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(73)	Innehaver	Guerbet, 15, rue des Vanesses, 93420 Villepinte, Frankrike
(72)	Oppfinner	PARATIAN, Jean-Michel, 17000 LA ROCHELLE, Frankrike CERF, Martine, 17870 BREUIL-MAGNÉ, Frankrike
(74)	Fullmektig	RWS, Europa House, Chiltern Park, Chiltern Hill, SL99FG CHALFONT ST PETER, Storbritannia

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(54)	Benevnelse	<b>METHOD FOR SYNTHESISING DIESTERS OF 2-BROMO GLUTARIC ACID</b>
(56)	Anførte publikasjoner	GB-A- 577 877 FABIO CARNIATO ET AL: "A Chemical Strategy for the Relaxivity Enhancement of GdIII Chelates Anchored on Mesoporous Silica Nanoparticles", CHEMISTRY A EUROPEAN JOURNAL, vol. 16, no. 35, 28 juillet 2010 (2010-07-28), pages 10727-10734, XP055315985, DE ISSN: 0947-6539, DOI: 10.1002/chem.201000499

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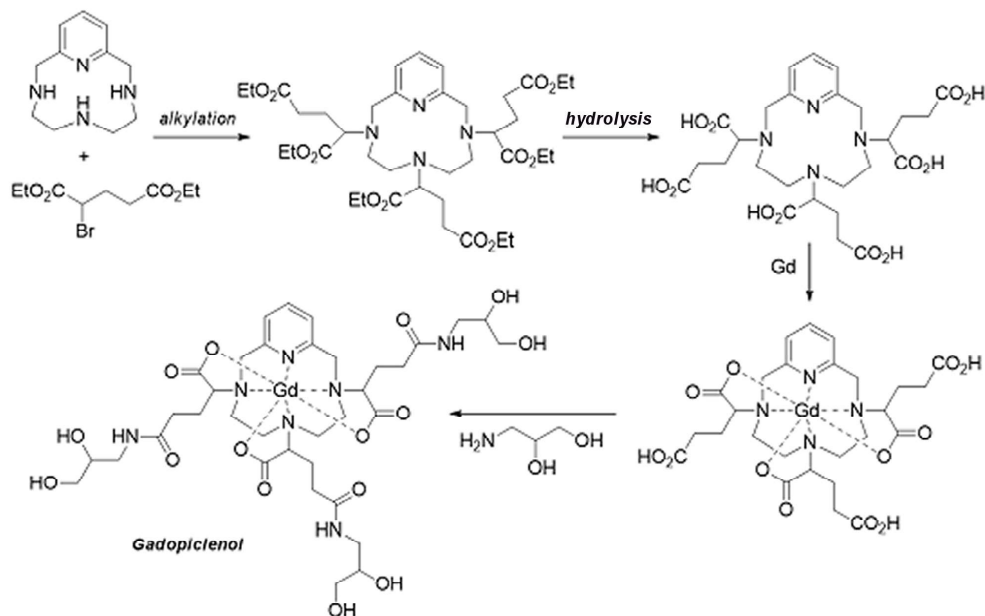
## Description

The present invention relates to a novel process for preparing 2-bromoglutaric acid diesters.

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$\alpha$ -Haloglutaric acids and esters thereof are useful basic building blocks in organic synthesis, which make it possible to incorporate, into a complex molecule, an  $\alpha$ -glutaric acid fragment via a simple nucleophilic substitution reaction.

- 10 EP 1 931 673 describes novel gadolinium complexes derived from PCTA, which have applications as contrast agents in the field of medical imaging. The side chains of some of these complexes, notably of gadopiclesol, include an  $\alpha$ -glutaric acid fragment. The synthesis of gadopiclesol, in the form of a mixture of all its stereoisomers, as described in EP 1 931 673, involves the alkylation of pyclene with diethyl 2-bromoglutarate, resulting
- 15 in an intermediate hexaester, which is then hydrolyzed to give the corresponding hexaacid, which is then complexed with a source of gadolinium. The gadopiclesol prepared according to the process described in EP 1 931 673 is finally obtained by reacting the gadolinium hexaacid complex with 3-amino-1,2-propanediol.



### 20 Synthesis of gadopiclesol

Diethyl 2-bromoglutarate (referred to as EBG hereinbelow) is a relatively unstable compound, which degrades over time, under the effect of the temperature or in the presence of water. More precisely, this particular  $\alpha$ -haloglutaric ester has a tendency to become hydrolyzed or to cyclize and thus to lose its bromine atom. Attempts to purify

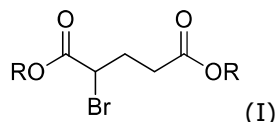
commercial EBG, or to develop novel synthetic routes for obtaining it with improved purity, and thus preventing its degradation, have been unfruitful.

5 The inventors thus sought an alternative to EBG, which would be more stable than it, while at the same time being sufficiently reactive to achieve the synthesis of gadopiclesol, for example. Thus, chloro derivatives of glutaric acid, which meet the criterion of improved stability relative to EBG, do not constitute a satisfactory option, insofar as they do not have sufficient reactivity. Iodo derivatives are, for their part, more reactive than their bromo analogs, but are also more unstable. The investigations conducted by the inventors  
10 enabled them to select di-(C<sub>3</sub>-C<sub>6</sub>)-alkyl 2-bromoglutarate compounds as an alternative to EBG, in particular in the synthesis of gadopiclesol. However, the corresponding commercial products do not have a high enough degree of purity to be used in the preparation of a pharmaceutical product intended for human administration, such as gadopiclesol.

15 It is thus necessary to develop a novel process for preparing di-(C<sub>3</sub>-C<sub>6</sub>)-alkyl 2-bromoglutarate compounds, which enables them to be obtained with a sufficient degree of purity, and which can be performed efficiently on an industrial scale.

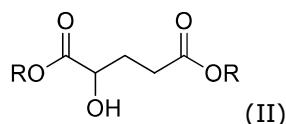
Now, the synthesis of 2-bromoglutaric acid diesters is very sparingly described in the  
20 literature. Patent CS 209266 B1, granted in 1983, is, to the inventors' knowledge, the only document that mentions the preparation of these compounds. It relates in general to a process for preparing an  $\alpha$ -haloglutaric acid or an alkyl diester thereof of formula  $R'O_2CCH_2CH_2CH(X)CO_2R''$ , in which R' and R'' are (C<sub>1</sub>-C<sub>5</sub>)alkyl groups and X corresponds to a bromine or chlorine atom, the emphasis however being clearly placed on the  
25 preparation of the chloro derivatives. Said derivatives are obtained by chlorination of the glutaric acid diester in the presence of an antimony-based catalyst. Although said document asserts that the method described makes it possible to perform monochlorination in the  $\alpha$  position with better selectivity than in the processes of the prior art, the fact remains that appreciable amounts of  $\beta$ -chloro or  $\alpha$ -dichloro and trichloro  
30 derivatives are formed, the selectivity with respect to the  $\alpha$ -monochloro product ranging between 63.16% and 86.1% depending on the nature of the antimony-based catalyst, the degree of conversion of the starting ester itself oscillating between 86.10% and 98.9%. It should be noted that the conditions for which the degree of conversion of the starting material is the highest allow the  $\alpha$ -monochloro product to be obtained with a selectivity of  
35 only 79%. Another major drawback of this process is, moreover, the use of antimony, which is extremely toxic. Chemistry: A European Journal, Vol. 16, No. 35, pages 10727-10734, describes an (S)-2-bromopentanedioic di-tert-butyl ester compound. GB 577 877 A discloses a process for preparing monobrominated dicarboxylic acids and esters.

The present invention thus relates to a process for preparing the 2-bromoglutaric acid diester of formula (I) below:

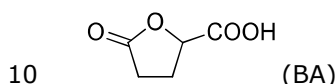


- 5 in which R represents a (C<sub>3</sub>-C<sub>6</sub>)alkyl group,  
comprising the following steps:

**(b)** formation of the 2-hydroxyglutaric acid diester of formula (II)



by reaction of butyrolactone acid of formula (BA)



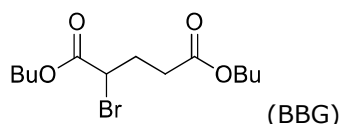
with the alcohol of formula ROH, in the presence of an acid such as sulfuric acid; and

**(c)** bromination of the 2-hydroxyglutaric acid diester of formula (II), by sparging with gaseous hydrobromic acid, leading to the 2-bromoglutaric acid diester of formula (I).

- 15 For the purposes of the present invention, the term "(C<sub>3</sub>-C<sub>6</sub>)alkyl group" means a linear or branched, saturated hydrocarbon-based chain including 3 to 6 carbon atoms. By way of example, mention may be made of propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl or hexyl groups, in particular the *n*-butyl group, also referred to as butyl.

- 20 The butyrolactone acid of formula (BA) is also referred to as carboxy-γ-butyrolactone.

According to a preferred embodiment, R corresponds to a butyl group, and the process according to the invention makes it possible to prepare dibutyl 2-bromoglutarate of formula (BBG), also known as dibutyl 2-bromo-1,5-pentanedioate (CAS No: 104867-13-2).



In a particular embodiment, the process according to the invention comprises a first step **(a)** of forming butyrolactone acid of formula (BA) by reacting L-glutamic acid with sodium nitrite in aqueous solution.

**Step (a)**

This first step consists in forming butyrolactone acid (BA) from L-glutamic acid, a commonly available starting material, according to a reaction that is well known to those skilled in the art.

L-Glutamic acid is introduced into water, the ratio of the mass of water used to the mass of L-glutamic acid introduced typically being greater than 1, notably greater than 1.5, typically equal to 2. The density of water being equal to 1 g/mL, in the continuation of the description, such a ratio of the mass of water (or, by analogy, of any other solvent or solution) to the mass of a solute will be designated by the expression "volume equivalent" or its abbreviation "vol. eq.".

Preferentially, the water used in the process is water of at least the same quality as deionized water, so as to avoid the formation of impurities, such as an  $\alpha$ -chloro impurity. In particular, it may be deionized water or water for injection (WFI).

The resulting aqueous solution is then typically heated with stirring, to a temperature advantageously between 40°C and 70°C, in particular between 45°C and 65°C, preferably between 50°C and 60°C, notably at 55°C.

An aqueous sodium nitrite solution is then added gradually to the L-glutamic acid solution, preferably with stirring and while maintaining the previously established temperature.

Said aqueous sodium nitrite solution is such that the amount of water used represents, for example, between 0.8 and 5.0 vol. eq., notably between 1.0 and 3.0 vol. eq., typically 2 vol. eq. relative to the mass of sodium nitrite which it contains.

The sodium nitrite may notably be introduced into the L-glutamic acid solution in slight excess relative to the stoichiometric proportions. The ratio of the amount of material introduced as sodium nitrite to the amount of material initially introduced as L-glutamic acid is then greater than 1, but typically less than 1.5, notably less than 1.3, advantageously less than 1.2. In other words, the amount of sodium nitrite introduced is greater than 1 molar equivalent (mol. eq.), but typically less than 1.5 mol. eq., notably less than 1.3 mol. eq., advantageously less than 1.2 mol. eq., relative to the amount of L-glutamic acid initially introduced, which itself corresponds to 1 molar equivalent.

The reaction mixture comprising sodium nitrite and L-glutamic acid is then typically kept under stirring at a temperature advantageously between 40°C and 70°C, in particular between 45°C and 65°C, preferably between 50°C and 60°C, notably at 55°C, for a period of time allowing the various compounds present in solution to be dissolved, typically between 2h and 10h, preferably between 2h and 5h.

It is then cooled to a temperature advantageously between 10°C and 45°C, preferentially between 10°C and 35°C, in particular between 15°C and 30°C, preferably between 20°C and 25°C, and then neutralized by addition of an acid solution, for example hydrochloric acid, preferably at 33% m/m, the amount of material introduced as hydrochloric acid then being close to, typically equal to Thus, the amount of material introduced as hydrochloric acid is greater than 1 molar equivalent (mol. eq.), but typically less than 1.5 mol. eq., notably less than 1.3 mol. eq., advantageously less than 1.2 mol. eq., relative to the amount of L-glutamic acid initially introduced.

The reaction mixture thus neutralized is then typically concentrated under vacuum, by gradually increasing the temperature, up to a value above 50°C, for example 60°C.

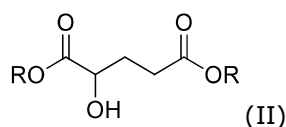
In the continuation of the description, the expression "under vacuum" is intended to denote a pressure of between 10 and 500 mbar, notably between 10 and 350 mbar, preferably between 10 and 150 mbar, in particular between 50 and 100 mbar, the temperature being specified, where appropriate.

As regards the vacuum concentration operation for producing crude butyrolactone acid (BA) on conclusion of step **(a)**, this is typically performed at a pressure of less than 100 mbar by gradually increasing the temperature until it reaches 60°C.

Preferentially, steps **(a)** and **(b)** are performed according to a one-pot embodiment, i.e. without an intermediate step of isolation or purification.

### **Step (b)**

Step **(b)** is directed toward forming the 2-hydroxyglutaric acid diester of formula (II)



by reaction of butyrolactone acid of formula (BA) with the alcohol of formula ROH.

In a preferred embodiment, butyrolactone acid (BA) is obtained from step **(a)** described previously, and has not been purified before being employed in step **(b)**.

During this step, the opening of the lactone and the formation of the two ester functions  
 5 -C(O)OR take place concomitantly or successively.

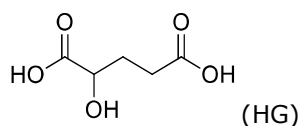
The alcohol ROH is preferably introduced in excess relative to the butyrolactone acid. Thus, the amount of ROH introduced is preferably greater than or equal to 2 molar equivalents (mol. eq.), notably greater than or equal to 4 mol. eq., advantageously between 2 and 10  
 10 mol. eq., in particular between 4 and 10 mol. eq., typically equal to 5 mol. eq., relative to the amount of butyrolactone acid initially introduced. It should be noted that when the butyrolactone acid is obtained from step **(a)**, the amount of ROH introduced is expressed relative to the amount of L-glutamic acid initially introduced, the number of mol. eq. indicated remaining unchanged.

15

In a preferred embodiment, step **(b)** is performed in the presence of the acetate of formula  $\text{CH}_3\text{COOR}$ . The amount of acetate introduced is then typically between 0.1 and 0.7 mol. eq., notably between 0.2 and 0.5 mol. eq., advantageously between 0.3 and 0.4 mol. eq., relative to the amount of alcohol ROH introduced.

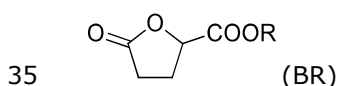
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The formation of the two ester functions -C(O)OR, which takes place during step **(b)**, may advantageously be performed by acid catalysis. Thus, step **(b)** is preferably performed in the presence of a catalytic amount of acid, for example sulfuric acid. Under such conditions, the lactone is liable to open up to form the 2-hydroxyglutaric acid of formula  
 25 (HG), the esterification of its carboxylic acid functions with the alcohol ROH subsequently taking place.



Thus, step **(b)** of the process according to the invention also comprises the formation of  
 30 the 2-hydroxyglutaric acid diester of formula (II) by reaction of 2-hydroxyglutaric acid of formula (HG) with the alcohol of formula ROH.

Conversely, butyrolactone acid (BA) can undergo a first esterification reaction before ring opening, to form the following esterified lactone of formula (BR) below.



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Thus, step **(b)** of the process according to the invention also comprises the formation of the 2-hydroxyglutaric acid diester of formula (II) by reaction of the esterified lactone of formula (BR) with the alcohol of formula ROH.

- 5 As will emerge clearly to those skilled in the art, the process according to the invention may be performed using as starting material for step **(b)** 2-hydroxyglutaric acid of formula (HG) or the esterified lactone of formula (BR) as an alternative to butyrolactone acid (BA).

10 In a preferred embodiment, the water present in the reaction mixture of step **(b)**, typically formed *in situ*, is removed by vacuum distillation, until a reaction medium having a mass fraction of water of less than 2% w/w, preferably less than 1.5% w/w, advantageously less than 0.8% w/w, is obtained.

15 Said reaction mixture of step **(b)** also notably comprises butyrolactone acid of formula (BA), the alcohol of formula ROH, and advantageously acetate of formula CH<sub>3</sub>COOR.

Advantageously, the vacuum distillation is a vacuum azeotropic distillation.

20 For the purposes of the present invention, the term "vacuum azeotropic distillation" means the distillation of an azeotropic mixture performed at a pressure of between 10 and 500 mbar, notably between 10 and 350 mbar, preferably between 10 and 150 mbar, in particular between 50 and 100 mbar, which makes it possible to remove one of the constituents of the azeotropic mixture.

25 In the present case, the azeotropic mixture is a water/ROH/CH<sub>3</sub>COOR ternary azeotropic mixture, and the vacuum azeotropic distillation allows the water to be removed from the mixture.

30 According to a preferred embodiment, R corresponds to a butyl group (Bu), and the azeotropic mixture is a water/BuOH/CH<sub>3</sub>COOBu ternary mixture. This azeotrope is characterized by a boiling point of between 85°C and 95°C, more precisely between 87°C and 93°C, even more precisely between 89°C and 91.5°C, typically equal to 89.4°C, at atmospheric pressure.

35 The vacuum azeotropic distillation of the water/BuOH/CH<sub>3</sub>COOBu ternary mixture is typically performed at a pressure of between 10 and 500 mbar, notably between 10 and 350 mbar, preferably between 10 and 150 mbar, in particular between 50 and 125 mbar, and at a temperature of between 20°C and 100°C, notably between 30°C and 70°C.

In a preferred embodiment, on conclusion of step **(b)**, the reaction medium is cooled to a temperature below 15°C, notably below 10°C, in particular between 0°C and 5°C.

- 5 This cooling step typically takes place after the vacuum distillation, which is preferably a vacuum azeotropic distillation of the reaction mixture, as described previously.

In a preferred embodiment, on conclusion of step **(b)**, the cooled reaction medium is left to separate by settling after addition of water so as to obtain the formation of an organic  
10 phase and a separate aqueous phase, said aqueous phase then being removed.

This operation is advantageously performed several times, typically between 2 and 5 times, in particular 3 times.

- 15 The amount of water added represents, for example, between 0.1 and 2 vol. eq. relative to the mass of butyrolactone acid initially used. It should be noted that when the butyrolactone acid comes from step **(a)**, the amount of water added is expressed relative to the mass of L-glutamic acid initially introduced, the number of vol. eq. remaining unchanged.

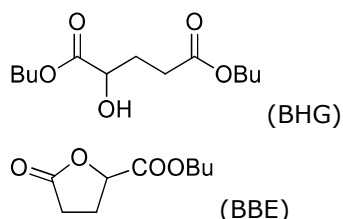
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When the water addition/separation by settling operation is performed several times, the amount of water added for the first cycle is typically between 1 and 2 vol. eq., and the amount of water added for the following cycles is typically between 0.1 and 0.5 vol. eq.

- 25 The reaction medium obtained on conclusion of step **(b)**, preferably the organic phase recovered after the water addition/separation by settling operation(s), typically comprises the 2-hydroxyglutaric acid diester of formula (II) as the majority species, and also the esterified lactone of formula (BR), in solution in the alcohol ROH, advantageously as a mixture with the acetate of formula  $\text{CH}_3\text{COOR}$ .

30

- According to a preferred embodiment, R corresponds to a butyl group (Bu), and the reaction medium obtained on conclusion of step **(b)**, preferably the organic phase recovered after the water addition/separation by settling operation(s), typically comprises dibutyl 2-hydroxyglutarate of formula (BHG) as the majority species, and also the  
35 butyrolactone acid butyl ester of formula (BBE), in solution in butanol BuOH, advantageously as a mixture with butyl acetate  $\text{CH}_3\text{COOBu}$ .



In a preferred embodiment, the reaction medium obtained on conclusion of step **(b)**, preferably the organic phase recovered after the water addition/separation by settling operation(s), is then dehydrated by vacuum distillation, at a pressure of between 10 and 500 mbar, notably between 10 and 350 mbar, preferably between 10 and 150 mbar, in particular between 50 and 100 mbar.

Advantageously, this is a vacuum azeotropic distillation of the water/ROH/CH<sub>3</sub>COOR mixture, in particular water/BuOH/CH<sub>3</sub>COOBu, and vacuum azeotropic distillation allows the water to be removed from the mixture.

In a preferred embodiment, the reaction medium obtained on conclusion of step **(b)**, preferably the organic phase recovered after the water addition/separation by settling operation(s), advantageously dehydrated by vacuum distillation, at a pressure of between 10 and 500 mbar, in particular between 10 and 350 mbar, preferably between 10 and 150 mbar, in particular between 50 and 100 mbar, is then concentrated under vacuum before being subjected to step **(c)**, so as to remove some of the ROH/CH<sub>3</sub>COOR mixture, in particular BuOH/CH<sub>3</sub>COOBu.

The amount of said mixture removed is typically between 1 and 2 vol. eq. relative to the mass of butyrolactone acid initially used or relative to the mass of L-glutamic acid initially introduced when the butyrolactone acid is obtained from step **(a)**.

In the continuation of the description, the operations of cooling, addition of water/separation by settling, dehydration by vacuum distillation and/or concentration under vacuum described previously are considered to be an integral part of step **(b)** when they are performed.

Preferentially, steps **(b)** and **(c)** are performed according to a one-pot embodiment, i.e. without an intermediate step of isolation or purification.

### **Step (c)**

Step **(c)** is directed toward forming the 2-bromoglutaric acid diester of formula (I) by bromination of the 2-hydroxyglutaric acid diester of formula (II) obtained in step **(b)**.

As will emerge clearly to a person skilled in the art from the detailed description of step **(b)**, the reaction medium obtained on conclusion of step **(b)** typically comprises the 2-hydroxyglutaric acid diester of formula (II) as the majority species, along with the esterified lactone of formula (BR), in solution in the alcohol ROH, advantageously as a mixture with the acetate of formula  $\text{CH}_3\text{COOR}$ .

Consequently, although step **(c)** is directed toward forming the 2-bromoglutaric acid diester of formula (I) by bromination of the 2-hydroxyglutaric acid diester of formula (II), the formation of the 2-hydroxyglutaric acid diester of formula (II) by reaction of the esterified lactone of formula (BR) with the alcohol ROH can typically continue during this step, the opening of the lactone being facilitated by the introduction of the brominating agent into the reaction medium.

Step **(c)** typically begins by setting the temperature of the reaction medium to a value of between  $5^\circ\text{C}$  and  $40^\circ\text{C}$ , advantageously between  $10^\circ\text{C}$  and  $30^\circ\text{C}$ , in particular to  $20^\circ\text{C}$ .

Gaseous hydrobromic acid is then gradually introduced into the reaction medium by sparging.

In a preferred embodiment, the amount of gaseous hydrobromic acid introduced is then typically between 1 and 1.5 mol. eq., notably between 1.2 and 1.3 mol. eq., relative to the amount of butyrolactone acid used in step **(b)** or relative to the amount of L-glutamic acid initially introduced in step **(a)**.

In a preferred embodiment, the reaction medium obtained after introduction of the gaseous hydrobromic acid is then dehydrated by vacuum distillation, at a pressure typically between 10 and 500 mbar, notably between 10 and 350 mbar, preferably between 10 and 150 mbar, in particular between 50 and 100 mbar, for a time typically between 3h and 8h, advantageously between 5h and 7h.

Advantageously, the vacuum distillation is a vacuum azeotropic distillation of the water/ROH/ $\text{CH}_3\text{COOR}$  mixture, in particular water/BuOH/ $\text{CH}_3\text{COOBu}$ . Such a vacuum azeotropic distillation allows the water to be removed from the mixture.

The temperature of the reaction medium is then typically restored to a value of between 5°C and 40°C, advantageously between 10°C and 30°C, in particular to 20°C.

5 In a preferred embodiment, the cycle of operations described previously, namely setting the temperature of the reaction medium to a value of between 5°C and 40°C, introducing gaseous hydrobromic acid in an amount typically between 1 and 1.5 mol. eq. relative to the amount of butyrolactone acid used in step **(b)** or relative to the amount of L-glutamic acid initially introduced in step **(a)**, vacuum distillation for a period of between 3h and 8h so as to remove water from the reaction medium, and restoring the temperature of the  
10 reaction medium to a value of between 5°C and 40°C, is repeated from 3 to 8 times, preferably from 4 to 6 times.

The reaction medium obtained on conclusion of step **(c)** typically comprises the 2-bromoglutaric acid diester of formula (I) in solution in the alcohol ROH, advantageously  
15 as a mixture with the acetate of formula  $\text{CH}_3\text{COOR}$ .

According to a preferred embodiment, R corresponds to a butyl group and the reaction medium obtained on conclusion of step **(c)** typically comprises dibutyl 2-bromoglutarate of formula (BBG) in solution in butanol BuOH, advantageously as a mixture with butyl  
20 acetate  $\text{CH}_3\text{COOBu}$ .

Alternatively, the hydrobromic acid can be formed *in situ* during the azeotropic distillation. In this alternative, a bromine salt, typically NaBr or KBr, is introduced into the reaction medium in place of the gaseous hydrobromic acid, and a strong acid, such as concentrated  
25 sulfuric acid (>96%), is then added.

A person skilled in the art will know how to adapt the subsequent treatment steps of the process accordingly, in particular so as to remove the salts present, for example sulfate salts, in the case of this alternative embodiment.

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#### **Steps (d) - (e)**

In a preferred embodiment of the process according to the invention, the reaction mixture obtained on conclusion of step **(c)** is subjected to the following additional steps:  
35 **(d)** introduction of the reaction mixture obtained on conclusion of step **(c)** into a basic aqueous solution, the solution obtained having a pH typically between 7.5 and 9.5;

**(e)** separation by settling of the solution obtained in step **(d)**, so as to obtain the formation of an organic phase and a separate aqueous phase, said aqueous phase being then removed;

**(f)** concentration under vacuum of the organic phase obtained in step **(e)**, until a  
5 temperature of between 65°C and 75°C is reached, followed by drying under vacuum;

**(g)** optionally, filtration,  
and recovery of the 2-bromoglutaric acid diester of formula (I).

In an alternative embodiment, steps **(d)** and **(e)** are not performed and step **(f)** is  
10 performed directly on the reaction mixture obtained on conclusion of step **(c)**, and is optionally followed by a filtration step **(g)**.

Step **(d)** may notably be performed by adding the reaction mixture obtained on conclusion of step **(c)** to an aqueous solution of bicarbonate ion, also called hydrogen carbonate, the  
15 amounts of potassium or sodium bicarbonate and water employed being able to be determined by a person skilled in the art so as to obtain, on conclusion of step **(d)**, a solution having a pH typically between 7.5 and 9.5, in particular between 8 and 9, and to be able to perform separation between an aqueous and an organic phase during step **(e)**.

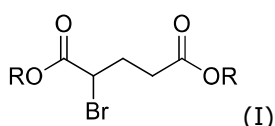
20 The organic phase obtained in step **(e)** or the reaction mixture obtained on conclusion of step **(c)** is then concentrated under vacuum in step **(f)**, at a pressure typically between 10 and 500 mbar, notably between 10 and 350 mbar, preferably between 10 and 150 mbar, in particular between 50 and 100 mbar, until a temperature above 50°C is reached, in particular above 60°C, for example 70°C, so as to remove some of the ROH/CH<sub>3</sub>COOR  
25 mixture, and then dried under vacuum, at a pressure typically between 10 and 350 mbar, preferably between 50 and 150 mbar, in particular between 50 and 100 mbar, until a temperature above 50°C is reached, in particular above 60°C, for example 70°C.

This step may be followed by a filtration step **(g)**, which may be performed using any  
30 method that is well known to those skilled in the art.

The process according to the invention makes it possible to obtain the 2-bromoglutaric acid diester of formula (I) in a yield of greater than 85%, advantageously greater than 90%, and a degree of purity, determined by HPLC analysis, of greater than or equal to  
35 90%, in particular greater than or equal to 93%, typically greater than or equal to 95%, preferably greater than or equal to 97%, notably greater than or equal to 98%, advantageously greater than or equal to 99%.

According to a preferred embodiment, R corresponds to a butyl group, and the process according to the invention makes it possible to prepare dibutyl 2-bromoglutarate of formula (BBG) in a yield and with a degree of purity as stated previously.

- 5 The present invention thus further relates to a 2-bromoglutaric acid diester of formula (I) below:



- in which R represents a (C<sub>3</sub>-C<sub>6</sub>)alkyl group, preferably a butyl group, having a degree of purity, determined by HPLC analysis, of greater than or equal to 90%,  
 10 in particular greater than or equal to 93%, typically greater than or equal to 95%, preferably greater than or equal to 97%, notably greater than or equal to 98%, advantageously greater than or equal to 99%.

### **Racemization step**

- 15 The 2-bromoglutaric acid diester of formula (I) may be obtained with a variable enantiomeric excess. If it is not racemic, it is possible to racemize it in an additional racemization step using a bromine salt, such as LiBr or tetrabutylammonium bromide, according to methods that are well known to those skilled in the art.

### **FIGURES**

Figure 1 shows the mass spectrum of BBG.

### **EXAMPLES**

- 25 The following abbreviations are used:

BBG:	dibutyl 2-bromoglutarate
Bu:	butyl
ee:	enantiomeric excess
HPLC:	High Performance Liquid Chromatography
NMR:	nuclear magnetic resonance
TBAB:	tetrabutylammonium bromide

### **I. Synthesis of dibutyl 2-bromoglutarate**

### I.1. Protocol

- 147.1 g (1 mol) of L-glutamic acid are dissolved in 294 g of water. This solution is heated to 55°C±5°C. 76 g (1.1 mol) of sodium nitrite dissolved in 152 g of water are slowly added.
- 5 Contact is maintained for at least 2 hours at 55°C±5°C until dissolution is complete, and the solution is then cooled to 20-25°C. After neutralization with about 122 g (1.1 mol) of 33% hydrochloric acid, the medium is concentrated under vacuum (< 100 mbar) by gradually increasing the temperature to 60°C.
- 10 The butyrolactone acid obtained is esterified with 370 g (5 mol) of butanol in the presence of 206 g of butyl acetate and 1.47 g (0.015 mol) of sulfuric acid under azeotropic distillation and under vacuum. The reaction medium is then cooled to 0-5°C and taken up in 221 g of water. The lower aqueous phase is removed and the organic phase washed twice more with 30 g of water. The organic phase obtained contains a mixture of butyl
- 15 hydroxyglutarate/butyl ester of butyrolactone (HPLC s/s: 90/10). The mixture is dehydrated by azeotropic distillation under 50-100 mbar and then concentrated by removing the equivalent of 195 g of solvent.

- The bromination is performed by performing the following operations five times in succession: sparging with 100 g (1.2 mol) of hydrobromic acid at 20±10°C, azeotropic
- 20 distillation under vacuum for at least 5 hours. The reaction medium is washed with an aqueous solution of 6 g of potassium hydrogen carbonate dissolved in about 60 g of water. The aqueous phase is discarded and the organic phase is washed with water and then concentrated under vacuum until a temperature of about 70°C is reached. BBG is obtained
- 25 in a yield of 90% and a purity of 97.1% s/s as determined by HPLC.

### I.2. Characterization of BBG

- Boiling point 115-120°C/0.03-0.04 kPa (0.2-0.3 mmHg), i.e. about 380°C at atmospheric
- 30 pressure.
- NMR performed on a JEOL 500 MHz machine:
- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) 4.34-4.39 (m, 1H, Br-CH-COO), 4.16-4.22 (m, 2H, Br-CH-COOCH<sub>2</sub>), 4.06-4.11 (m, 2H, CH<sub>2</sub>-COOCH<sub>2</sub>), 2.50-2.59 (m, 2H, OOC-CH<sub>2</sub>-CH<sub>2</sub>-CHBr), 2.25-2.43 (m, 2H, OOC-CH<sub>2</sub>-CH<sub>2</sub>-CHBr), 1.55-1.69 (m, 4H, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 1.34-1.45 (m,
- 35 4H, CH<sub>3</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 0.92-0.96 (m, 6H, CH<sub>3</sub>-CH<sub>2</sub>-CH<sub>2</sub>)
- Mass spectrometry



The presence of bromine in the molecule was confirmed by a mass spectrum performed using a Waters QDa mass spectrometer coupled to a Waters I-Class UHPLC machine. The mass spectrum recording was performed in positive electrospray mode at a cone voltage of 10 V.

5 The mass spectrum obtained is shown in Figure 1.

The doublets with a difference of 2 confirm the presence of bromine in the molecule.

The mass at 323-325 corresponds to the parent peak, and the mass at 249-251 to the loss of butoxide.

### 10 **I.3. HPLC analysis**

- **Equipment:**

- HPLC machine consisting of a pumping system, an injector, a chromatography column, a UV detector and a data station.

- Spherisorb ODS 2, 250 x 4.6 mm – 5 µm column.

15

- 96% Sulfuric acid Suprapur® (Merck 1.00714 or equivalent).

- Acetonitrile (HPLC gradient grade, J.T Baker reference 8143 or equivalent).

- Deionized water (Elga HPLC grade, or equivalent).

- **Method:**

20 - Mobile phase:

Route A: 100% acetonitrile

Route B: 0.1% v/v aqueous sulfuric acid solution

- Preparation of the samples:

0.2 g of BBG to be analyzed is placed in a 20 mL volumetric flask, followed by a sufficient amount of acetonitrile to make 20 mL of solution.

25

- Analytical conditions:

Column temperature	25°C
Sample temperature	Ambient
Flow rate	1.0 mL/min
Injection volume	20 µl
UV detection	220 nm
Analysis time	70 min

- Gradient:

30

Time	% acetonitrile	% H <sub>2</sub> SO <sub>4</sub> (0.1%)
0	1	99

5	1	99
20	60	40
50	80	20
60	80	20
62	1	99
70	1	99

## II. Racemization of dibutyl 2-bromoglutarate

During the synthesis, the asymmetric carbon retains its configuration and becomes partially racemized on bromination. The BBG is typically obtained with an enantiomeric excess ranging from 50% to 80%. If the BBG obtained is not racemic, it is possible to racemize it using a bromine salt.

### II.1. With LiBr

Racemization of the BBG with 1 mol% LiBr by contact for 2 hours at 60°C.

Washing of the racemic BBG with 2 × 2 weight equivalents of 0.1 M sodium bicarbonate solution at 25°C.

Washing with 0.5 weight equivalent of water under vacuum (pressure ≤ 30 mbar) and temperature of the reaction medium at ≤ 70°C.

This process was applied with 3418 g of BBG and 9.22 g of LiBr in 97.9% yield.

Chiral HPLC monitoring was performed to achieve racemization.

- **Equipment:**

- HPLC apparatus equipped with a UV detector.
- Chiralpak IC - 5 µm - 250 x 4.6 mm column from Daicel.

- **Method:**

- Mobile phase: 95% heptane/5% isopropyl alcohol

- Preparation of the samples:

50 mg of BBG to be analyzed are placed in a 10 mL volumetric flask, followed by a sufficient amount of heptane to make 10 mL of solution.

- Analytical conditions:

HPLC in normal phase, elution of the mobile phase in isocratic mode.

Flow rate	0.7 mL/min
Injection volume	10 µl

UV detection	270 nm
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- Calculation of the enantiomeric excess:

$$\% ee = (\text{peak area 1} - \text{peak area 2}) / (\text{peak area 1} + \text{peak area 2}) \times 100$$

Conditions	% peak area		% enantiomeric excess
	Enantiomer 1	Enantiomer 2	
Starting material	21.46	78.54	-57.08
Contact 2h/60°C	48.96	51.04	-2.08
Contact 2h30/60°C	49.68	50.32	-0.64

5

## II.2. with TBAB

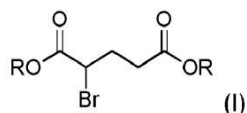
It was shown that racemization is also possible with TBAB under the same conditions as with LiBr, without solvent and at room temperature.

10

3.2 g of TBAB are added to 323 g of BBG. The medium is stirred for at least 5 hours to reach an ee < 1%. The TBAB is removed by two successive washes with 150 ml of water. The BBG is concentrated under vacuum at a temperature below 70°C.

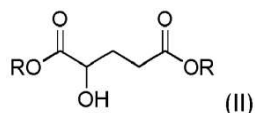
**Patentkrav**

1. Framgangsmåte for å framstille diester av 2-bromglutarsyre av formel (I) nedenfor:



- 5 der R representerer en (C<sub>3</sub>-C<sub>6</sub>)alkyl-gruppe, idet framgangsmåten omfatter følgende trinn:

(b) danne en 2-hydroksyglutarsyrediester av formel (II)



ved å la butyrolaktonsyre av formel (BA) reagere



med alkoholen av formel ROH, i nærvær av en syre, som for eksempel svovelsyre, og (c) bromere hydroksyglutarsyrediesteren av formel (II) ved å boble gassformig hydrogenbromid gjennom den, noe som gir en 2-bromglutarsyrediester av formel (I).

- 15 2. Framgangsmåte ifølge krav 1, kjennetegnet ved at trinn (b) utføres i nærvær av acetatet av formel CH<sub>3</sub>COOR.

3. Framgangsmåte ifølge krav 1 eller 2, kjennetegnet ved at i trinn (b) fjernes vannet ved vakuumdestillasjon.

20

4. Framgangsmåte ifølge ett av kravene 1 til 3, kjennetegnet ved at i trinn (b) er mengdene av butyrolaktonsyren av formel (BA) og alkoholen ROH som føres inn slik at molforholdet ROH/BA er mellom 2 og 10.

- 25 5. Framgangsmåte ifølge ett av kravene 1 til 4, kjennetegnet ved at etter trinn (b) avkjøles reaksjonsmediet til under 15 °C og settes til utskilling etter tilsetning av vann for å danne en organisk fase som er distinkt fra en vannfase, idet vannfasen så fjernes og den organiske fasen dehydreres ved vakuumdestillasjon og/eller konsentreres under vakuum før den inngår i trinn (c).

30

6. Framgangsmåte ifølge ett av kravene 1 til 5, kjennetegnet ved at trinn c) omfatter følgende trinn i rekkefølge:

– etablere en temperatur i reaksjonsmediet på mellom 5 og 40 °C,

- innføre gassformig hydrogenbromid i en mengde på mellom 1 og 1,5 molekvivalenter i forhold til mengden av butyrolaktonsyre (BA) som ble brukt i trinn (b),
- vakuumdestillasjon med en varighet på fortrinnsvis mellom 3 og 8 timer for å fjerne vann fra reaksjonsmediet,
- 5    – reetablere en temperatur i reaksjonsmediet på mellom 5 og 40 °C, idet trinnene fortrinnsvis gjentas i rekkefølge 3 til 8 ganger.

7.     Framgangsmåte ifølge ett av kravene 1 til 6, kjennetegnet ved at den omfatter et første trinn (a) der det dannes butyrolaktonsyre av formel (BA) ved å la L-glutaminsyre  
10    reagere med natriumnitritt i vannløsning.

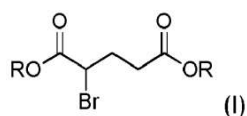
8.     Framgangsmåte ifølge ett av kravene 1 til 7, kjennetegnet ved at reaksjonsblandingen fra trinn (c) underkastes følgende tilleggstrinn:  
(d) føre reaksjonsblandingen fra trinn (c) inn i en basisk vannløsning, idet den  
15    resulterende løsningen har en pH på typisk mellom 7,5 og 9,5,  
(e) skille løsningen fra trinn (d) for å danne en organisk fase som er distinkt fra en vannfase som så fjernes,  
(f) konsentrere den organiske fasen fra trinn (e) under vakuum inntil temperaturen er mellom 65 og 75 °C, og så tørke den under vakuum,  
20    (g) eventuelt filtrere, og  
utvinne 2-bromglutarsyrediesteren av formel (I).

9.     Framgangsmåte ifølge ett av kravene 1 til 8, kjennetegnet ved at 2-bromglutarsyrediesteren av formel (I) fra trinn (c), (f) eller (g) gjennomgår et ekstra  
25    racemiseringstrinn der det tilsettes et bromsalt som LiBr eller tetrabutylammoniumbromid.

10.    Framgangsmåte ifølge ett av kravene 1 til 9, kjennetegnet ved at R svarer til en *n*-butylgruppe.

30    11. Framgangsmåte ifølge ett av kravene 3 til 10, kjennetegnet ved at vakuumdestillasjonsoperasjonene i trinn (b) og (c) er azeotrope.

12.    Forbindelse av formel (I) nedenfor:



35    der R representerer en (C<sub>3</sub>-C<sub>6</sub>)alkyl-gruppe, fortrinnsvis en butylgruppe, som har en renhetsgrad, bestemt ved HPLC-analyse, på høyere enn eller lik 90 %.

13. Forbindelse ifølge krav 12, kjennetegnet ved at R svarer til en  $n$ -butylgruppe.
14. Forbindelse ifølge krav 12 eller 13, kjennetegnet ved at renhetsgraden er høyere  
5 enn eller lik 95 %.
15. Forbindelse ifølge ett av kravene 12 til 14, kjennetegnet ved at renhetsgraden er høyere enn eller lik 97 %.

1/1

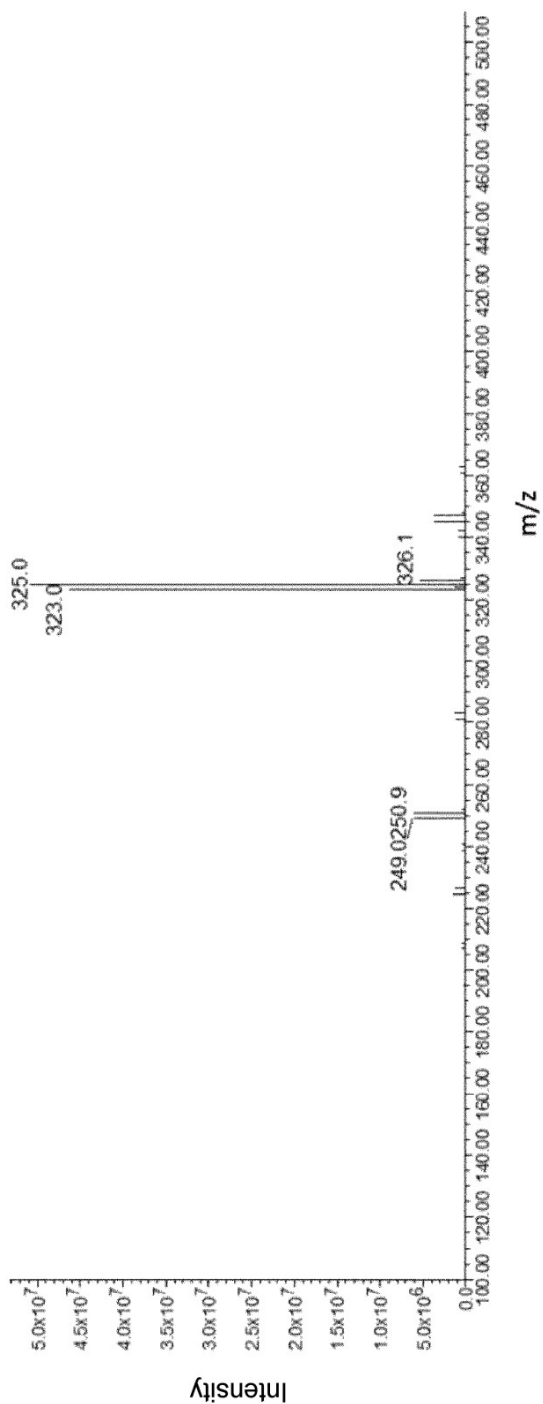


Fig. 1