METHOD FOR PREPARING METHIONINE ANALOGUES

The present invention concerns a method for preparing methionine analogues, as well as selenium derivatives of methionine analogues, from abundant and accessible compounds, derived from biomass.

The methionine and the analogues thereof such as 2-hydroxy-4-methylthiobutanoic acid (**HMTBA**) and 2-oxo-4-methylthiobutanoic acid (**KMB**), as well as salts, chelates, in particular metal chelates (of Zn, Ca Mn, Mg, Cu, Na...) and the esters of these acids, such as the isopropyl and tert-butyl esters of HMTBA, are widely used in animal nutrition. The selenium derivatives of the methionine and of the hydroxy-analogues thereof are also constituents of major interests in animal nutrition.

Given the continuously growing volumes, consumed worldwide, of these ingredients, it is necessary to develop manufacturing methods from renewable, energy-efficient and non-polluting sources.

The authors have thus developed a method for preparing these compounds from organic acids, the salts or the derivatives thereof, which may be obtained from biomass, in particular by biological transformations such as fermentation methods.

Summary

1. In one aspect, the present invention refers to a method for preparing a compound or a salt thereof, said compound having the formula (I),

$$\mathbf{R^1OOC\text{-}C(=X)\text{-}CHR^2R^3} \qquad \mathbf{(I)}$$

Where X is selected from O; N-R' where R' represents H or a C1-C6 alkyl group; and N-OR" where R" represents H, a C1-C6 alkyl group or an alkylaryl group;

R^1 represents H or a C1-C6 alkyl group;

R^2 represents H, a C1-C6 alkyl group, or an alkylaryl group; and

R^3 represents CH_2SR^4 or CH_2SeR^4 with R^4 representing H or a C1-C6 alkyl group

from a compound of formula (II), or a salt thereof,

$$\mathbf{R^1OOC\text{-}C(=X)\text{-}CHR^2R^5} \qquad \mathbf{(II)}$$

Where R^1, R^2 and X have the above definition; and

R^5 represents H or $COOR^6$ with R^6 representing H or a C1-C6 alkyl group,

said method being carried out in the presence of a compound of formula (III)

$$CH_2(Y)(Z) \qquad \textbf{(III)}$$

Where Y represents H; OR^7 with R^7 representing H, a C1-C6 alkyl group or an acyl group of formula CO-R^4 with R^4 meeting the preceding definition; SR^4 or SeR^4 with R^4 meeting the preceding definition; or NR^8R^9, with R^8 and R^9, identical or different, representing each or together, a C1-C6 alkyl group, or an alkylaryl group;

Z, identical to or different from Y, represents OR^{10} with R^{10} representing H, a C1-C6 alkyl group, or CO-R^4 with R^4 meeting the preceding definition; a cyclic or acyclic $N(COR^4)(COR^4)$ group, with R^4 meeting the preceding definition; or $NR^{11}R^{12}$, with R^{11} and R^{12}, identical or different, representing each or together, a C1-C6 alkyl group, or an alkylaryl group;

Or Y and Z represent together =O;

Said method being characterized in that

The compound (II) is reacted with the compound (III) to lead to an intermediate having the structure (IV)

$$R^1OOC\text{-}C(=X)\text{-}CHR^2\text{-}CH_2Z \qquad \textbf{(IV)}$$

Where R^1, R^2, X and Z have the definition above

The compound (IV) thus obtained is reacted with R^4SH or a salt thereof, or R^4SeH or a salt thereof, with R^4 meeting the preceding definition, already present in the reaction medium or added during the method,

Then, upon completion of the reaction, the compound (I) or a salt thereof is isolated.

In another aspect, the present invention refers to a compound having the following formula (IV)

$$R^1OOC\text{-}C(=X)\text{-}CHR^2\text{-}CH_2Z \qquad \textbf{(IV)}$$

Where X is selected from O; N-R' Where R' represents H or a C1-C6 alkyl group; and N-OR" where R" represents H, a C1-C6 alkyl group, or an aryl group,

R^1 represents H or a C1-C6 alkyl group;

R^2 represents H, a C1-C6 alkyl group or an alkylaryl group; and

Z represents OR^{10} with R^{10} representing H; a C1-C6 alkyl group or CO-R^4 with R^4 representing H or a C1-C6 alkyl group, a cyclic or acyclic $N(COR^4)(COR^4)$ group, with R^4 representing H or a C1-C6 alkyl group; or

$NR^{11}R^{12}$, with R^{11} and R^{12}, identical or different, representing each or together, a C1-C6 alkyl group, or an alkylaryl group.

In a further aspect, the present invention refers to a method for manufacturing D, L-methionine, D- or L-methionine, D,L-2-hydroxy-4-methylthiobutanoic acid (HMTBA), D- or L-HMTBA, from 2-oxo-4-methylthiobutanoic acid (KMB), characterized in that KMB is prepared according to a method as disclosed herein, and then KMB is chemically or biologically transformed into methionine or HMTBA.

Detailed Description

According to the invention, this method allows preparing a compound or a salt thereof, said compound having the formula (I),

$$R^1OOC\text{-}C(=X)\text{-}CHR^2R^3 \qquad (I)$$

Where X is selected from O; N-R' where R' represents H or a C1-C6 alkyl group; and N-OR" where R" represents H, a C1-C6 alkyl group or an alkylaryl group;

R^1 represents H or a C1-C6 alkyl group;

R^2 represents H, a C1-C6 alkyl group, or an alkylaryl group; and

R^3 represents CH_2SR^4 or CH_2SeR^4 with R^4 representing H or a C1-C6 alkyl group,

from a compound of formula (II), or a salt thereof,

$$R^1OOC\text{-}C(=X)\text{-}CH_2R^2R^5 \qquad (II)$$

Where R^1, R^2 and X have the definition above; and