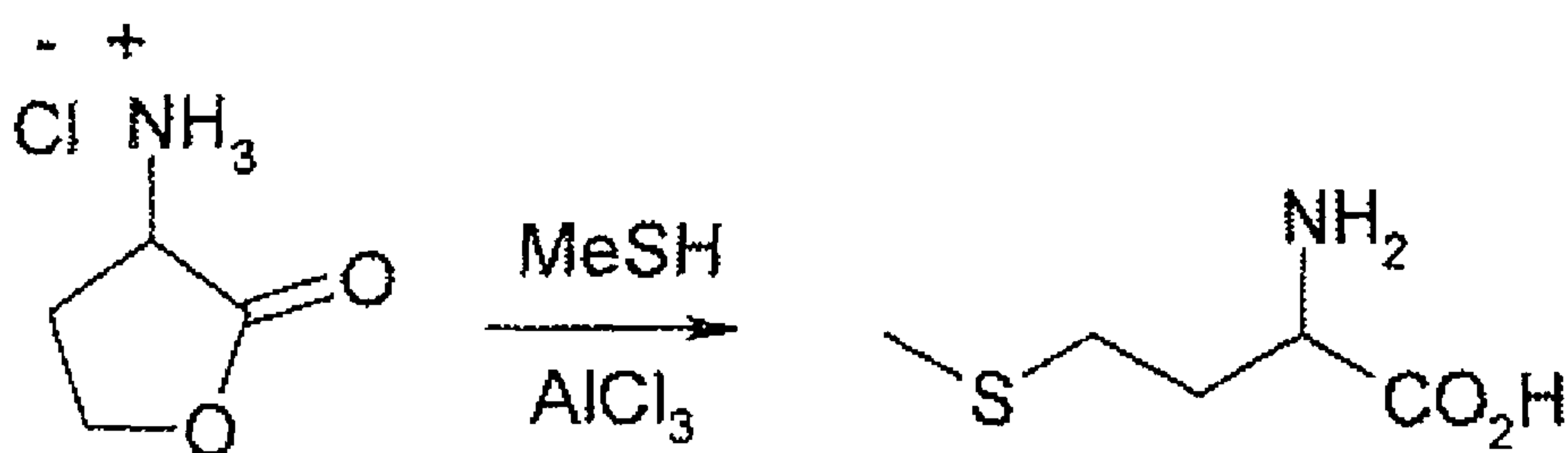
hydrobromide salt to give L-methionine



5 In a high-pressure autoclave, aluminium bromide (75 mmol) was carefully added to MeSH (50 ml). Subsequently, the bromide salt of the aminolactone (obtained from Aldrich) (25 mmol) was added. The autoclave was shaken for 1 hour at room temperature and
 10 thereafter for 2 hours at 40°C. The autoclave was cooled and expanded. After removal of the MeSH, the residue was quenched with water and the pH made basic using NaOH. The resultant precipitate was removed by filtration. The methionine yield was 33%.

15

Example 7 - Reaction of 2-amino-4-butyrolactone hydrochloride salt to give 2-amino-4-methylthiobutyric acid



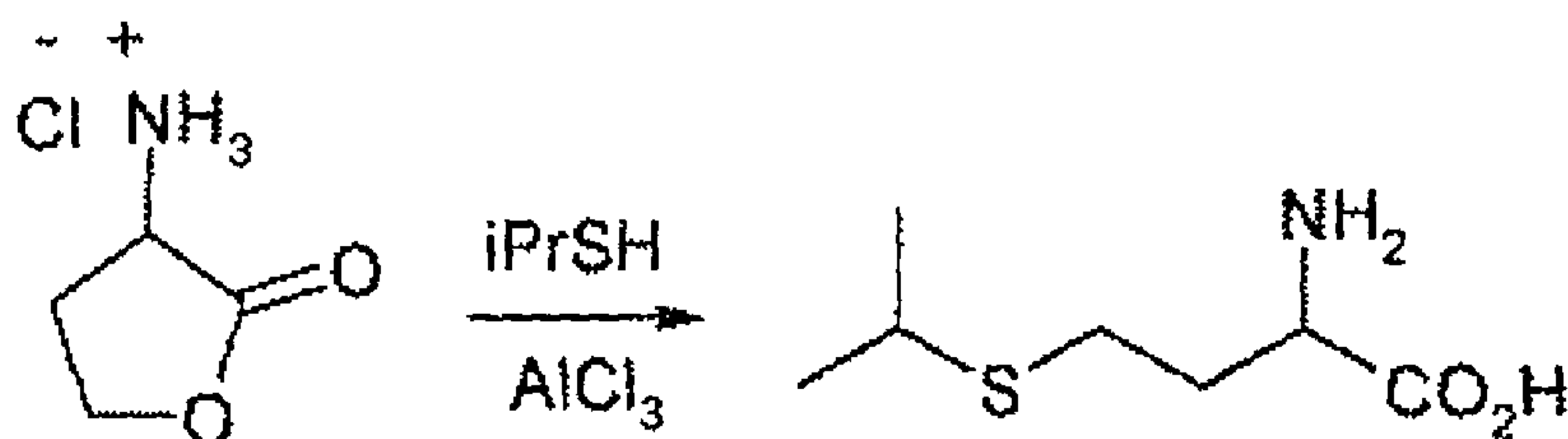
20 The chloride salt of the aminolactone (10 mmol) and also AlCl₃ (30 mmol) were charged into an autoclave and slowly admixed with MeSH (30 ml) and stirred. Subsequently the mixture was stirred for 71 hours at room temperature. After quenching the reaction mixture
 25 with water, the yield of 2-amino-4-methylthiobutyric acid was determined by HPLC as 27%.

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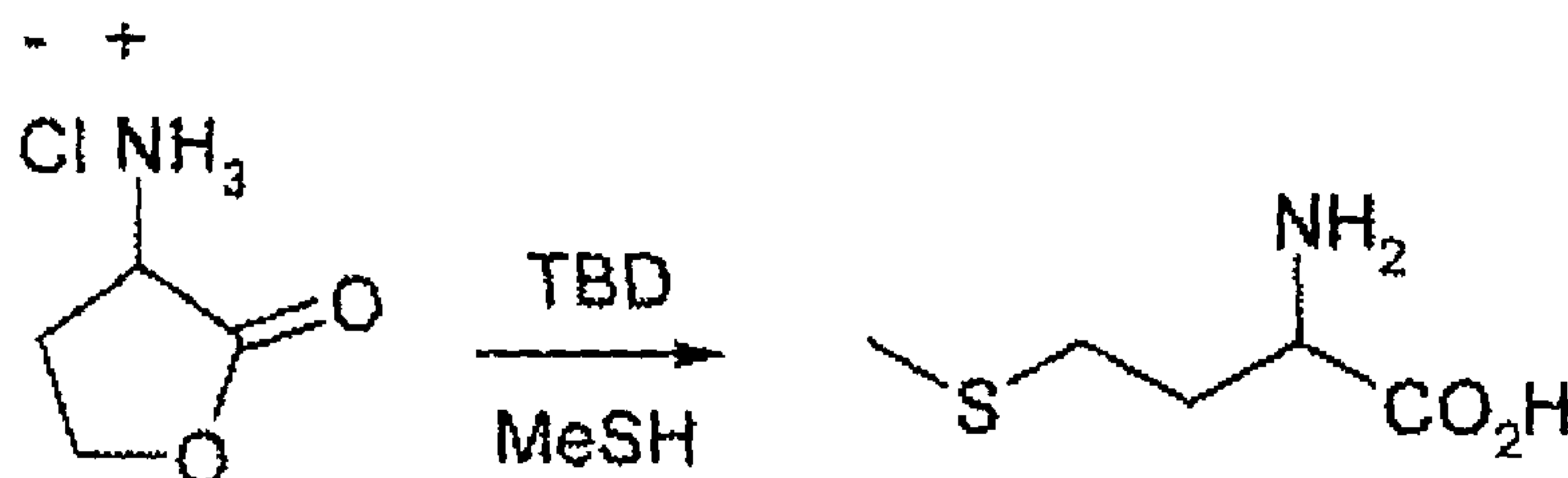
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Example 8 - Reaction of 2-amino-4-butyrolactone hydrochloride salt to give 2-amino-4-isopropylthiobutyric acid (does not come under the patent claims)



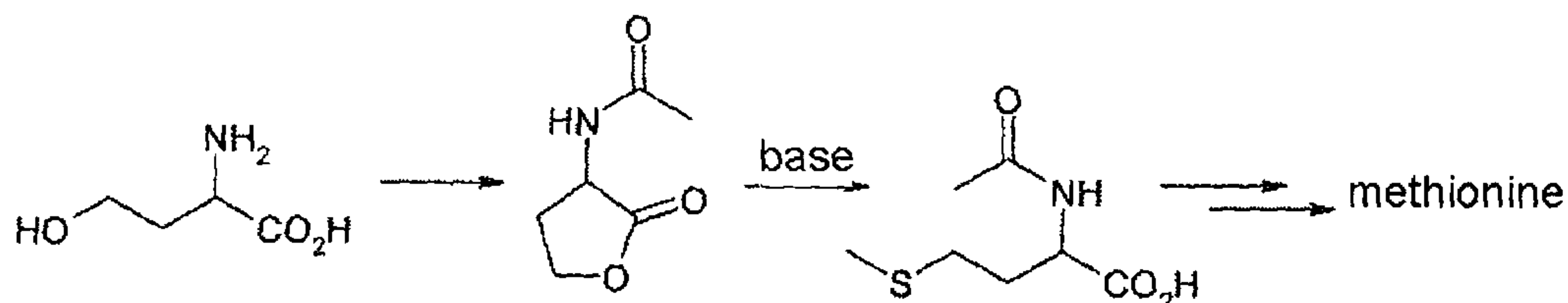
5 i-Propylthiol (iPrSH, 20 ml) was admixed with AlCl₃ (30 mmol) and stirred. Subsequently the chloride salt of the aminolactone (10 mmol) was added and the mixture was stirred for 24 hours at room temperature. After
 10 quenching the reaction mixture with water, the yield of 2-amino-4-isopropylthiobutyric acid was determined as 77% by HPLC.

Example 9 - Reaction of 2-amino-4-butyrolactone hydrochloride salt to give L-methionine



The 2-amino-4-butyrolactone hydrochloride salt
 20 (70 mmol) and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) (140 mmol) were charged into the autoclave and liquid MeSH was added. The sealed autoclave was heated to 70°C over 2.5 hours. Subsequently the autoclave was gently cooled and expanded. The MeSH was removed and the
 25 residue analysed by HPLC. The L-methionine yield was 21%.

Example 10 - Cyclization of L-homoserine and N-acylation to give N-acetyl-2-amino-4-butyrolactone and further reaction to give N-acetyl-L-methionine (precursor of L-methionine)



L-Homoserine (2 mol) was suspended in 900 ml of acetic anhydride and admixed with a spatula tip full of dimethylaminopyridine (DMAP). It was slowly heated to 60°C. After approximately 1 hour, the temperature rapidly increased to 100°C. Subsequently the reaction mixture was stirred at 80°C for 90 minutes and concentrated to dryness under vacuum. The resultant yellow oil was taken up in isopropanol (600 ml) and allowed to stand overnight at 0°C. The resultant crystals were filtered off, washed with cold isopropanol and dried under vacuum. The yield was 60% N-acetyl-2-amino-4-butyrolactone isolated, the purity 99% (according to HPLC).

Subsequently the N-acetyl-2-aminobutyrolactone (1 eq) was reacted with various bases in MeSH to give N-acetylmethionine. A mixture of N-acetylamino lactone, base and MeSH (14 eq) was heated in a sealed autoclave. After cooling, expansion and removal of MeSH, the remaining oil was analysed by HPLC. Further details and the yield of N-acetyl-L-methionine achieved are listed in the table below:

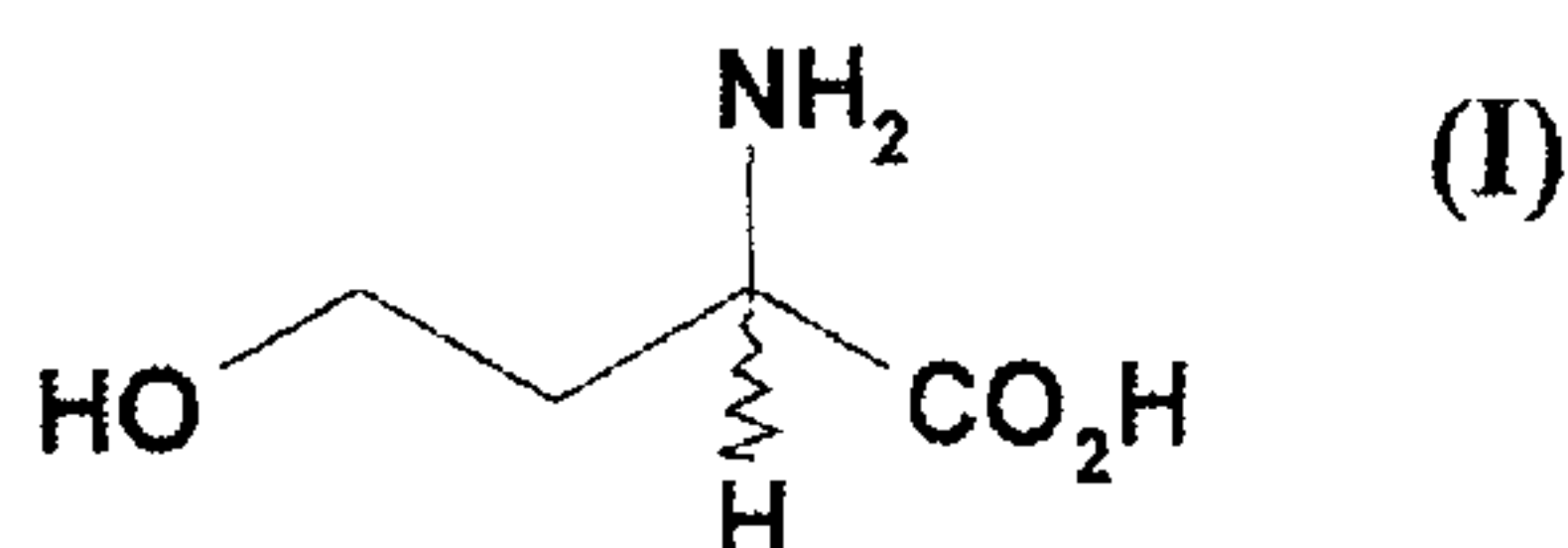
Base/ Case a) to e)	Equivalent with respect to starting material	Temperature (°C)	Time (h)	Yield of N-acetyl- L-met (%)
a) NMe ₃	14	140	2.5	24.5%
b) NEt ₃	14	140	7	19%
c) TMG*	1	70	2.5	30.8%
d) TMG*	10	70	2.5	57.8%
e) TBD**	1	70	2.5	88.0%

* Tetramethylguanidine,

** 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

Claims

1. Method for production of L-methionine,
D-methionine or any desired mixtures of L- and
5 D-methionine starting from homoserine,
characterized in that L-homoserine, D-homoserine
or corresponding mixtures of L- and D-homoserine
of the formula I



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are converted to methionine by chemical
transformation, without passing through any of the
intermediates N-carbamoylhomoserine, 4-(2-
15 bromoethyl)hydantoin and 4-(2-methylthio-
ethyl)hydantoin.

2. Method according to Claim 1, characterized in that
the chemical transformation of L- and/or D-homo-
20 serine is carried out using MeSH if appropriate in
the presence of an acid catalyst.

3. Method according to Claim 2, characterized in that
use is made of 1 to 100 mol equivalents of MeSH,
25 preferably 1 to 50 mol equivalents.

4. Method according to Claim 2 or 3, characterized in
that use is made of an **acid catalyst** selected from
the group consisting of Brönstedt acids having a
30 pK_a of ≤ 3 .

5. Method according to Claim 4, characterized in
that, as acid catalyst, use is made of HCl, HBr,
HI, H_2SO_4 , alkali metal HSO_4 , H_3PO_4 , alkali metal
35 H_2PO_4 , where alkali metal is lithium, sodium,
potassium, rubidium or caesium, polyphosphoric

- acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-aryl-sulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetra-fluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).
- 5
6. Method according to Claim 2 or 3, characterized in that use is made of a **Lewis acid catalyst**.
- 10 7. Method according to Claim 6, characterized in that, as Lewis acid catalyst, use is made of at least one **low-molecular-weight Lewis acid** selected from the group AlCl₃, ZnCl₂, BF₃·OEt₂, SnCl₂, FeCl₃.
- 15 8. Method according to Claim 4, characterized in that, as acid catalyst, use is made of a **strongly acidic ion-exchange resin**.
- 20 9. Method according to Claim 8, characterized in that, as acid catalyst, use is made of an optionally substituted, for example by divinylbenzene, crosslinked polystyrenesulphonic acid resin.
- 25 10. Method according to Claim 4, characterized in that use is made of a **heterogeneous acid catalyst** from the group (WO₃- and Cs₂O)-containing aluminium oxide, zeolite and montmorillonite.
- 30 11. Method according to one or more of Claims 2 to 10, characterized in that the reaction is carried out in **solution and/or in suspension** in the presence of water and/or an organic solvent.
- 35 12. Method according to Claim 11, characterized in that use is made of water and/or at least one low-molecular-weight organic solvent selected from the group consisting of C₃ to C₆ ketones, preferably MIBK or acetone, straight-chain or branched C₁ to

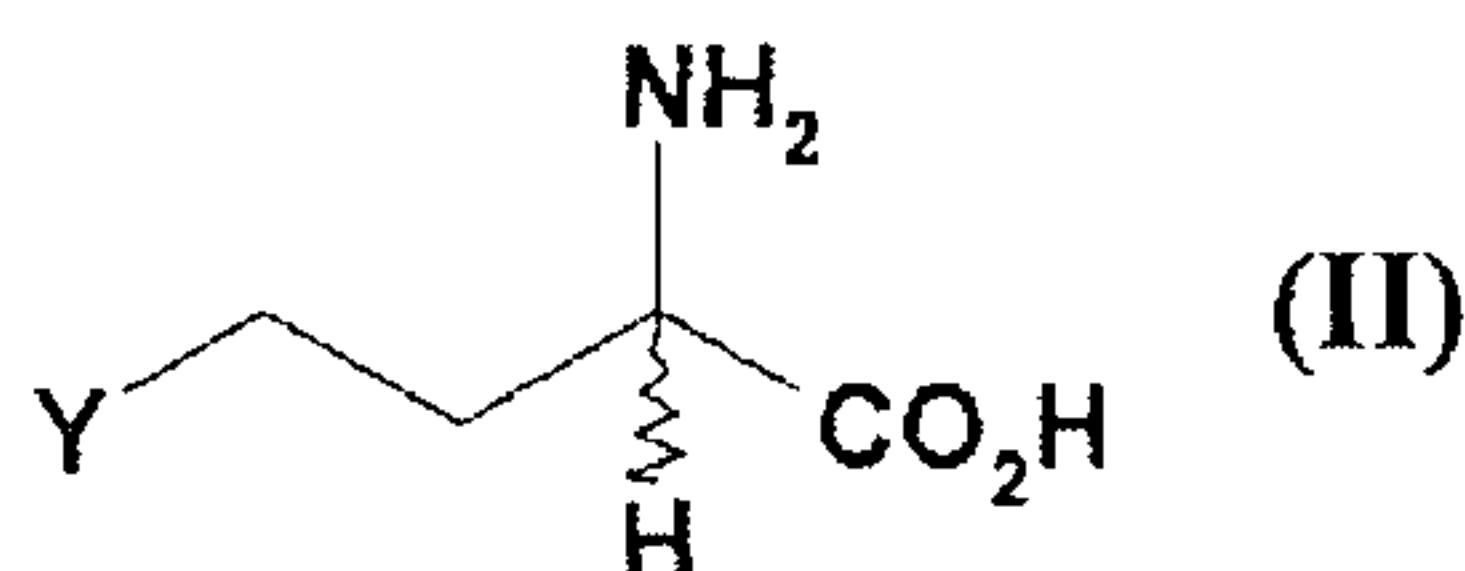
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C₄ alcohols, C₄ to C₁₀ carboxylic esters, preferably ethyl or butyl acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate, propylene carbonate, butylene carbonate.

13. Method according to Claim 1, characterized in that the chemical transformation of L- and/or D-homoserine is carried out in such a manner that, in a first step, by introduction of a **leaving group Y on the C₄ atom** of homoserine, a compound of the formula II



is produced, where Y is halogen (= chlorine, bromine or iodine), sulphonyloxy (= pTsO, C₆H₅SO₃, H₃CSO₃, H₅C₂SO₃ or CF₃SO₂), sulphate (OSO₃H) or phosphate (OPO₃H), which is then reacted in a second step with **MeSH** to give L-methionine, D-methionine or a corresponding mixture of L- and D-methionine.

14. Method according to Claim 13, characterized in that, for introduction of the leaving group Y, when Y = halogen, in the first step use is correspondingly made of PCl₅, PCl₃, BBr₃, PI₃, POCl₃, SOCl₂ or SOBr₂.

15. Method according to Claim 13, characterized in that, for introduction of the leaving group Y, when Y = sulphonyloxy, in the first step use is correspondingly made of p-TsCl, C₆H₅SO₂Cl, H₃CSO₂Cl, H₅C₂SO₂Cl or CF₃SO₂Cl.

16. Method according to Claim 13, characterized in that, for introduction of the leaving group Y, when Y = sulphate, in the first step use is correspondingly made of SO₃, H₂SO₄ or oleum.

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17. Method according to one or more of Claims 13 to 16, characterized in that the reaction of the compound of the formula II with **MeSH** is performed in the presence of a basic or acid catalyst.

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18. Method according to Claim 17, characterized in that, as basic catalyst, use is made of NaOH, KOH, pyridine, trimethylamine, triethylamine or an acetate, carbonate or hydrogencarbonate of the alkali metals or alkaline earth metals, alkali metal being lithium, sodium, potassium, rubidium or caesium and alkaline earth metal being magnesium, calcium or barium.

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19. Method according to Claim 17, characterized in that, as acid catalyst, use is made of HCl, HBr, HI, H₂SO₄, alkali metal HSO₄, H₃PO₄, alkali metal H₂PO₄, where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-aryl-sulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

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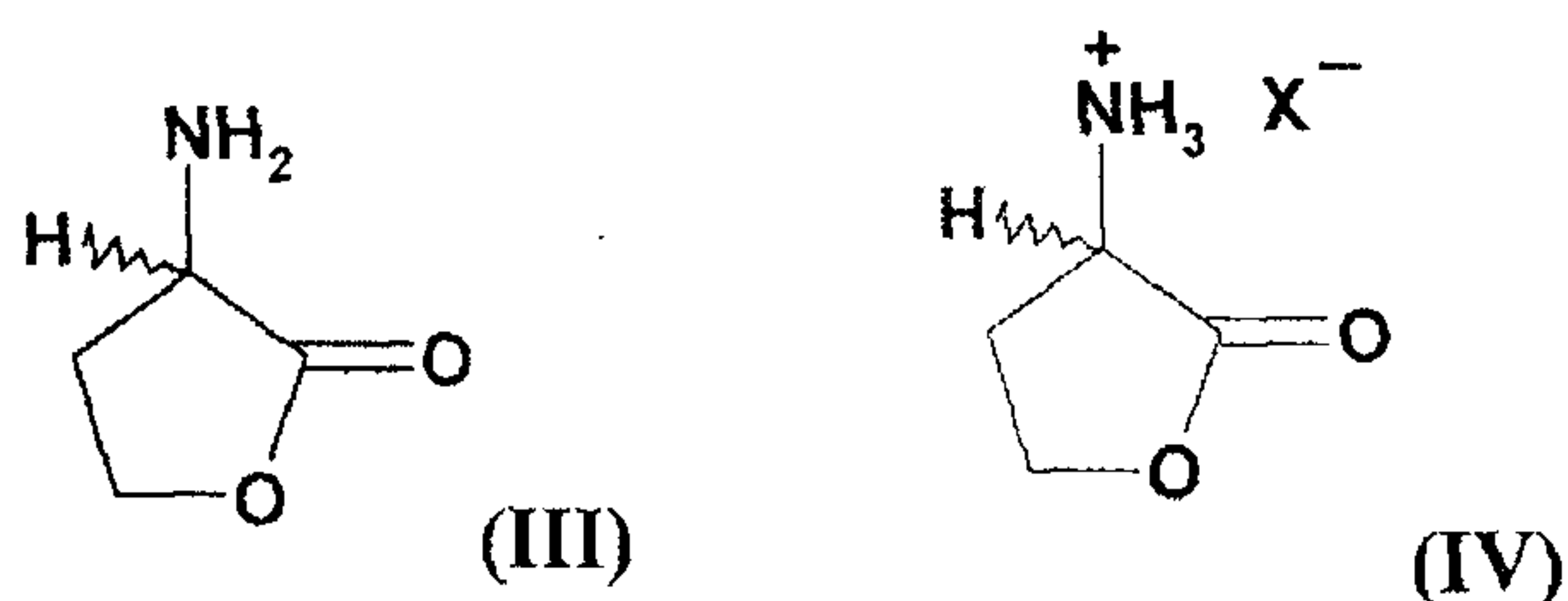
20. Method according to one or more of Claims 17 to 19, characterized in that the reaction is carried out in the presence of an organic solvent and/or water.

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21. Method according to Claim 20, characterized in that use is made of water and/or at least one low-molecular-weight organic solvent selected from the group consisting of C₃ to C₆ ketones, preferably

MIBK or acetone, straight-chain or branched C₁ to C₄ alcohols, C₄ to C₁₀ carboxylic esters, preferably ethyl or butyl acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate, propylene carbonate or butylene carbonate.

22. Method according to Claim 1, characterized in that the chemical transformation of L- and/or D-homoserine is carried out in such a manner that, in a first step, by **acid-catalysed cyclization**, the corresponding 2-amino-4-butyrolactone of the formula III or salt thereof (formula IV)



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is produced, where X is Cl, Br, I, HSO₄, (SO₄)_{1/2}, H₂PO₄, (HPO₄)_{1/2}, (PO₄)_{1/3} or R'-SO₃ (where R' = methyl, ethyl, phenyl, tosyl), which is then reacted in a second step with **MeSH** to give L-methionine, D-methionine or a corresponding mixture of L- and D-methionine.

20

23. Method according to Claim 22, characterized in that use is made of an **acid catalyst** selected from the group consisting of Brönstedt acids having a pK_a of ≤ 3 .

25

24. Method according to Claim 23, characterized in that, as acid catalyst, use is made of HCl, HBr, HI, H₂SO₄, alkali metal HSO₄, H₃PO₄, alkali metal H₂PO₄, where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-

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arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

5

25. Method according to Claim 22, characterized in that, as acid catalyst, use is made of a **strongly acidic ion-exchange resin**.

10 26. Method according to Claim 25, characterized in that, as acid catalyst, use is made of an optionally substituted, preferably by divinylbenzene, crosslinked polystyrenesulphonic acid resin.

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27. Method according to Claim 22, characterized in that use is made of a **heterogeneous acid catalyst** from the group (WO₃- and Cs₂O)-containing aluminium oxide, zeolite and montmorillonite.

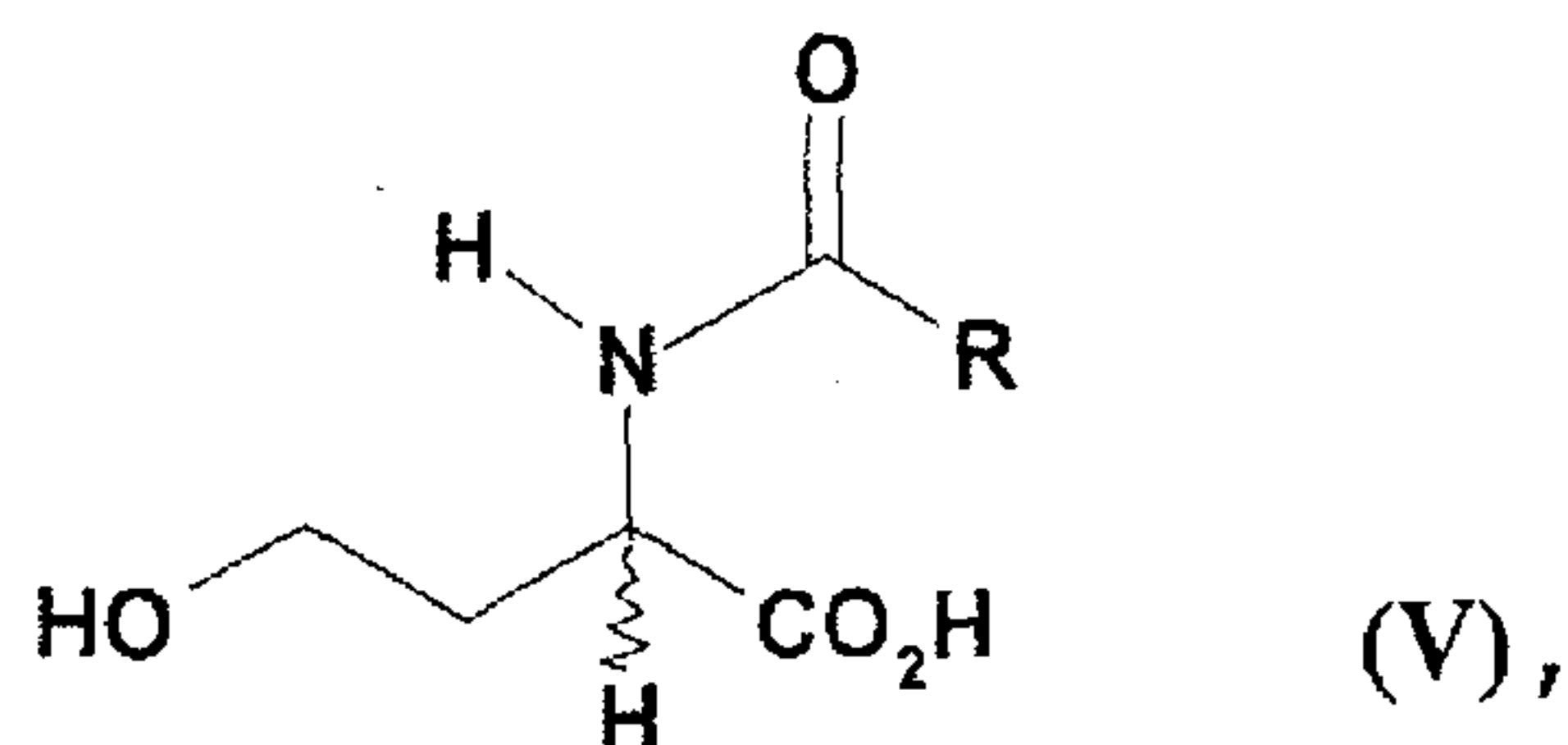
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28. Method according to Claim 25, characterized in that a **Lewis acid catalyst** is used.

25 29. Method according to Claim 28, characterized in that, as Lewis acid catalyst, use is made of at least one **low-molecular-weight Lewis acid** selected from the group AlCl₃, ZnCl₂, BF₃·OEt₂, SnCl₂, FeCl₃.

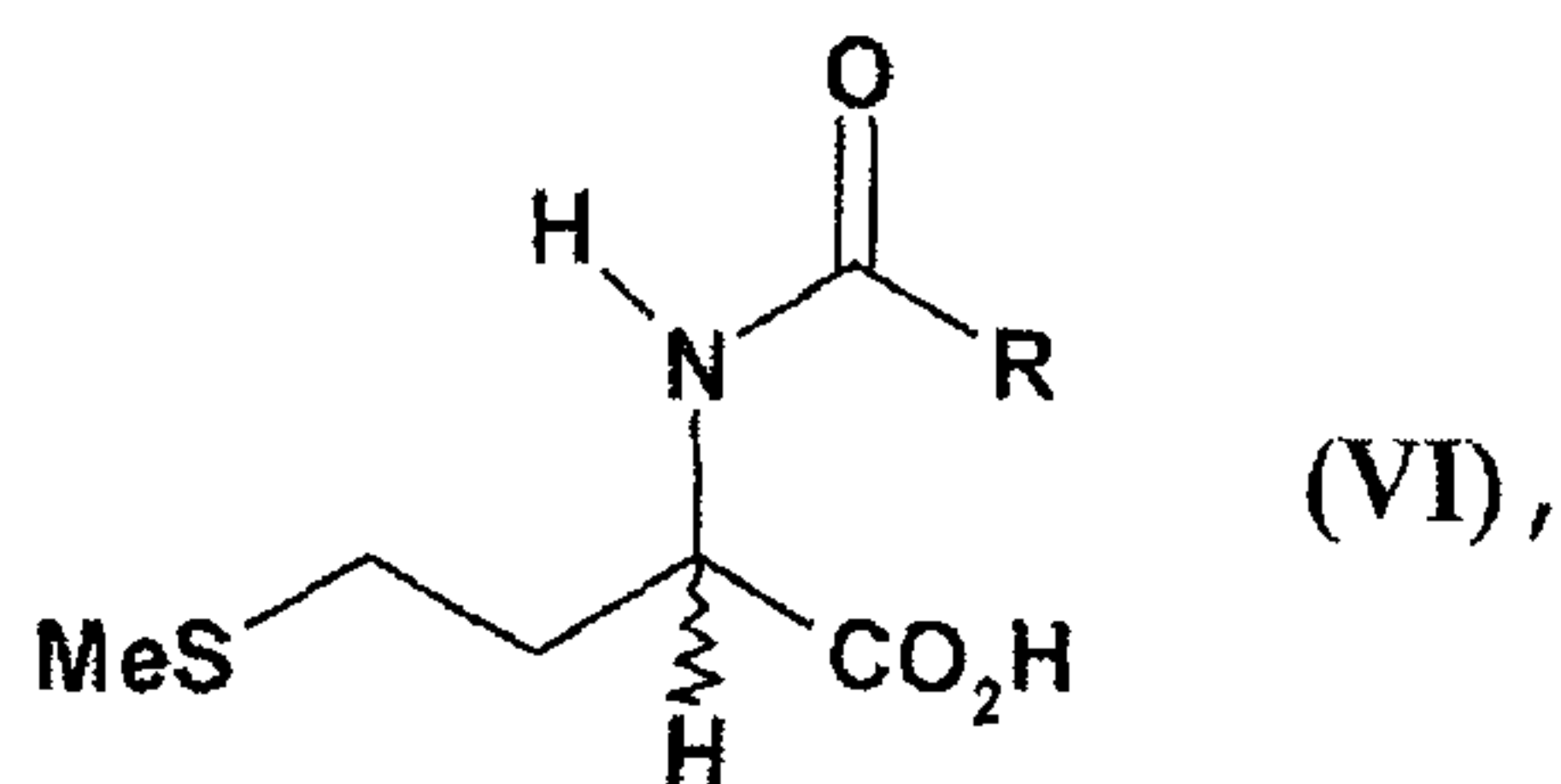
30 30. Method according to Claim 1, characterized in that the chemical transformation of L- and/or D-homoserine is carried out in such a manner that the following steps are carried out:

35 a) **N-acylation** using an acylating agent to give N-acyl-L- and/or D-homoserine of the formula V,



where R = hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where
 5 halogen = F or Cl, preferably CF₃ or CCl₃, benzyloxycarbonyl or C₁- to C₄-alkyloxycarbonyl, preferably tert-butyloxycarbonyl, or methyloxycarbonyl,

10 b) reaction of the N-acylhomoserine V obtained in step a) with **MeSH** in the presence of a basic or acid catalyst to give N-acylmethionine of the formula VI



15 c) **hydrolysis** of the N-acyl-L- and/or D-methionine obtained in step b) to give the corresponding methionine.

20 31. Method according to Claim 30, characterized in that, in step a), use is made of an acylating agent of the general formula R-CO-X¹, where X¹ can be R¹COO, OR² (R² = methyl or ethyl), Cl, Br, and R and R¹ can be identical or different and are
 25 hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where halogen = F or Cl,

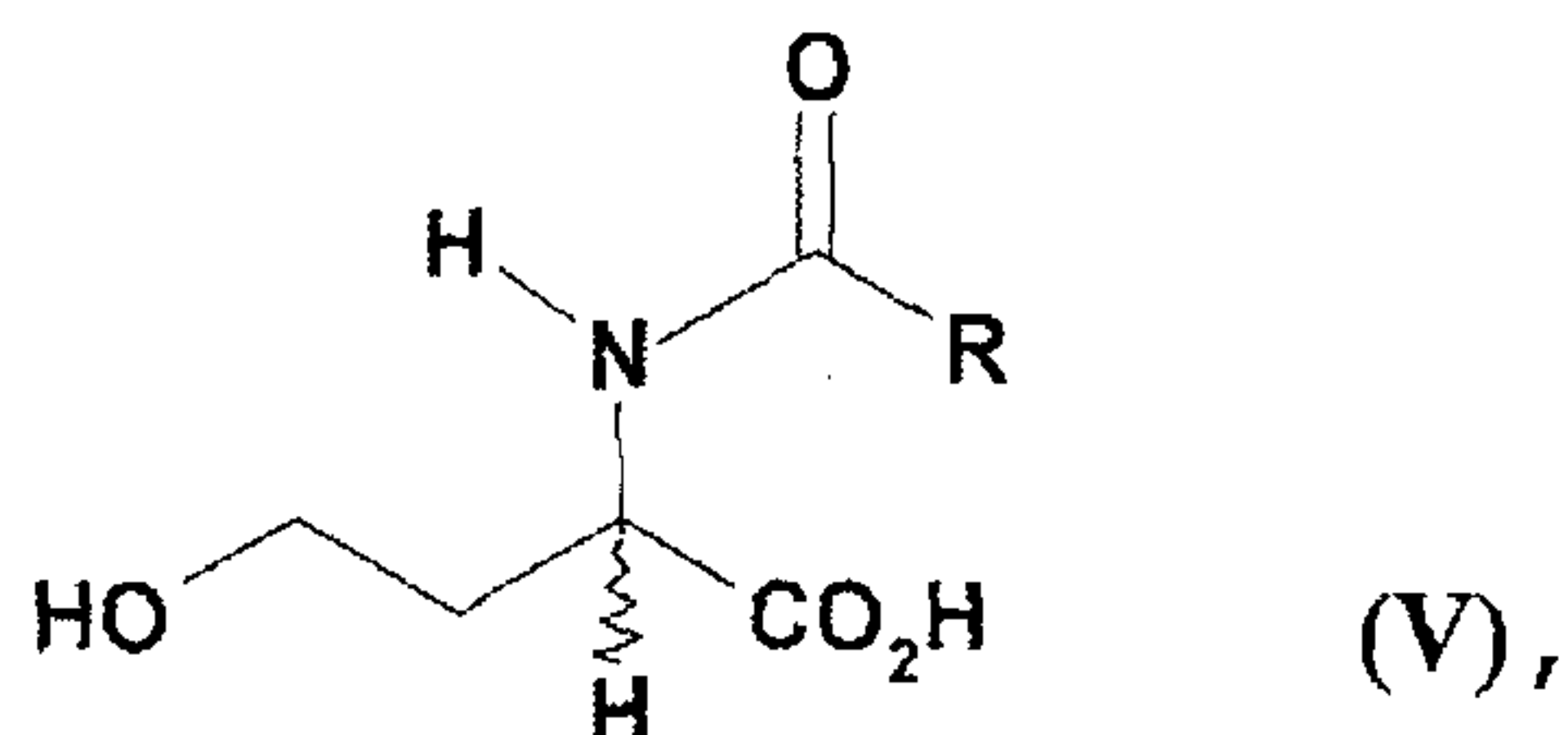
preferably CF_3 or CCl_3 , benzyloxycarbonyl, or C_1 -to C_4 -alkyloxycarbonyl, preferably tert-butyloxycarbonyl, or methyloxycarbonyl.

5 32. Method according to Claim 30 or 31, characterized in that, in step b), as basic catalyst, use is made of NaOH, KOH, pyridine, trimethylamine, triethylamine, or an acetate, carbonate or
10 hydrogencarbonate of the alkali metals or alkaline earth metals, where alkali metal is lithium, sodium, potassium, rubidium or caesium, and alkaline earth metal is magnesium, calcium or barium.

15 33. Method according to one of Claims 30 to 31, characterized in that, in step b), as acid catalyst, use is made of HCl, HBr, HI, H_2SO_4 , alkali metal HSO_4 , H_3PO_4 , alkali metal H_2PO_4 , where
20 alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C_1 - C_{12} -alkylsulphonic acid, C_6 - C_{10} -arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetrafluoroethylene and
25 perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

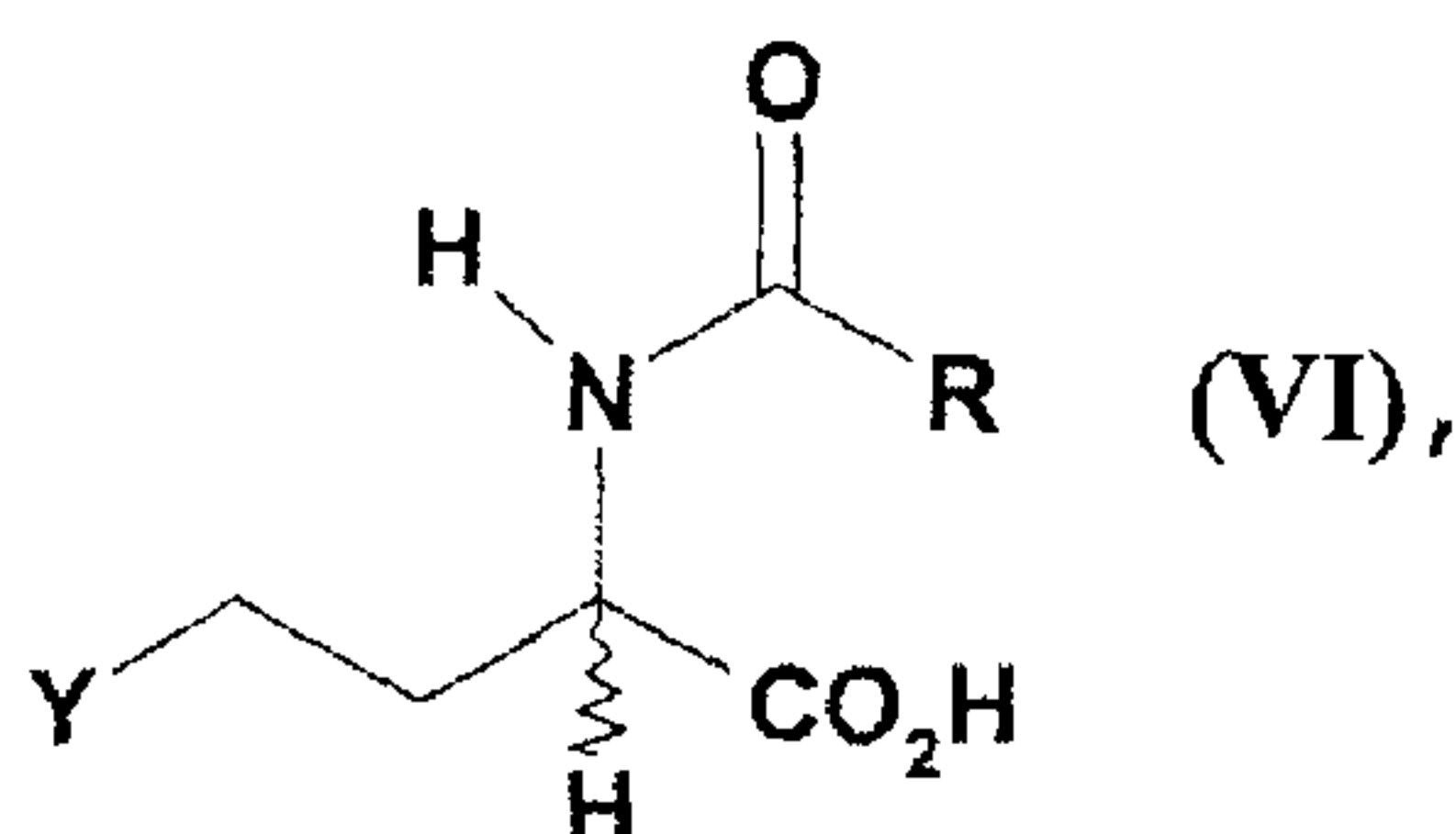
34. Method according to Claim 1, characterized in that the chemical transformation of L- and/or D-homoserine is carried out in such a manner that the
30 following steps are carried out:

a) **N-acylation** using an acylating agent to give the N-acyl-L- and/or D-homoserine of the formula V



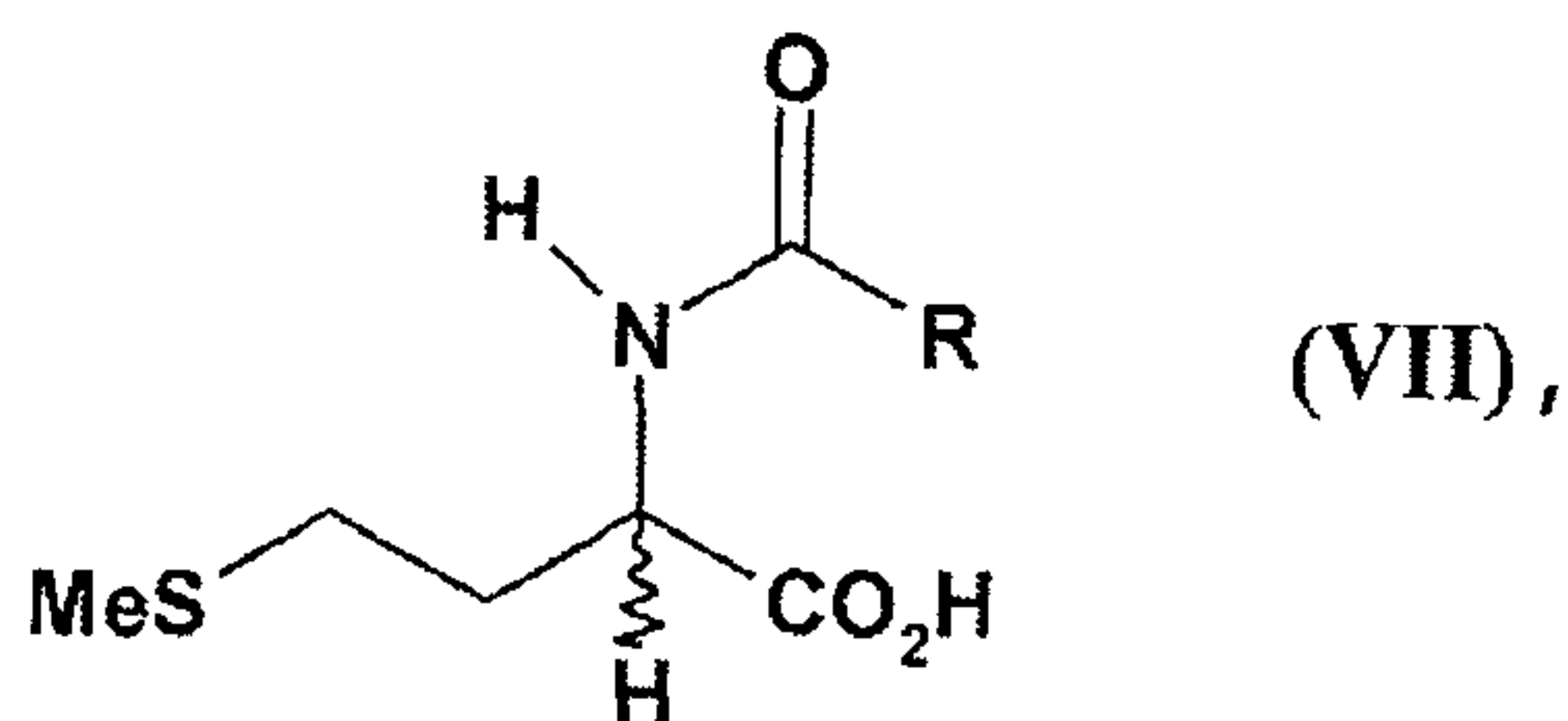
where R is hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where
 5 halogen = F or Cl, preferably CF₃ or CCl₃, benzyloxycarbonyl or C₁- to C₄-alkyloxycarbonyl, preferably tert-butyloxycarbonyl, or methyloxycarbonyl,

- 10 b) conversion of the compound V obtained in step a) by introduction of a **leaving group Y on the C4 atom** into a compound of the formula VI



15 where Y is halogen (= chlorine, bromine or iodine), sulphonyloxy (= pTsO, C₆H₅SO₃, H₃CSO₃ or H₅C₂SO₃), sulphate (OSO₃H), phosphate (OPO₃H),

- 20 c) reaction of the compound VI obtained in step b) with MeSH in the presence of a basic or acid catalyst to give N-acyl-L-methionine, N-acyl-D-methionine or a corresponding mixture of
 25 N-acyl-L- and/or D-methionine of the formula VII



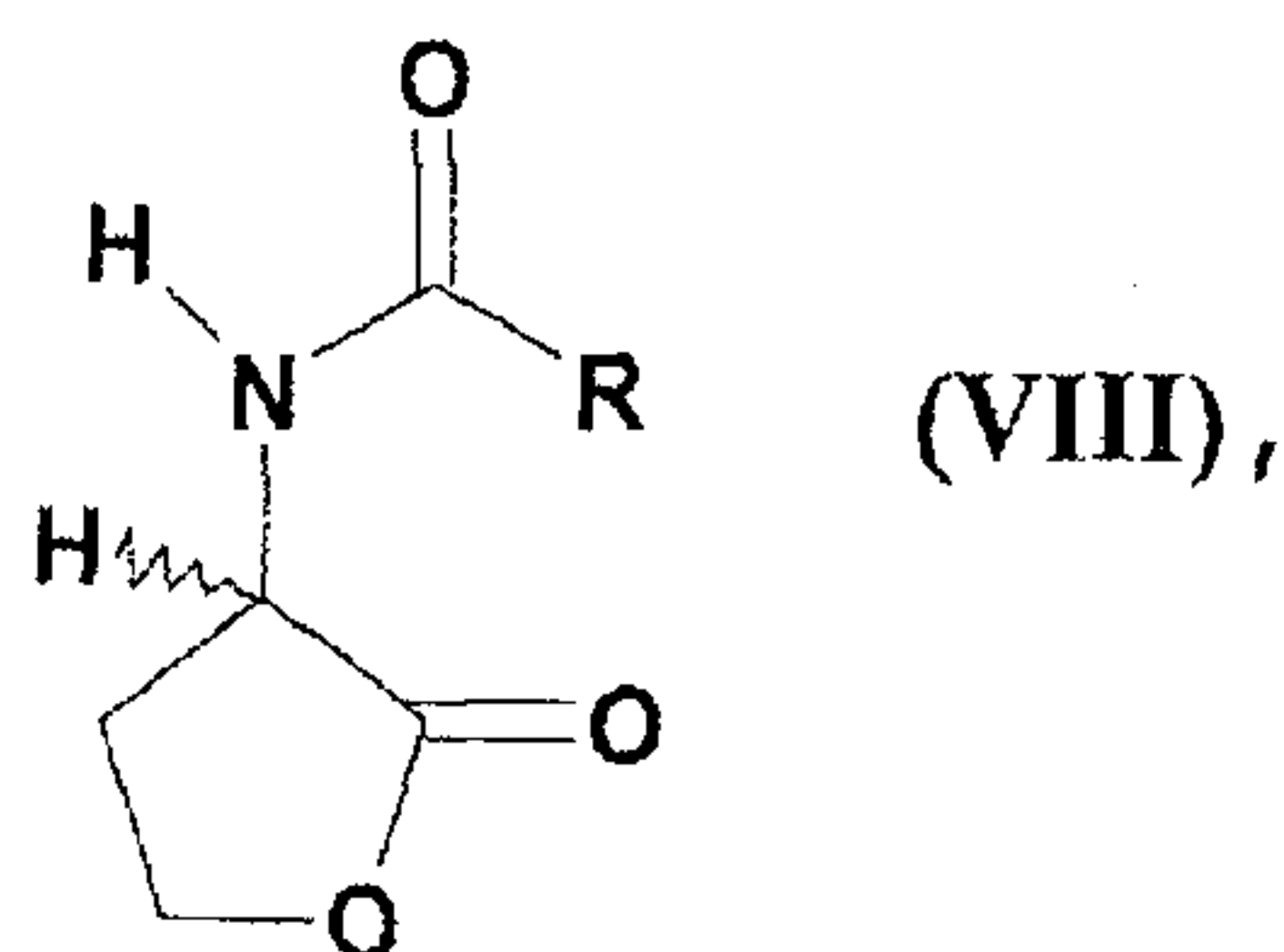
- 5 d) **hydrolysis** of the N-acyl-L- and/or D-methionine VII obtained in step c) to give L- and/or D-methionine.
- 10 35. Method according to Claim 34, characterized in that, in step a), use is made of an acylating agent of the general formula $R-CO-X^1$, where $X^1 = R^1COO$, OR^2 ($R^2 =$ methyl or ethyl), Cl or Br and R and R^1 can be identical or different and are hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where halogen = F or Cl, preferably CF_3 or CCl_3 , benzyloxycarbonyl or C_1 - to C_4 -alkyloxycarbonyl, preferably tert-butyloxycarbonyl, or methyloxycarbonyl.
- 15 36. Method according to Claim 34 or 35, characterized in that, to introduce the leaving group $Y =$ halogen, use is made in the first step correspondingly of PCl_3 , BBr_3 , PI_3 , $SOCl_2$ or $SOBr_2$.
- 20 37. Method according to Claim 34 or 35, characterized in that, to introduce the leaving group Y in the first step, when $Y =$ sulphonyloxy, use is correspondingly made of p-TsCl, $C_6H_5SO_2Cl$, H_3CSO_2Cl , $H_5C_2SO_2Cl$ or CF_3SO_2Cl , when $Y =$ sulphate (OSO_3H), use is correspondingly made of SO_3 , H_2SO_4 or oleum, and when $Y =$ phosphate (OPO_3H), use is correspondingly made of polyphosphoric acid.
- 25 38. Method according to one of Claims 34 to 37, characterized in that, in step c), as basic
- 30

catalyst, use is made of NaOH, KOH, pyridine, trimethylamine, triethylamine, or an acetate, carbonate or hydrogencarbonate of the alkali metals or alkaline earth metals, where alkali metal is lithium, sodium, potassium, rubidium or caesium and alkaline earth metal is magnesium, calcium or barium.

39. Method according to one of Claims 34 to 37, characterized in that, in step c), as acid catalyst, use is made of HCl, HBr, HI, H₂SO₄, alkali metal HSO₄, H₃PO₄, alkali metal H₂PO₄, where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C₁-C₁₂-alkylsulphonic acid, C₆-C₁₀-arylsulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid, or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).

40. Method according to Claim 1, characterized in that the chemical transformation of L- and/or D-homoserine is carried out in such a manner that the following steps are carried out:

a) **N-acylation and cyclization** using an acylating agent to give the N-acyl-L- and/or D-homoserine lactone of the formula VIII



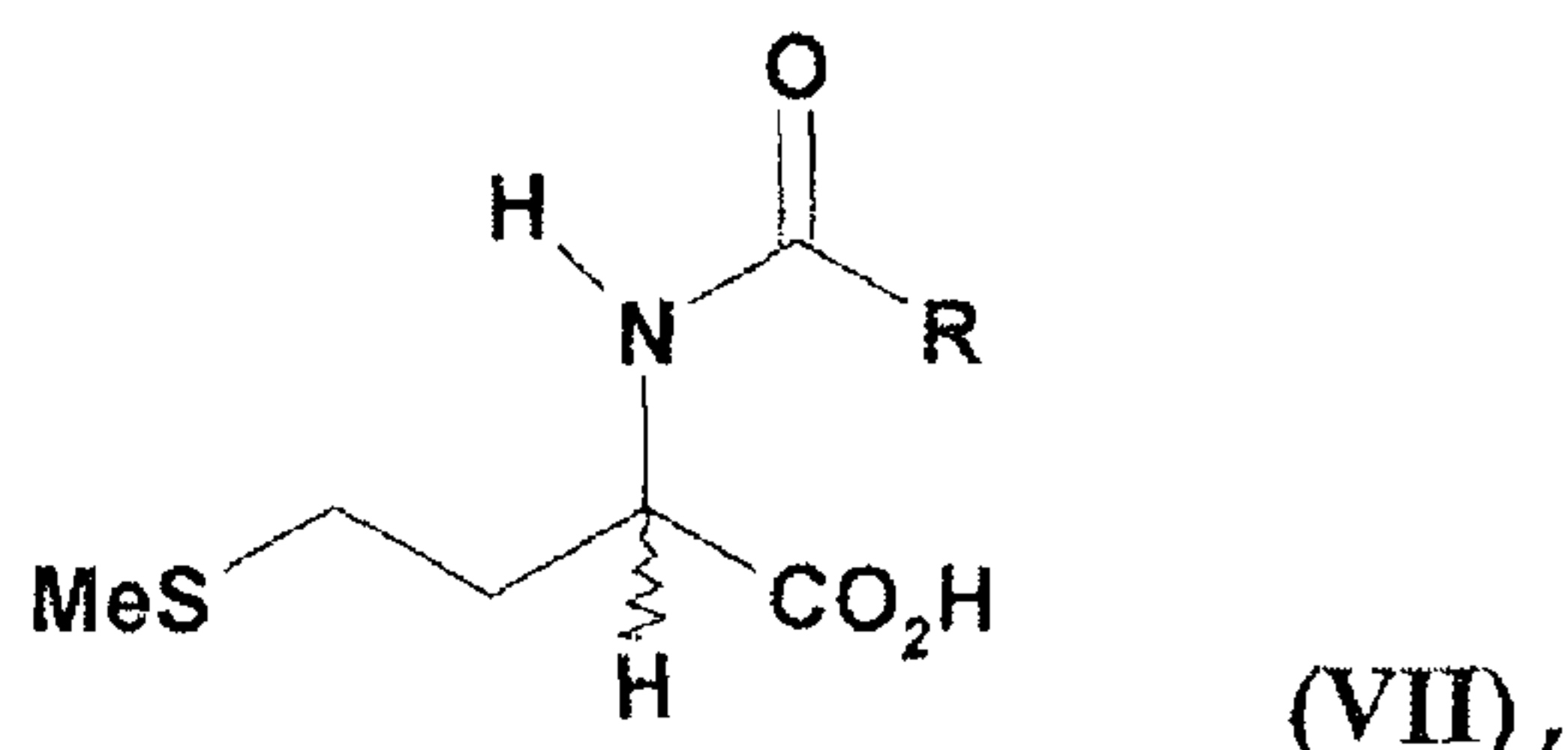
where R is hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di- or trihaloalkyl, where

halogen = F or Cl, preferably CF₃ or CCl₃,
benzyloxycarbonyl or C₁- to C₄-alkyloxycarbonyl,
preferably tert-butyloxycarbonyl, or methyloxy-
carbonyl,

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b) reaction of the N-acylhomoserine lactone
obtained in step a) with MeSH in the presence
of a basic or acid catalyst to give N-
acylmethionine of the formula VII

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c) **hydrolysis** of the N-acylmethionine obtained in
step b) to give methionine at temperatures of
> 95°C.

20

41. Method according to Claim 40, characterized in
that, in step a), use is made of an **acylating
agent** of the general formula R-CO-X¹, where X¹ =
R¹COO, OR² (R² = methyl or ethyl), Cl or Br, and R
and R¹ can be identical or different and are
hydrogen, methyl, ethyl, n-propyl, isopropyl,
n-butyl, sec-butyl, tert-butyl, phenyl, mono-, di-
or trihaloalkyl, where halogen = F or Cl,
preferably CF₃ or CCl₃, benzyloxycarbonyl or C₁- to
C₄-alkyloxycarbonyl, preferably tert-butyloxy-
carbonyl or methyloxycarbonyl.

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42. Method according to Claim 40 or 41, characterized
in that, in step a), as **solvent**, use is made of a
carboxylic acid RCOOH or R¹COOH, where R or R¹ have
the meaning given above, if appropriate in the
presence of a further cosolvent from the group
consisting of C₃ to C₆ ketones, preferably MIBK or

- 5 acetone, C₄ to C₁₀ carboxylic esters, preferably ethyl or butyl acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate, propylene carbonate or butylene carbonate.
- 10 43. Method according to one or more of Claims 40 to 42, characterized in that, in step a), use is made of a **pyridine derivative**, preferably dimethylaminopyridine (DMAP), or carbonyldiimidazole, as catalyst.
- 15 44. Method according to one or more of Claims 40 to 43, characterized in that **step a)** is carried out **at temperatures** of 20 to 100°C, preferably at 50 to 90°C.
- 20 45. Method according to one or more of Claims 40 to 44, characterized in that, in **step b)**, use is made of **a basic catalyst** selected from the group consisting of tetraalkylammonium hydroxides having a maximum of 48 carbon atoms, hydroxides, carbonates, hydrogencarbonates, acetates of alkali metals or alkaline earth metals, where alkali metal is lithium, sodium, potassium, rubidium or caesium and alkaline earth metal is magnesium, calcium or barium, tertiary amines having a maximum of 36 carbon atoms and 1 to 4 nitrogen atoms, tetra(C₁-C₄-alkyl)guanidine, bicyclic amines, preferably DBU (1,8-diaza-bicyclo[5.4.0]undec-7-ene) and TBD (1,5,7-triaza-bicyclo[4.4.0]dec-5-ene), and strongly alkaline ion-exchange resins and also pyridine.
- 35 46. Method according to Claim 45, characterized in that, **as basic catalyst**, use is made of a trialkylamine of the general formula NR³R⁴R⁵, where R³, R⁴ and R⁵ can be identical or different and are

a linear or branched C₁- to C₁₂-alkyl radical, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl or sec-butyl.

- 5 47. Method according to Claim 46, characterized in that, as basic catalyst, use is made of N(methyl)₃, N(methyl)₂(ethyl), N(methyl)(ethyl)₂, N(ethyl)₃, N(n-propyl)₃, N(ethyl)(isopropyl)₂ or N(n-butyl)₃.
- 10 48. Method according to Claim 45, characterized in that, as basic catalyst, use is made of DABCO, DBU, TBD, hexamethylenetetramine, tetramethylethylenediamine or tetramethylguanidine.
- 15 49. Method according to Claim 45, characterized in that, as basic catalyst, use is made of R³R⁴R⁵R⁶N-hydroxide, Li-, Na-, K-, Rb-, Cs-hydroxide, Mg-, Ca-, Ba-hydroxide, where R³, R⁴, R⁵ and R⁶ can be identical or different and are a
20 linear or branched C₁- to C₁₂-alkyl radical, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl or sec-butyl.
- 25 50. Method according to Claim 45, characterized in that, as alkaline ion exchanger, use is made of an R⁷R⁸NR⁹-substituted crosslinked polystyrene resin, where R⁷, R⁸ and R⁹ can be identical or different and are a linear or optionally branched C₁- to C₄-
30 alkyl radical, preferably methyl, ethyl, n-propyl, n-butyl.
- 35 51. Method according to one or more of Claims 40 to 50, characterized in that, in step b), use is made of 1 to 20 mol equivalents of base, calculated as hydroxide or N equivalent, preferably 1 to 10.
52. Method according to one or more of Claims 40 to 50, characterized in that, in **step b)**, use is made of **an acid catalyst** selected from the group

consisting of Brönstedt acids having a pK_a of < 3 , or Lewis acids.

53. Method according to Claim 52, characterized in that, as acid catalyst, use is made of HCl, HBr, HI, H_2SO_4 , alkali metal HSO_4 , H_3PO_4 , alkali metal H_2PO_4 , where alkali metal is lithium, sodium, potassium, rubidium or caesium, polyphosphoric acid, C_1 - C_{12} -alkylsulphonic acid, C_6 - C_{10} -aryl-sulphonic acid, trifluoromethanesulphonic acid, trifluoroacetic acid or a copolymer of tetrafluoroethylene and perfluoro-3,6-dioxo-4-methyl-7-octenesulphonic acid (Nafion).
54. Method according to Claim 52, characterized in that, as acid catalyst, use is made of a **strongly acidic ion-exchange resin**.
55. Method according to Claim 54, characterized in that, as acid catalyst, use is made of an optionally substituted, preferably by divinylbenzene, crosslinked polystyrenesulphonic acid resin.
56. Method according to Claim 52, characterized in that use is made of a **heterogeneous acid catalyst** from the group (WO_3 - and Cs_2O)-containing aluminium oxide, zeolite and montmorillonite.
57. Method according to Claim 52, characterized in that a **Lewis acid catalyst** is used.
58. Method according to Claim 57, characterized in that, as Lewis acid catalyst, use is made of at least one **low-molecular-weight Lewis acid** selected from the group comprising $AlCl_3$, $ZnCl_2$, $BF_3 \cdot OEt_2$, $SnCl_2$ and $FeCl_3$.
59. Method according to one or more of Claims 40 to

58, characterized in that the reaction in step b) is carried out in **solution and/or in suspension** in an organic solvent.

- 5 60. Method according to Claim 59, characterized in that use is made of water and/or at least one low-molecular-weight organic solvent selected from the group consisting of C₃ to C₆ ketones, preferably MIBK or acetone, straight-chain or branched C₁ to
10 C₄ alcohols, C₄ to C₁₀ carboxylic esters, preferably ethyl or butyl acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate,
15 propylene carbonate or butylene carbonate.
61. Method according to one or more of Claims 41 to 60, characterized in that the hydrolysis **in step c)** is carried out in aqueous **solution and/or**
20 **suspension**.
62. Method according to Claim 61, characterized in that use is made additionally of at least one low-molecular-weight organic solvent selected from the group consisting of C₃ to C₆ ketones, preferably MIBK or acetone, straight-chain or branched C₁ to
25 C₄ alcohols, C₄ to C₁₀ carboxylic esters, preferably ethyl or butyl acetate, C₃ to C₆ carboxamides, preferably DMF or dimethylacetamide, C₆ to C₁₀ aromatics, preferably toluene, and C₃ to C₇ cyclic carbonates, preferably ethylene carbonate,
30 propylene carbonate or butylene carbonate.
63. Method according to one or more of Claims 41 to 62, characterized in that the reaction in step c) is carried out at a **temperature** of 90 to 180°C, preferably at 100 to 160°C, in particular at 120 to 150°C, very particularly preferably at 130 to 140°C.

- 5 64. Method according to one or more of Claims 41 to 63, characterized in that the reaction in step c) is carried out in addition in the presence of an acid, basic or Lewis acid catalyst, or a combination of acid and Lewis acid catalyst.
- 10 65. Method according to one or more of Claims 1 to 64, characterized in that the L-homoserine used has been produced via fermentation.
- 15 66. Method according to one or more of Claims 1 to 64, characterized in that use is only made of homoserine having L configuration.
- 20 67. Method according to Claim 66, characterized in that the L-homoserine used has been produced by fermentation.
- 25 68. Method according to one or more of Claims 65 to 67, characterized in that use is made of an L-homoserine-containing solid product which was produced from an L-homoserine-containing fermentation broth by removal of water.
- 30 69. Method according to Claim 68, characterized in that the L-homoserine-containing fermentation broth was produced by culturing an L-homoserine-excreting microorganism in a suitable nutrient medium.
- 35 70. Method according to Claim 69, characterized in that the microorganism is a bacterium.
71. Method according to Claim 70, characterized in that it is a bacterium of the genus *Corynebacterium* or *Escherichia*.
72. Method according to one or more of Claims 68 to

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71, characterized in that the concentration of the L-homoserine in the fermentation broth is at least 1 g/l.