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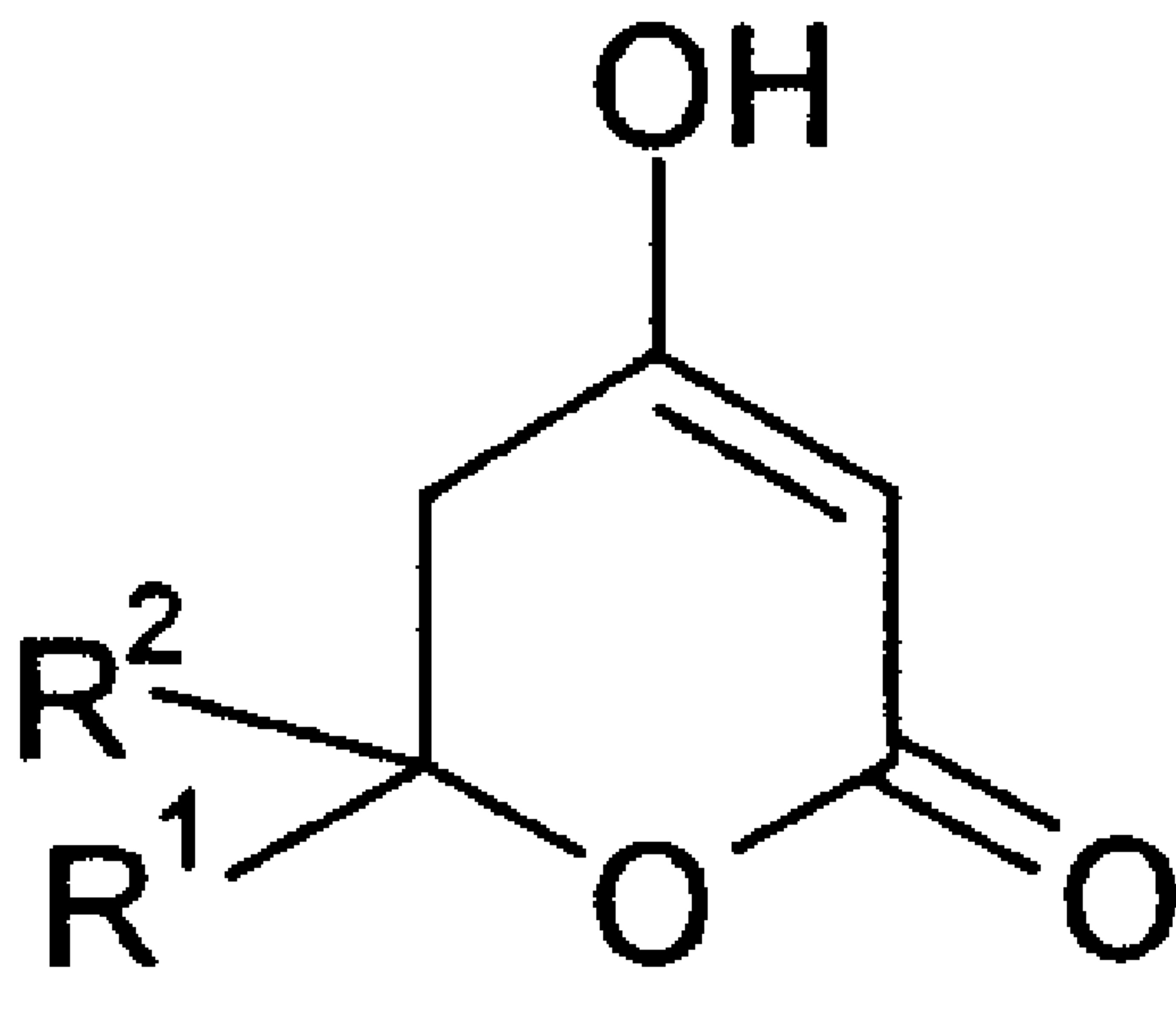
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(54) Title: CONTINUOUS PROCESS FOR PREPARING DIHYDROPYRONES



(I)

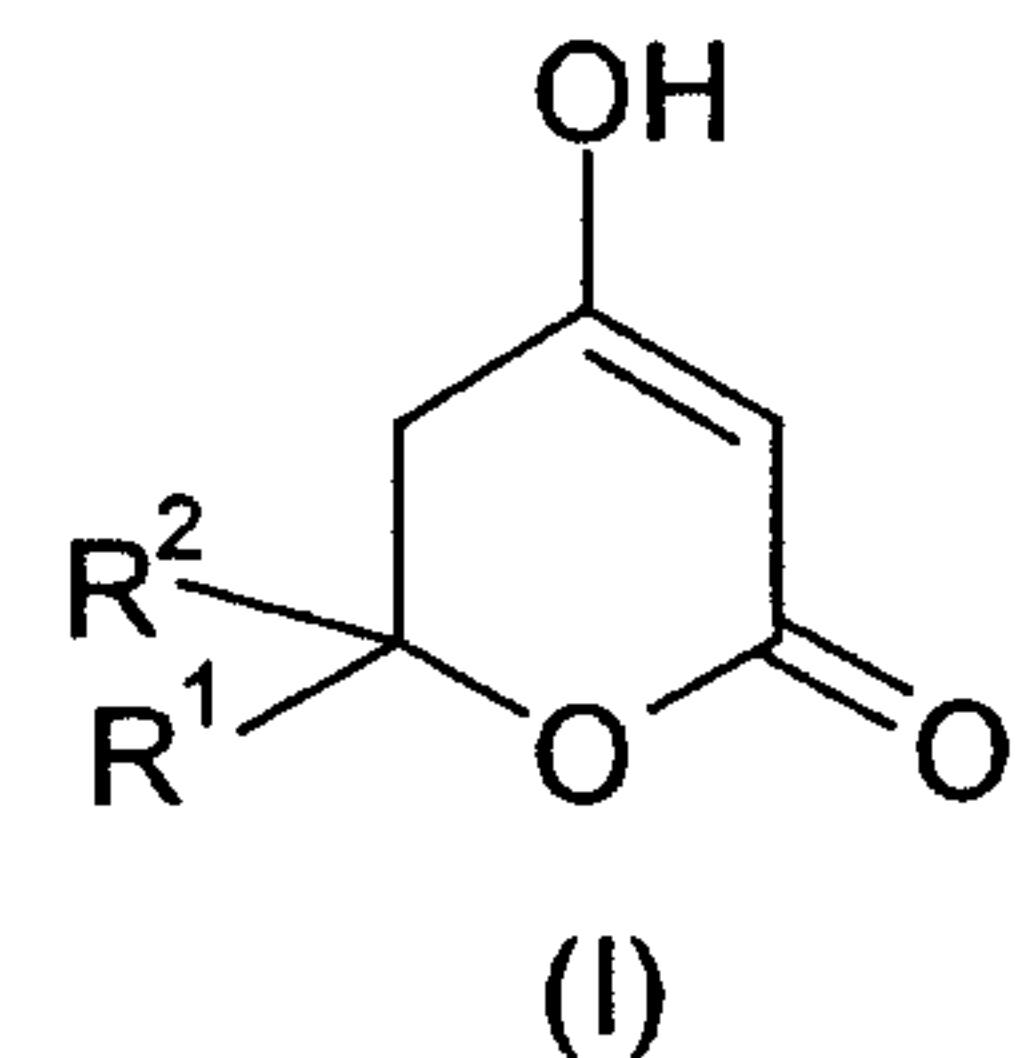
(57) Abrégé/Abstract:

The invention relates to a continuous process for preparing dihydropyranes of general formula I, (see formula I) wherein the groups R¹ and R² may have the meanings given in the claims.

Abstract

The invention relates to a continuous process for preparing dihydropyrones of general formula I.

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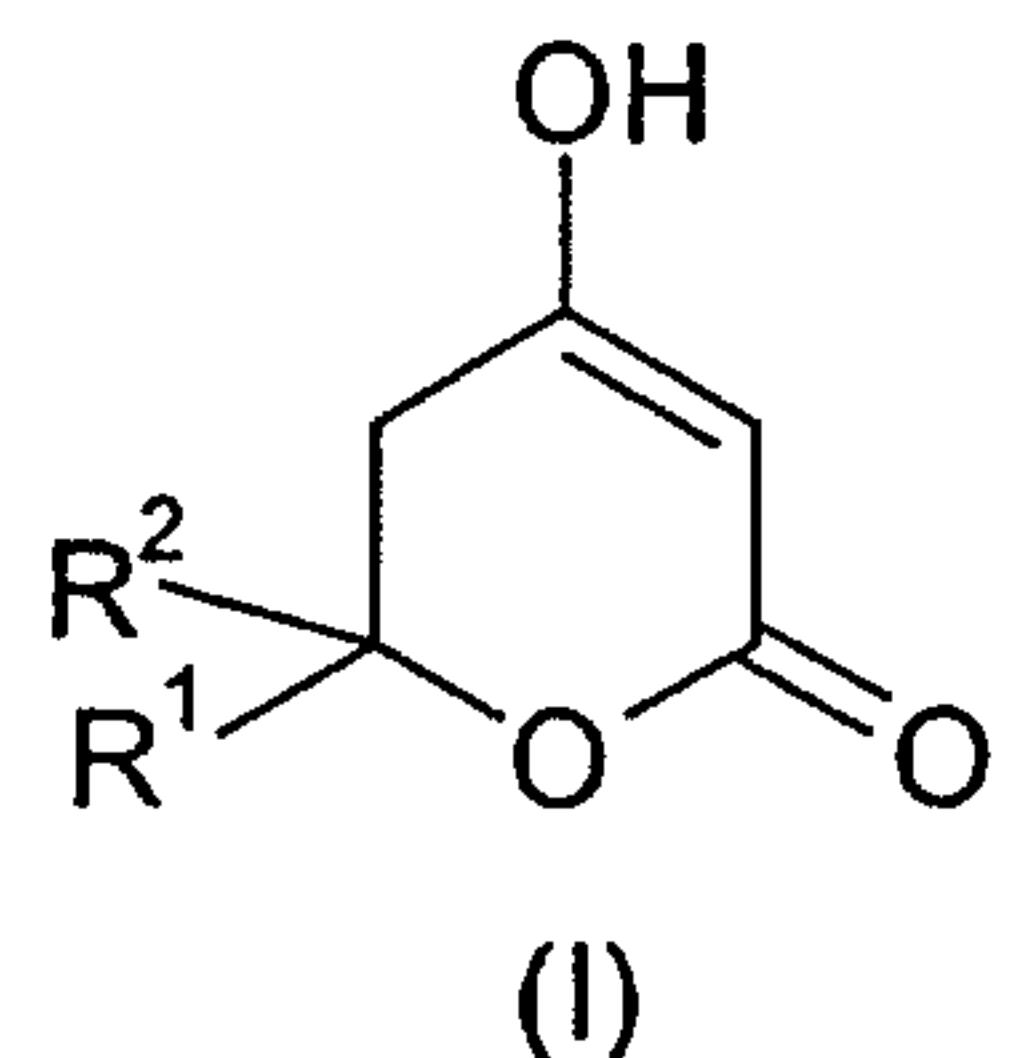


wherein the groups R¹ and R² may have the meanings given in the claims.

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Continuous process for preparing dihydropyrones

5 The invention relates to an improved process for preparing dihydropyrones of general formula I,



wherein the groups R¹ and R² may have the meanings given in the claims.

10

Background to the invention

15 Dihydropyrones are important as intermediate products in drug synthesis. In particular, 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one is an important intermediate product in the synthesis of tipranavir, an HIV protease inhibitor. The compounds of formula I and processes for preparing them are known from the prior art, e.g. from International Patent Application WO 98/19997 and from the "Journal of Medicinal Chemistry, 1998, Vol. 41, No. 18". Recently, a 20 process for preparing a racemic mixture of 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one has been described, which comprises in step a) reacting a dianion of methylacetoacetate with 1-phenyl-3-hexanone and in a subsequent step b) cyclising the resulting β -ketoester by alkaline hydrolysis followed by acidification. This process is carried out discontinuously and achieves a 72% yield.

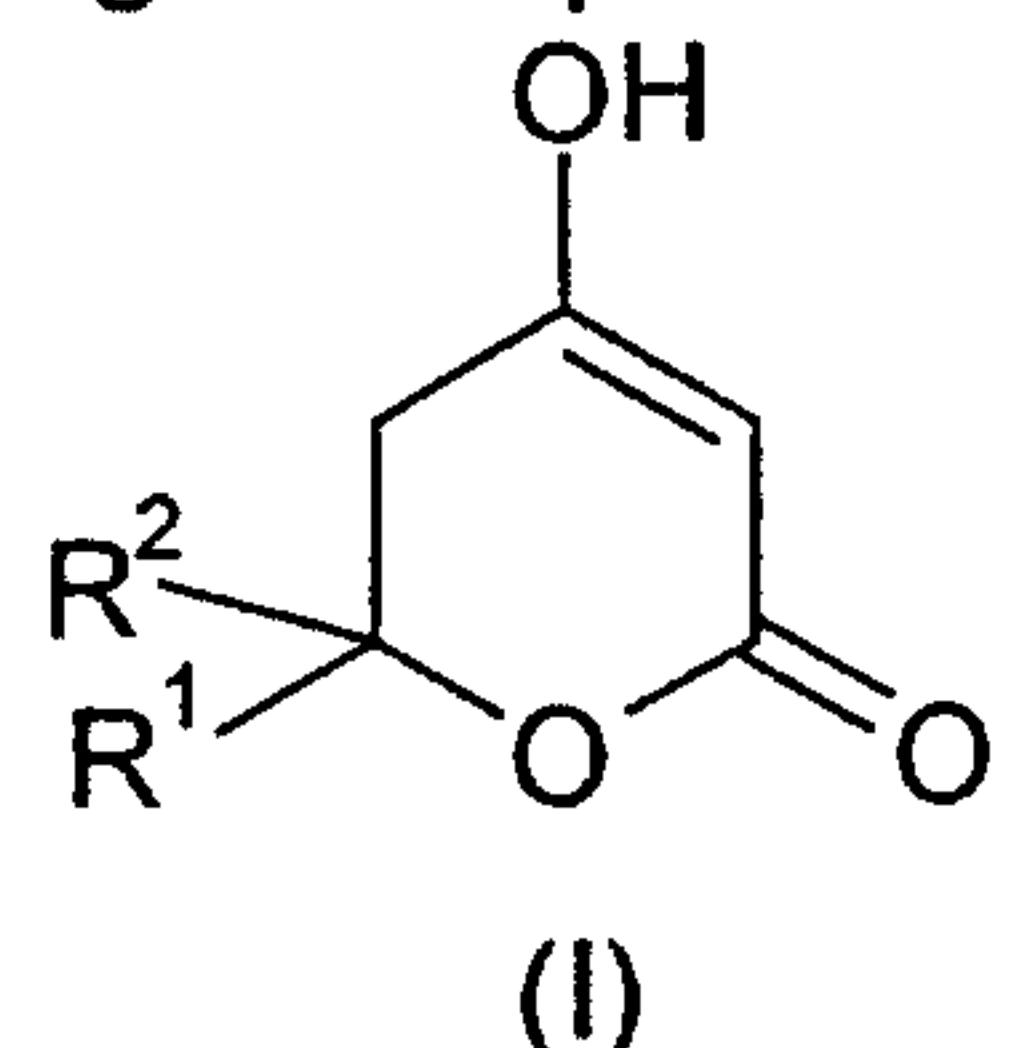
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The problem of the invention is therefore to provide a process which enables dihydropyranones to be prepared with a high degree of purity and in a significantly improved yield compared with the prior art.

Detailed description of the invention

Surprisingly, it has been found that the compounds of formula I can be obtained with a high degree of purity and in a significantly improved yield if step a) is carried 5 out continuously in a microreactor.

The invention therefore relates to a process, suitable for use in the laboratory and on an industrial scale, for preparing a compound of general formula (I),

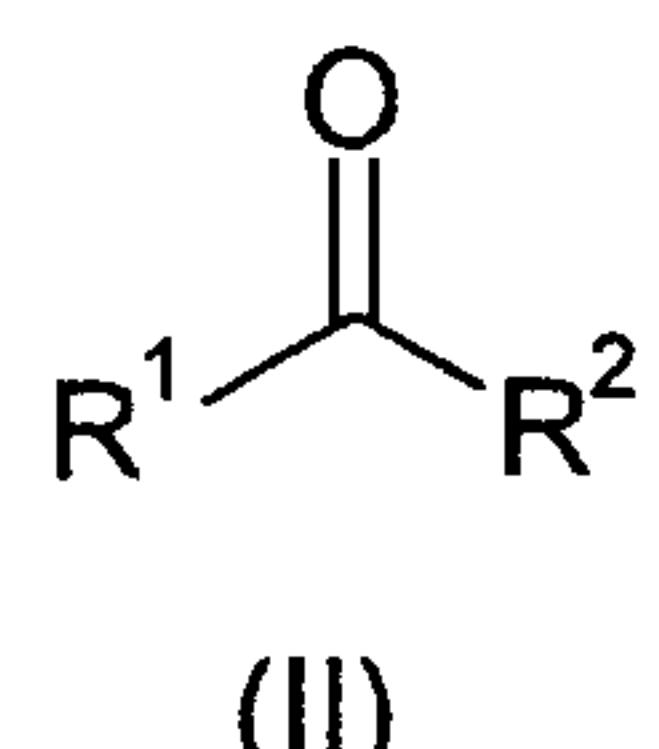


10 wherein

R^1 denotes a C_1 - C_8 -alkyl, C_6 - C_{10} -aryl- C_1 - C_4 -alkyl or C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl group, and

R^2 denotes a C_1 - C_8 -alkyl group,

15 a) by reacting a ketone of formula (II)



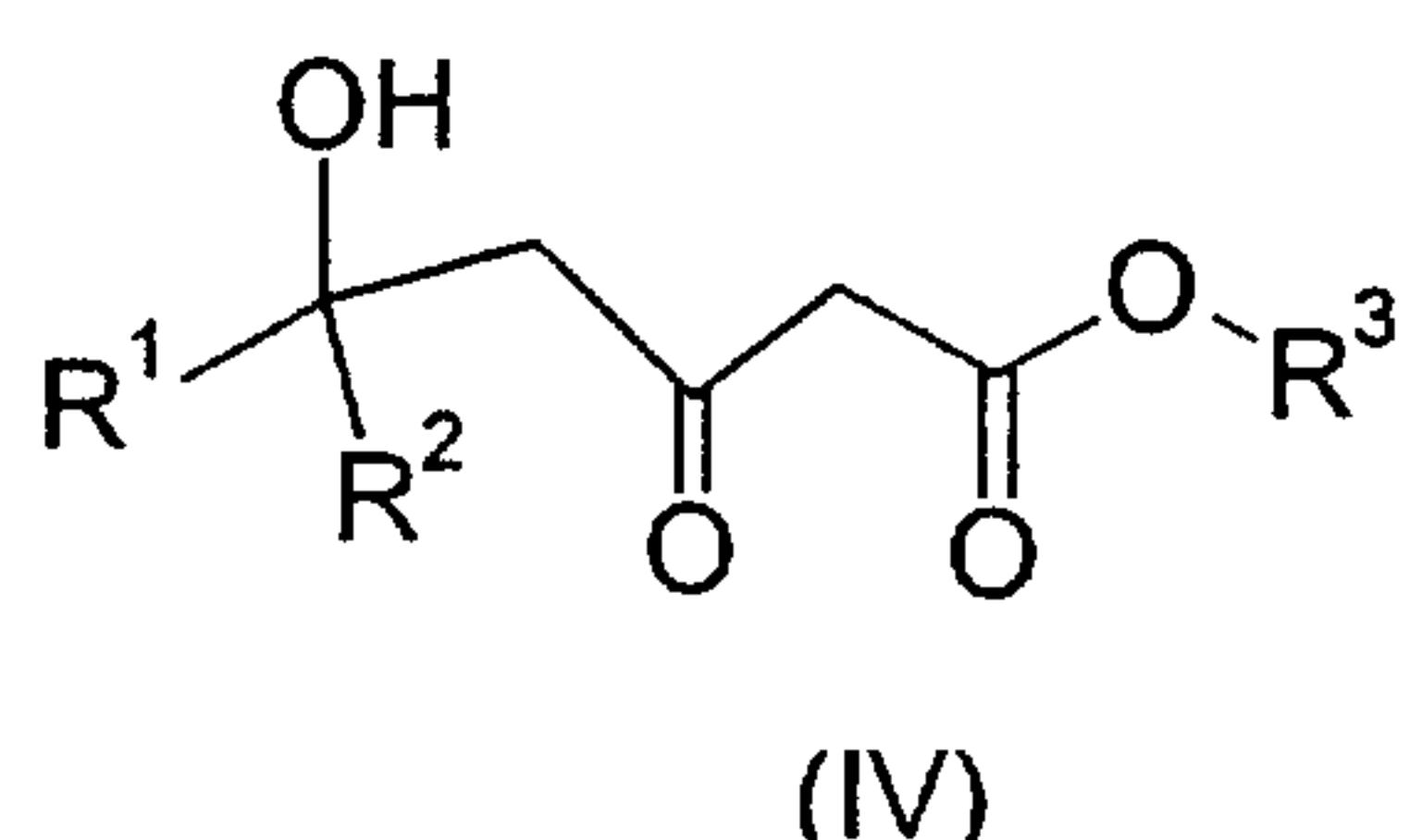
wherein R^1 and R^2 are as hereinbefore defined,

20

with an acetoacetate in the presence of a strong base

and

25 b) by cyclising the resulting compound of formula (IV)



wherein

R^3 denotes a C_1 - C_4 -alkyl or benzyl group,

5 wherein the ketone of formula II is continuously reacted with an acetoacetate in the form of its dianion in a microreactor.

The microreactors which are suitable for the process according to the invention are known, for example, from "Microreactors; Wolfgang Ehrfeld, Volker Hessel, 10 Holger Löwe; Wiley-VCH; ISBN 3-527-29590-9; Chapter 3 Micromixers". Microreactors which may be used in the process according to the invention generally have a housing made of stainless steel, glass, titanium or metal alloys and an inlay or inlay structures of thermally oxidised silicon, copper, aluminium, nickel, silver, metal alloys, Foturan glass or metal-coated plastics, glass or ceramic 15 materials.

The educt currents may be mixed both turbulently as well as by laminar flow, preferably by laminar flow. The preferred channel structures for laminar mixing generally include interdigital structures, star-shaped structures or structures of a 20 worm-type mixer. Types of microreactor which may be used for the process according to the invention may be obtained, for example, from the companies Institut für Mikrotechnik Mainz GmbH, Cellular Process Chemistry GmbH or Mikroglas AG.

25 Particularly preferred according to the invention is a process wherein a microreactor with an interdigital channel structure, most preferably a microreactor of the LIGA type (produced by **Lithographie, Galvanoformung, Abformung** [lithography, electroforming and moulding]) with an interdigital channel structure, produced for example by the Institut für Mikrotechnik Mainz GmbH, is used for 30 reaction step a).

Particularly preferred is a process wherein a current of educt A containing the compound of formula (II) and a current of educt B containing an acetoacetate in the form of a dianion are continuously mixed together in the mixing element of a 35 microreactor and the liquid reaction mixture is conveyed into a capillary, particularly a holding capillary.

Also particularly preferred is a process wherein the capillary is 0.1 to 10 m, preferably 0.3 to 8 m, preferably 0.5 to 6 m, most preferably 0.8 to 4 m, particularly preferably about 1 m long and has an internal diameter of 0.05 to 5 mm, preferably 0.1 to 4 mm, preferably 0.3 to 3 mm, particularly preferably about 1 mm.

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Particularly preferred is a process wherein 1-phenyl-3-hexanone is used as the compound of formula (II) in step a).

Also particularly preferred is a process wherein in step a) the acetoacetate is used
10 in the form of a dilithium, monolithium, monosodium or disodium salt.

Of particular importance is a process wherein the molar ratio of the compound of formula (III) to the compound of formula (II) used is 2:1 to 1:2, preferably 1:1 to 1:1.5, particularly preferably 1:1 to 1:1.2, most preferably about 1:1.

15

Also of particular importance is a process wherein the reaction in step a) is carried out at a temperature of -78 to +85 °C, preferably at -40 to +50 °C, preferably at -30 to +20 °C, more preferably at -25 to +10 °C, particularly preferably at -20 to 0 °C, most preferably at -15 to -5 °C, especially preferably at about -10 °C.

20

Also preferred is a process wherein the reaction in step a) is carried out at an overall flow rate, calculated by adding together the flow rates of the compound of formula II and the acetoacetate, of 1.5 to 5 ml/min, preferably at 1.8 to 4 ml/min, particularly preferably at 2 to 3.5 ml/min, particularly preferably at about 2.5 ml/min.

Also particularly preferred is a process wherein the flow rate of the compound of formula (II) to that of the acetoacetate is in a ratio of 1:1 to 1:2, preferably 1:1.1 to 1:1.8, particularly preferably 1:1.2 to 1:1.5, particularly preferably about 1:1.3.

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To achieve these flow rates it is generally advantageous to use low-vibration pumps, preferably rotary pumps, preferably ceramic rotary pumps or HPLC pumps. The flow rates may be adapted to different types of reactors to obtain the optimum space/time yield.

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Also particularly preferred is a process wherein the reaction is carried out in a plurality of microreactors connected in series or in parallel.

The 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one obtained according to the invention is preferably used to prepare tipranavir.

In the present invention, the term "alkyl" denotes a straight-chain or branched alkyl group with 1 to 8 carbon atoms, preferably 2 to 7 carbon atoms, preferably 3 to 6 carbon atoms. Methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec. butyl, tert.butyl, n-pentyl, isopentyl or neopentyl are particularly preferred.

The term "aryl" denotes an aromatic hydrocarbon group with 6 to 10 carbon atoms, preferably phenyl or naphthyl, particularly preferably phenyl, which may be substituted by one or more alkyl groups.

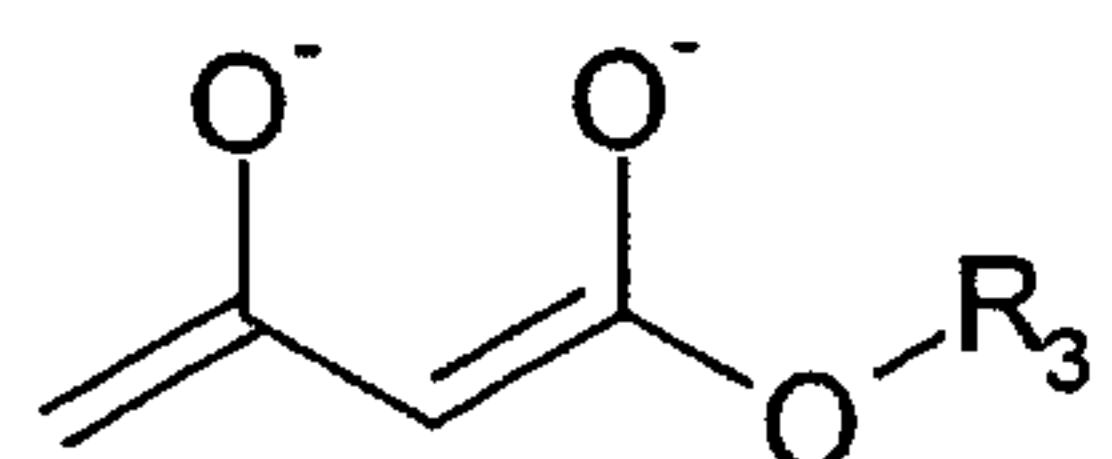
Examples of cycloalkyl groups with 3 - 8 carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

R^1 is preferably phenylmethyl, phenylethyl or phenylpropyl, most preferably 2-phenylethyl,
 R^2 is preferably methyl, ethyl, n-propyl or n-butyl, most preferably n-propyl.
 R^3 is preferably methyl, ethyl, n-propyl or benzyl, most preferably ethyl.

Metal hydrides, metal organyls, metal amides, metal dialkylamides or metal hexamethyldisilazanes are preferably used as strong bases.

Examples of metal cations include lithium, sodium, potassium, rubidium, caesium, magnesium, calcium, titanium, silicon, tin and lanthanoids, preferably lithium or sodium, most preferably lithium.

Particularly preferred bases are sodium hydride, lithium diethylamide, butyl lithium, lithium diisopropylamide, lithium hexamethyl disilazane, sodium hexamethyl disilazane or potassium hexamethyl disilazane or combinations thereof. As a rule, 2 or more equivalents of these bases are used, preferably 1.8 to 3.0, particularly 1.9 to 2.5 equivalents. The acetoacetate is generally in the form of a dianion of formula III in the presence of these bases.



(III)

The process according to the invention is generally carried out in the presence of an inert diluent. Preferred diluents are non-polar organic solvents such as e.g. aliphatic or aromatic hydrocarbons, ethers or mixtures thereof. In a particularly preferred embodiment, the diluent is selected from among dimethoxyethane, diethylether, *tert*-butyl-methylether, tetrahydrofuran, n-hexane, cyclohexane, toluene, xylene or a mixture of these solvents, particularly tetrahydrofuran and dimethoxyethane.

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10 In addition to the abovementioned diluents the reaction may also contain one or more amines such as, for example, diethylamine, diisopropylamine or tetramethylethylenediamine.

15 The advantage of the process according to the invention is in the high purity and unexpectedly high yield of dihydropyranone of more than 90 %, which results from the continuous microreactor process of step a). The compound of formula IV may be further processed as a product of the microreactor process without further purification.

20 The following examples serve to illustrate the process according to the invention still further. They are intended solely as examples of procedures without restricting the invention to their content.

Example 1: 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one

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Step a)

A mixture I of 81.9 g of 1-phenyl-3-hexanone and 840 ml of tetrahydrofuran and a mixture II of 72.9 g of ethyl-acetoacetate, 117 ml of diethylamine and 450 ml of n-butyllithium in n-hexane (2.5 molar) in 361 ml of tetrahydrofuran at -10 °C are pumped towards each other into a microreactor made by the company Institut für Mikrotechnik Mainz GmbH (of the Liga type with interdigital channel structure) and mixed together. The volume flow of mixture I is set to 1 ml/min and the volume flow of mixture II is set to 1.1 ml/min. The solution of product is passed through a capillary (length 1 m, diameter 1 mm) and then taken up in saturated ammonium chloride solution/hydrochloric acid solution at a pH of 5 - 6.

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Step b)

140 g of the crude β -ketoester resulting from step a) are taken up in 200 ml of methanol at 5 to 10 °C. Solid potassium hydroxide is added at 5 to 10 °C with stirring and then the mixture is stirred for about 15 hours at ambient temperature.

5 The methanol is distilled off and the residue is mixed with 500 ml of water. It is extracted twice with 200 ml of toluene. After the organic phase has been separated off, another 400 ml of fresh toluene are added to the aqueous phase. This is acidified with conc. sulphuric acid to pH 1.9. The aqueous phase is separated off and the organic phase is extracted 3 times more with water. The 10 organic phase is evaporated to dryness *in vacuo* (60 mbar) at 40 °C. The crude product is dissolved in 200 ml of toluene at 60 °C and then filtered. 200 ml of n-octane are slowly added dropwise to the filtrate with stirring at 40 °C. It is seeded with 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one crystals and stirred for about 15 hours at ambient temperature. 400 ml of n-octane are 15 added dropwise to the resulting crystal mass which is then cooled to 0 - 5 °C. After stirring for about 1 hour at 0 - 5 °C the crystals are suction filtered, washed with n-octane and dried. The yield is 92 %.

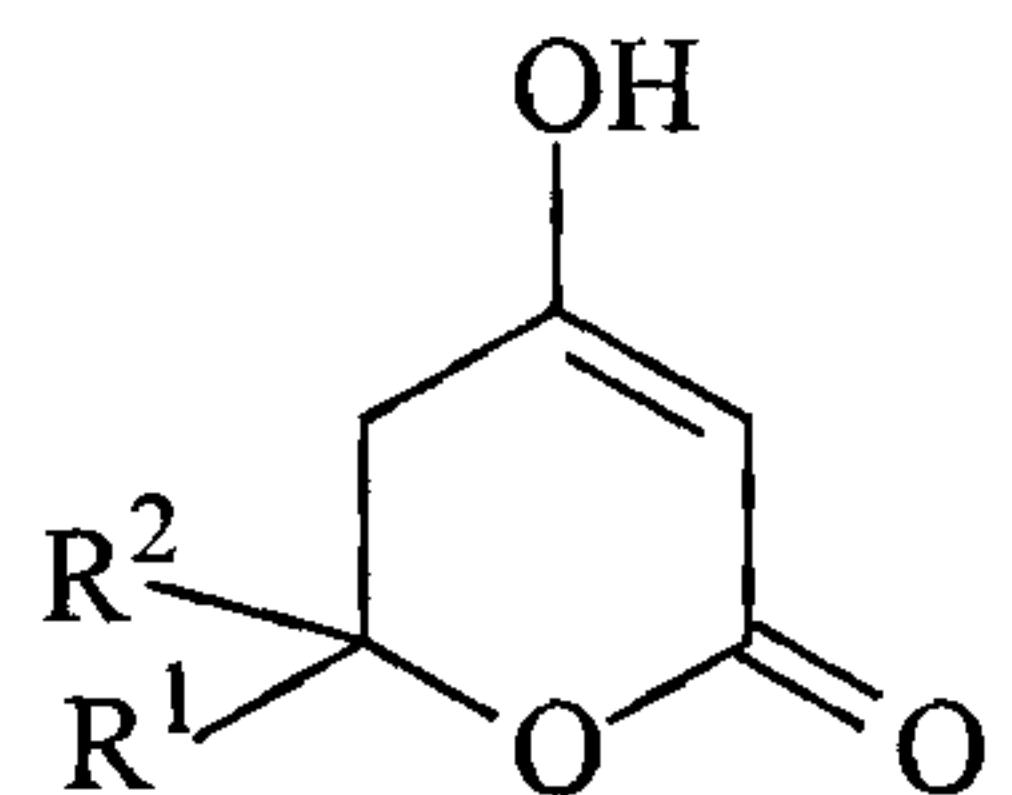
Analogously to Example 1, 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran- 20 2-one was prepared by carrying out step a) in a microreactor under the conditions specified in the following Table:

Example No.	Temperature[[°] C]	Volume flow I (1-phenyl-3-hexanone) [ml/min]	Volume flow II (Acetoacetate) [ml/min]	Yield of ketoester [HPLC % area]
2	-25	1	1	84.5
3	-25	1	1.1	87.9
4	-25	1	1.2	83.8
5	-25	1	1.3	86.4
6	-25	2	2.4	81.1
7	-20	1	1.2	87.2
8	-20	2	2.4	83.8
9	-10	1	1.2	86.5
10	-10	2	2.4	86.8
11	10	2	2.4	82.1

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CLAIMS:

1. A process for preparing a compound of general formula (I),



(I)

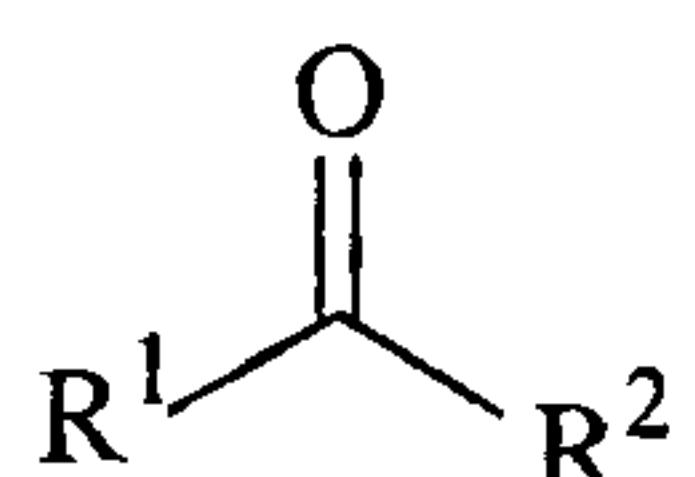
5 wherein

R^1 denotes a C_1 - C_8 -alkyl, C_6 - C_{10} -aryl- C_1 - C_4 -alkyl or C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl group, and

R^2 denotes a C_1 - C_8 -alkyl group,

the process comprising:

10 a) reacting a ketone of formula (II)



(II)

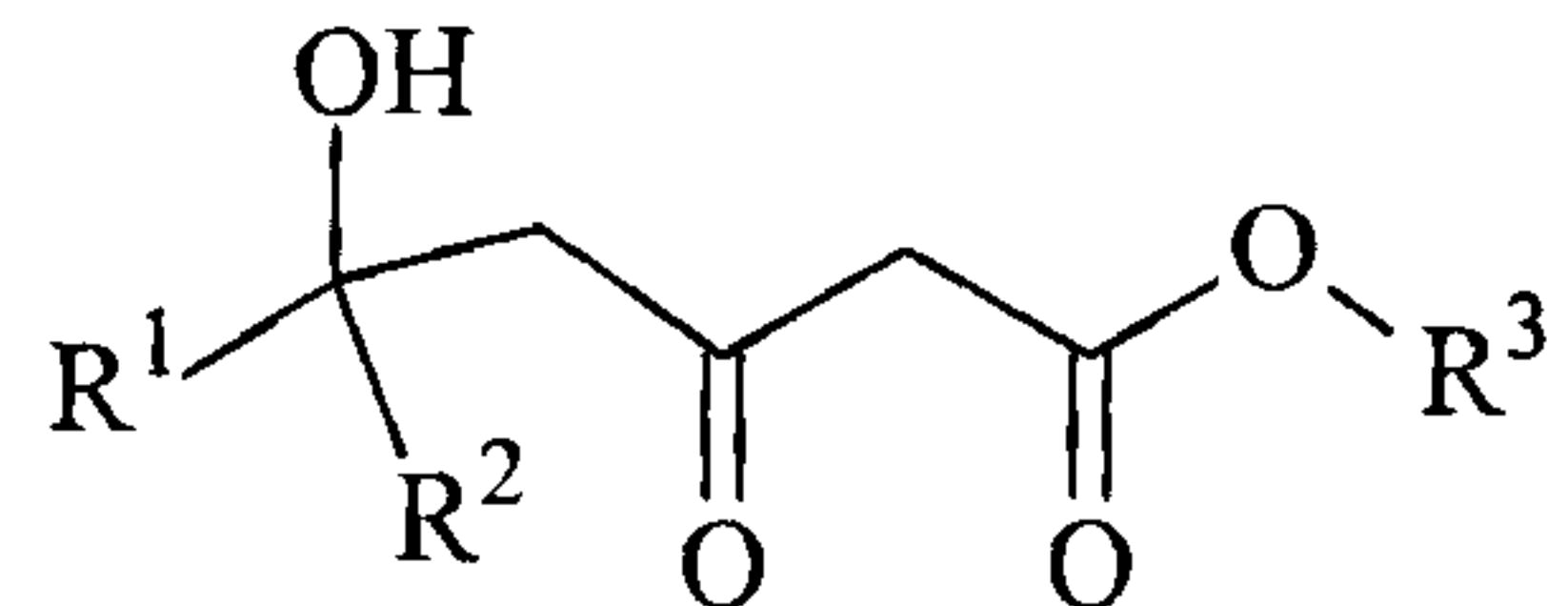
wherein R^1 and R^2 are as hereinbefore defined,

with an acetoacetate in the presence of a strong base to form a compound of formula (IV); and

15 b) cyclising the compound of formula (IV)

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(IV)

wherein

R^3 denotes a C_1-C_4 -alkyl or benzyl group,

by means of a base;

5 wherein the compound of formula II is continuously mixed and reacted with the acetoacetate in its dianion form in a microreactor.

2. The process according to claim 1, wherein the microreactor with an interdigital channel structure is used 10 for the reaction in step a).

3. The process according to claim 1 or 2, wherein a current of educt A containing the compound of formula (II) and a current of educt B containing the acetoacetate in the dianion form are continuously mixed together in a mixing 15 element of the microreactor to form a liquid reaction mixture, and the liquid reaction mixture is passed into a holding capillary.

4. The process according to claim 3, wherein the holding capillary is 0.1 to 10 m long and 0.05 to 5 mm in 20 diameter.

5. The process according to any one of claims 1 to 4, wherein 1-phenyl-3-hexanone is used as the compound of formula (II) in step a).

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6. The process according to any one of claims 1 to 5, wherein in step a) the acetoacetate is used in the presence of at least 2 equivalents of the strong base, which is sodium hydride, butyllithium or lithium dialkylamide.

5 7. The process according to any one of claims 1 to 6, wherein the acetoacetate is added to the compound of formula (II) in a molar ratio of 2:1 to 1:2.

8. The process according to any one of claims 1 to 7, wherein the reaction in step a) is carried out at a 10 temperature of from -78 to +85°C.

9. The process according to any one of claims 1 to 8, wherein the reaction in step a) is carried out at an overall flow rate of from 1.5 to 5 ml/min.

10. The process according to any one of claims 1 to 9, 15 wherein the flow rate of the compound of formula (II) to the flow rate of the acetoacetate in its dianion form is in a ratio of 1:1 to 1:2.

11. The process according to any one of claims 1 to 10, wherein the reaction is carried out in a 20 plurality of microreactors connected in series or in parallel.

12. Use of a 5,6-dihydro-4-hydroxy-6-phenethyl-6-propyl-2H-pyran-2-one obtained by the process according to any one of claims 1 to 11 for the preparation of tipranavir.

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PATENT AGENTS

