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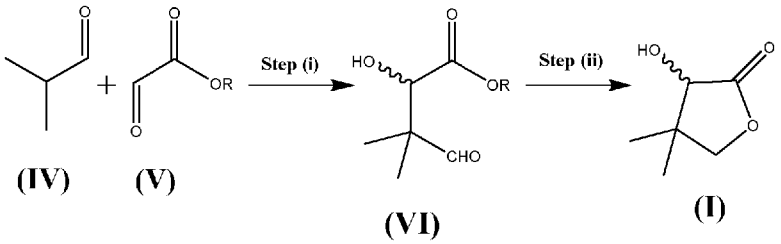
(54) Title: SYNTHESIS OF A RACEMIC MIXTURE OF PANTOLACTONE



(57) Abstract: The invention relates to an improved synthesis of a racemic mixture of pantolactone (I).

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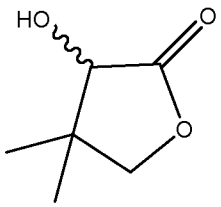
SYNTHESIS OF A RACEMIC MIXTURE OF PANTOLACTONE

The present invention relates to an improved synthesis of a racemic mixture of pantolactone.

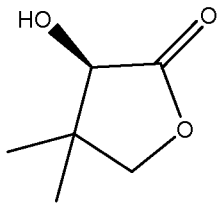
Pantolactone, which is the compound of formula (I)



(I)

has two optically active enantiomers.

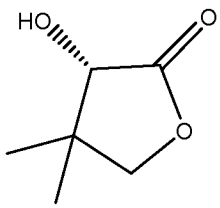
(R)-Pantolactone which is the compound of formula (I')



(I')

,

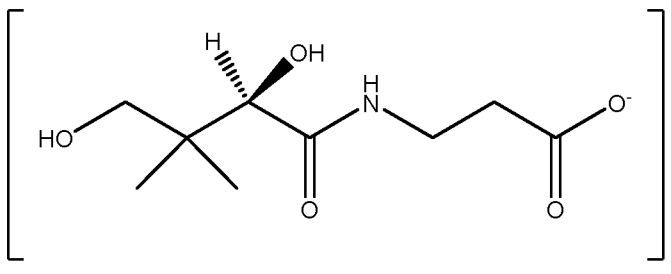
and (S)-pantolactone, which is the compound of formula (I'')



(I'')

.

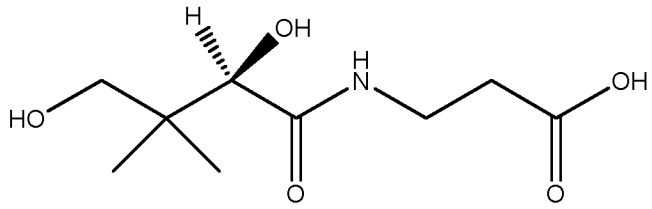
(R)-pantolactone is a starting material for the synthesis of calcium (R)-pantothenate (compound of formula (II))



Ca^{2+} **(II)**

,

which is the commercial form of pantothenic acid (compound of formula (III))



(III)

Pantothenic acid, which also known as vitamin B5, is a water-soluble vitamin. Pantothenic acid is an essential nutrient. There are many health benefits of vitamin B5, some of which include a healthy heart, lower stress levels, and applications in skin and hair care.

Instead of pantothenic acid, calcium pantothenate is often used in dietary supplements because, as a salt, it is more stable than pantothenic acid.

Natural sources of vitamin B5 are for example mushrooms, broccoli, cabbage, legumes, salmon, eggs, fish, brewer's yeast, nuts, milk, and dairy products like cheese, wheat, peanuts, soybeans, molasses, and collard greens.

An alternative way to obtain vitamin B5 is by chemical synthesis. An important starting material is as said above (R)-pantolactone. A usual way to produce vitamin B5 is the reaction of calcium β-alaninate with (R)-pantolactone in boiling ethanol or methanol.

The other enantiomer of pantolactone, which is (S)-pantolactone, can be used as such or it can be used as intermediate in various synthesis. Alternatively, (S)-pantolactone can also be transformed into (R)-pantolactone.

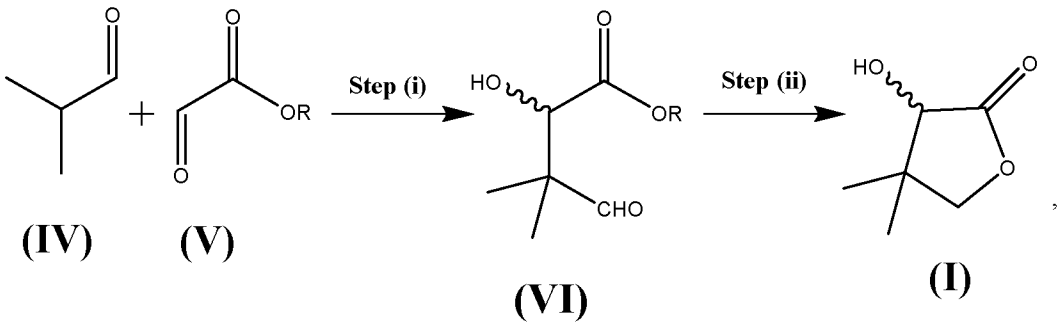
The racemic mixture of pantolactone is a 1:1 mixture of (R)-pantolactone and (S)-pantolactone. This mixture can be used as such (or in any formulation) or it can be used as intermediate for further chemical (or biochemical) reactions.

Due to the importance of the racemic mixture of pantolactone, there is always a need for an improved process of production of a racemic mixture of pantolactone.

Nowadays there are several processes known to produce a racemic mixture of pantolactone. There are chemical as well as biochemical methods. Also, combinations of chemical and biochemical methods are known.

The present invention relates to a two-step synthesis of a racemic mixture of pantolactone. Preferably the present invention relates to a two-step and one-pot synthesis of in good yields.

The newly found process of the racemic mixture of pantolactone has the following reaction schemes

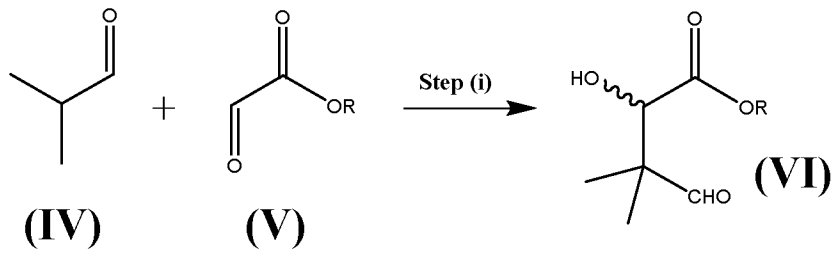


wherein R is a C_1-C_{10} alkyl moiety which is a substituted or an un-substituted alkyl.

The first step (step (i)) is carried out in the presence of at least one specific organocatalyst.

The reaction steps are discussed in more detail below.

Step (i)



(IV) (V)

The first step (step (i)) is carried out in the presence of a least one organo-catalyst.

The organo-catalyst has a pyrrolidine ring, which is substituted.

The organo-catalysts used in step (i) are known. They are available commercially or they can be produced according to known methods.

The reaction of step (i) is usually carried out in a solvent (or a mixture of solvents). Suitable solvents are alcohols, hydrocarbons, halogenated hydrocarbons (for example chloroform and dichloromethane), ethers, esters and amides (for example DMF). Especially preferred are secondary and tertiary alcohols (such as isopropanol (propan-2-ol) and tert- butyl alcohol (2-methylpropan-2-ol)).
The reaction mixture of step (i) should not comprise any water. This means that the water content is kept to a minimum and that no water is added to the reaction mixture of step (i) intentionally.

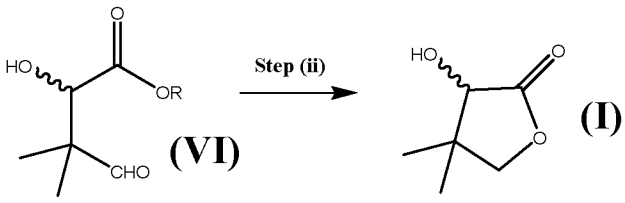
Therefore, another preferred embodiment of the present invention is a process as described wherein step (i) the reaction mixture does not comprise any water

The reaction is usually carried at temperatures of 0°C – 80°C, preferably 10°C – 40°C, more preferably 20°C – 30°C.

The amount of the organo-catalyst is usually from 0.1 – 10 mol-% (in regard to the starting material). Preferably from 1 – 5 mol-%.

The starting material (the compounds of formula (IV) and (V)) are usually added in equimolar amounts. A slight excess of one of the compounds is acceptable as well.

Step (ii)



The reaction of step (ii) is a transfer hydrogenation. The reaction of step (ii) is carried out in the presence of a hydrogen donor (such as a formate or an alcohol).

The transfer hydrogenation is catalyzed by at least one transition metal catalyst.

The transition metal catalyst can be added as such to the reaction mixture.

Alternatively, the transition metal catalyst can be formed by the addition of ligand and by the addition of the transition metal in the form of a salt.

Furthermore, it is also possible that the organo-catalyst of step (i) serves as ligand to form the transition metal catalyst used in step (ii). In this case the transition metal is added to the reaction mixture in the form of a salt.

These alternative ways how to obtain the transition metal catalyst could also be combined (which means that a catalyst can be added as well as a ligand and a transition metal salt).

Preferred transition metals are Ru, Ir, Rh, Fe, Co and Mn, more preferred are Ru, Ir and Rh.

As stated above, the transition metals can be added in form of a salt (such as dichloro(p-cymene)ruthenium(II) dimer).

The reaction of step (ii) is usually carried out at elevated temperatures. Preferably, the reaction temperature of step (ii) is between 20°C and 100 °C, more preferably between 30°C and 70 °C.

In the reaction of step (ii), the amount of hydrogen donor is between 1 and 2 mol-eq in regard of the compound of formula (VI).

In the reaction of step (ii), the amount of the transition metal salt used to form the catalyst is between 0.01 and 10 mol-%, preferably 0.1- 10 mol, more preferably 1 – 5 mol-%, in regard of the compound of formula (VI).

The following examples serve to illustrate the invention. If not otherwise stated the temperature is given in °C.

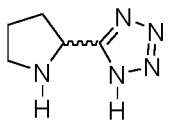
Examples

The organocatalysts used are either commercially available or can be prepared using known methods

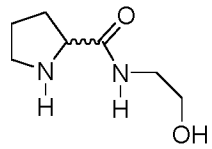
Example 1: General procedure for step (i) testing various organocatalysts producing ethyl-2-hydroxy-3,3-dimethyl-4-oxobutanoate (VI)

To a vial containing the organocatalyst (0.01 mmol, 10.0 mol%) 0.20 mL of a stock solution of isobutanal (91.0 µL, 1.00 mmol) and ethyl glyoxalate (50.0 wt.% in toluene, 198 µL, 1.00 mmol) in t-BuOH (2.00 mL) was added. The mixture was stirred at room temperature for 4 – 72 h. Conversion was measured by NMR or GC.

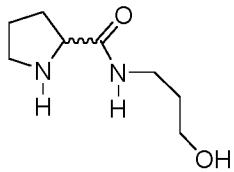
The results of the experiment are shown in the table below.



(rac-VIIa)



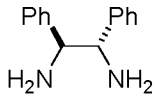
(rac-VIIb)



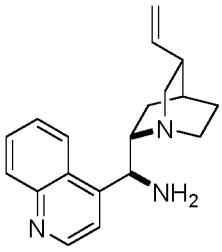
(rac-VIIc)

Example #	Organocatalyst	Conversion (%)
1a	rac-VIIa	88
1b	rac-VIIb	99
1c	rac-VIId	94

Comparative examples (Comp-A and Comp-B) were performed with organocatalysts A and B under the same conditions.



A



B

Example #	Organocatalyst	Conversion (%)
Comp-A	A	3
Comp-B	B	0

Example 2

To a solution of N-(2-hydroxyethyl)pyrrolidine-2-carboxamide (rac-VIIb, 79.1 mg, 500 µmol, 5.00 mol%) in t-BuOH (10.0 mL), isobutanal (910 µL,10.0 mmol, 1.00 eq.) and ethyl glyoxalate (50.0% in toluene, 1.98 mL,10.0 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue purified by column chromatography (cyclohexane/ethyl acetate, 4:1) yielding ethyl 2-hydroxy-3,3-dimethyl-4-oxobutanoate (VI) (1.47 g, 84%) as a colorless oil. 1H NMR (400 MHz, CDCl3) δ = 9.57 (1H, s), 4.32 (1H, s), 4.30– 4.18 (2H, m), 3.06 (1H, br), 1.27 (3H, t), 1.14 (3H,s), 1.05 (3H, s). The analytical data was in agreement with an authentic sample.

General procedure for transfer hydrogenation (step (ii))

The transition metal catalyst or the transition metal salt and the ligand were added to a solution of ethyl 2-hydroxy-3,3-dimethyl-4-oxobutanoate (VI) from example 1. The mixture was degassed, sodium formate was added and the mixture was stirred at the desired temperature until the reduction was complete. The reaction mixture extracted with MTBE and the combined organic phases were dried, filtered and concentrated in vacuo.

Example 3

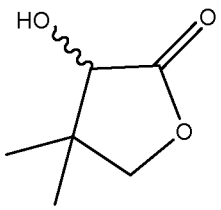
Ethyl 2-hydroxy-3,3-dimethyl-4-oxobutanoate (VI) was reacted with 5 equivalents of sodium formate and 0.5 mol% of RuCl(p-cymene)[(S,S)-Ts-DPEN] in water at 40 °C. Full conversion was obtained after 17 hours yielding pantolactone (I)

Example 4 – One pot, sequential synthesis of pantolactone (I)

To a solution of N-(2-hydroxyethyl)pyrrolidine-2-carboxamide (rac-VIIb, 237 mg, 1.50 mmol, 5.00 mol%) in t-BuOH (30.0 mL), isobutanal (2.74 mL, 30 mmol, 1.00 eq.) and ethyl glyoxalate (50.0 wt.% in toluene, 5.95 mL, 30.0 mmol, 1.00 eq.) were added. The mixture was stirred at room temperature for 24 h. Water (150 mL) was added and the solution was degassed with argon for 1 h, before $(RuCl_2(cymene))_2$ (91.9 mg, 150 mmol, 0.50 mol%) and sodium formate (10.2 g, 150 mmol, 5.00 eq.) were added. The mixture was stirred overnight. A solution of aq. HCl (1M, 200 mL) was added and the reaction mixture extracted with MTBE (3x 600 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/ ethyl acetate, 2:1) yielding the product (rac-pantolactone, 2.4 g, 62%) as a white solid. The analytical data was in agreement with an authentic sample.

Claims

1. Process for the production of a racemic mixture of the two enantiomeric forms of the compound of formula (I)

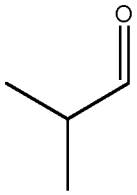


(I)

,

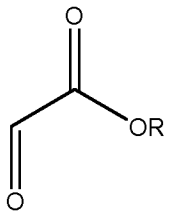
wherein a first step (step (i))

a compound of formula (IV)



(IV)

and a compound of formula (V)

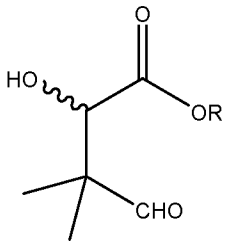


(V)

,

wherein R is a C_1-C_{10} alkyl moiety, which can be a substituted or an un-substituted alkyl,

are reacted to form a compound of formula (VI)



(VI)

,

wherein R has the same meaning as defined above,

in the presence of at least one organo-catalyst,

and subsequently in a second step (step (ii))

the compound of formula (I) is formed by a transfer hydrogenation in the presence of hydrogen donor and a transition metal catalyst.

2. Process according to claim 1, wherein the organo-catalyst has a pyrrolidine ring, which is substituted.

3. Process according to anyone of the preceding claims, wherein the reaction of step (i) is carried out in at least one solvent, preferably alcohols, hydrocarbons, halogenated hydrocarbons (for example chloroform and dichloromethane), ethers, esters and amides (for example DMF).

4 Process according to anyone of the preceding claims, wherein the reaction mixture of step (i) does not comprise any water.

5. Process according to anyone of the preceding claims, wherein the reaction of step (i) is carried at temperatures of 0°C – 80°C, preferably 10°C – 40°C, more preferably 20°C – 30°C.

6. Process according to anyone of the preceding claims, wherein the amount of the organo-catalyst in step (i) is from 0.1 – 10 mol-%, preferably from 1 – 5 mol-%. (regarding the starting material).

7. Process according to anyone of the preceding claims, wherein the transfer hydrogenation of step (ii) is catalyzed by at least one transition metal catalyst, which is added as such to the reaction mixture of step (ii).

8. Process according to anyone of the preceding claims 1 – 7, wherein the transfer hydrogenation of step (ii) is catalyzed by at least one transition metal catalyst, which is formed by the addition of ligand and by the addition of the transition metal in the form of a salt.

9. Process according to anyone of the preceding claims 1 – 7, wherein the transfer hydrogenation of step (ii) is catalyzed by at least one transition metal catalyst,

wherein the organo-catalyst of step (i) serves as ligand to form the transition metal catalyst.

10. Process according to anyone of the preceding claims, wherein the transition metal is chosen from the group consisting of Ru, Ir, Rh, Fe, Co and Mn, preferably Ru, Ir and Rh.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/063159

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D307/33
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORRIS MARKERT ET AL: "Asymmetric Histidine-Catalyzed Cross-Aldol Reactions of Enolizable Aldehydes: Access to Defined Configured Quaternary Stereogenic Centers", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 131, no. 46, 25 November 2009 (2009-11-25), pages 16642-16643, XP055495036, ISSN: 0002-7863, DOI: 10.1021/ja907054y scheme 1, reaction 1d + 1a -> 3d; scheme 3, synthesis of (R)-pantolactone 7 [NB: ethyl glyoxylate is compound 1d not 1g]	1-10

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

[ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2019	05/07/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ladenburger, Claude

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ULF SCHEFFLER ET AL: "Histidine-Catalyzed Asymmetric Aldol Addition of Enolizable Aldehydes: Insights into its Mechanism", JOURNAL OF ORGANIC CHEMISTRY, vol. 77, no. 5, 2 March 2012 (2012-03-02), pages 2310-2330, XP055495035, ISSN: 0022-3263, DOI: 10.1021/jo202558f scheme 1, reaction 1 + 11 -> 13j; table 1; page 2317, conclusion, total synthesis of pantolactone (derivative of 13j); table 4, entry 9	1-10

X	MARCEL HEIDLINDEMANN ET AL: "Chemoenzymatic Synthesis of Vitamin B5-Intermediate (R)-Pantolactone via Combined Asymmetric Organo- and Biocatalysis", JOURNAL OF ORGANIC CHEMISTRY, vol. 80, no. 7, 3 April 2015 (2015-04-03), pages 3387-3396, XP055495038, ISSN: 0022-3263, DOI: 10.1021/jo502667x abstract; schemes 1-6; table 2	1-10

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