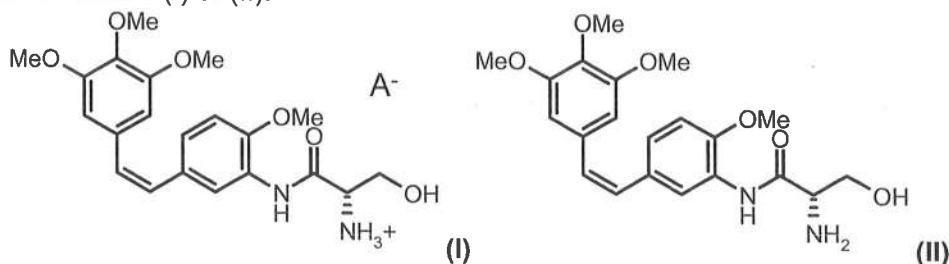


COMBRETASTATIN DERIVATIVE PREPARATION METHOD

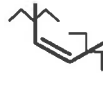
The present patent application relates to a process for the preparation of a combretastatin derivative of formula (I) or (II):



- 5 A^- denoting the anion associated with an acid AH. More particularly, A denotes Cl^- .

[Technical problem]

The compounds (I) and (II) belong to the family of the combretastatin derivatives or stilbene derivatives which are anticancer compounds. They are described in Applications
 10 **EP 0 731 085**, **EP 1 264 821**, **EP 1 068 870** and **EP 1 407 784**. The preparation of these derivatives is based, in one of the stages, on the formation of the C=C double bond. In this

stage, two isomers **Z** and **E** may be formed but only the **Z** isomer () exhibits a truly effective anticancer activity. The preparation process should thus result in a high **Z/E** ratio.

15

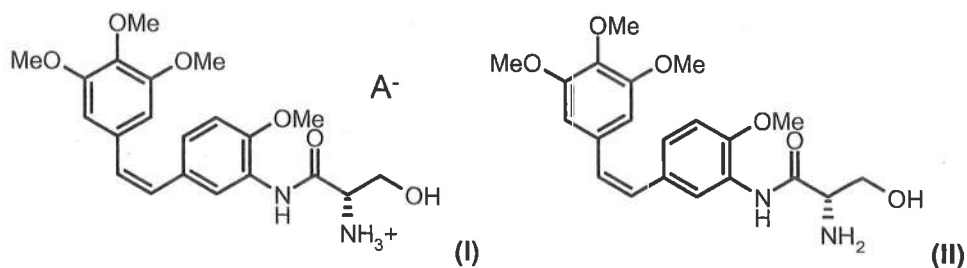
The Applicant Company has developed an alternative process for the preparation of the compounds (I) and (II) which is based on the use of the intermediates **P₂** or **P'₂** described below. This process exhibits the advantage of eliminating the stage during which a cytotoxic intermediate is formed. This alternative process thus exhibits fewer stages comprising toxic
 20 compounds, which makes it easier to manage it from an industrial viewpoint.

[Prior art]

The papers *J.Fluor.Chem.*, **2003**, 123, 101-108, and *Synlett.*, **2006**, 18, 2977, describe the preparation of combretastatins using one of the stages of the Wittig reaction. The Wittig
 25 reaction is also envisaged in Patent **US 7 265 136** and in International Applications **WO 03/084919** and **WO 2009/118474**.

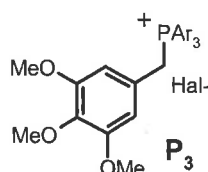
[Brief description of the invention]

The invention relates to a process for the preparation of a combretastatin derivative of
 30 formula (I) or (II):

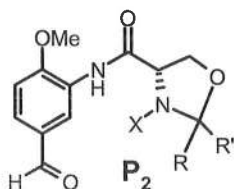


A^- denoting the anion associated with an acid AH, comprising the following stages:

- triaryl(3,4,5-trimethoxybenzyl)phosphonium halide P_3



- 5 in which Ar denotes an aryl group chosen from phenyl or thienyl, optionally substituted by a (C_1-C_4) alkyl, (C_1-C_4) alkoxy or halogen group, is reacted, in the presence of a base, with:
- P_2 of formula:

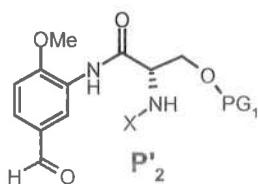


in which R and R' represent:

- 10
- each a (C_1-C_4) alkyl group;
 - or else R represents a phenyl group optionally substituted by a (C_1-C_4) alkoxy group and R' represents a hydrogen atom;
 - or else R and R' form, together with the carbon atom to which they are connected, a (C_3-C_7) cycloalkyl group;

15

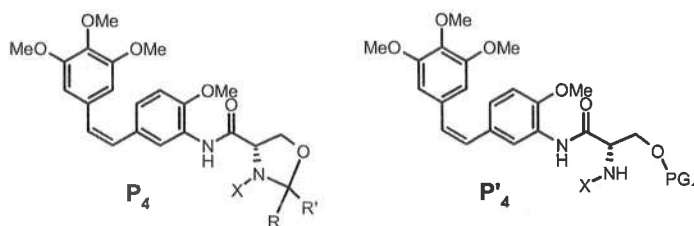
- or else P'_2 of formula:



in which PG_1 represents a protective group for the alcohol functional group,

- 20 X representing boc, Fmoc or CBZ,

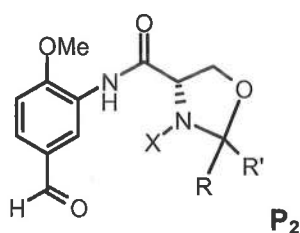
so as to respectively obtain the compound P_4 or P'_4 :



- then, during a deprotection stage in the presence of an acid and/or of a base, the compound of formula **P₄** or **P'₄** results, after an optional purification stage, in the compound of formula (I) or (II).

5

The invention also relates to a compound of formula **P₂**:

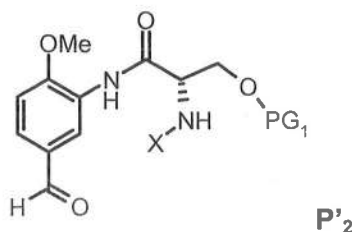


in which **R** and **R'** represent:

- each a (C₁-C₄)alkyl group;
 - or else **R** represents a phenyl group optionally substituted by a (C₁-C₄)alkoxy group and **R'** represents a hydrogen atom;
 - or else **R** and **R'** form, together with the carbon atom to which they are connected, a (C₃-C₇)cycloalkyl group;
- and **X** represents boc, Fmoc or CBZ.

15

The invention also relates to the compound of formula **P'₂**:



in which **PG₁** represents a protective group for the alcohol functional group and **X** represents boc, Fmoc or CBZ.

20

- R** and **R'** can, for example, both represent a methyl (Me) group or can form, together with the carbon atom to which they are connected, the cyclohexyl group. **X** can, for example, represent boc. **PG₁** can, for example, represent one of the following protective groups: THP (tetrahydropyran), MEM (methoxyethoxymethyl), boc, trityl or acetyl (Ac). **Ar** can represent the phenyl or thienyl group, optionally substituted by a (C₁-C₄)alkyl or (C₁-C₄)alkoxy group. **A⁻** can denote Cl⁻.

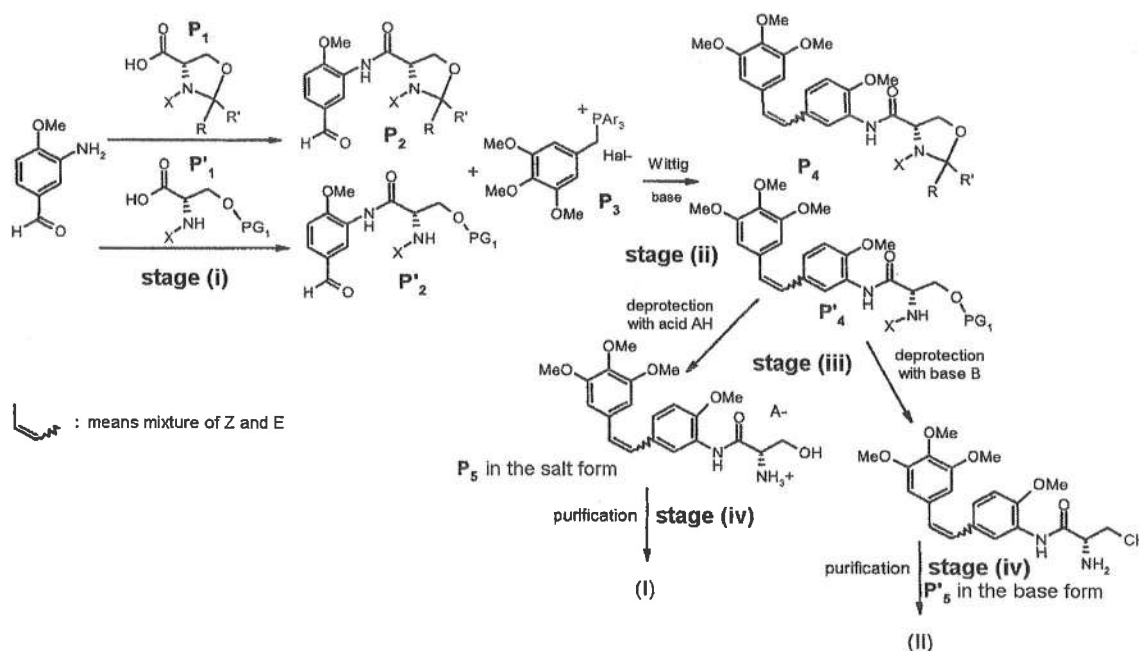
25

The invention also relates to the use of one of the two compounds **P₂** and **P'₂** as intermediate in the preparation of a compound of formula (I) or (II).

- 5 The invention also relates to the use of one of the two compounds **P₄** and **P'₄** as intermediate in the preparation of a compound of formula (I) or (II).

[Detailed description of the invention]

The general **Scheme 1** describes stages (i) to (iv) of the process:

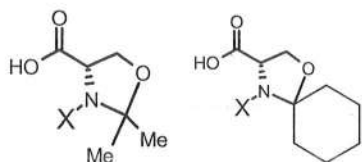


Scheme 1

Stage (i): coupling of 3-amino-4-methoxybenzaldehyde and of a protected serine of formula:

- 15 • **P₁**, in which **R** and **R'** represent:
- each a (C₁-C₄)alkyl group;
 - or else **R** represents a phenyl group optionally substituted by a (C₁-C₄)alkoxy group, for example methoxy, and **R'** represents a hydrogen atom;
 - or else **R** and **R'** form, together with the carbon atom to which they are
- 20 connected, a (C₃-C₇)cycloalkyl group;
- or else of formula **P'₁**, in which **PG₁** represents a protective group for the alcohol functional group. On conclusion of this coupling, **P₂** or **P'₂** respectively is obtained.
 - **X** represents boc, Fmoc or CBZ.

P₁ can more particularly be one of the following compounds:

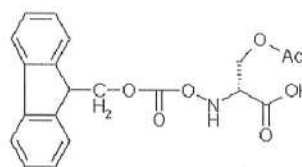


and in particular those for which **X** = boc (for example, compound 8 of *Synthesis*, **2006**, 8, 1289-1294, for which R = R' = Me).

5 **P'₁** can more particularly be one of the following compounds:

X = boc, PG₁ = THP: see compound 13a of Ex. 13 of **WO 06042215**;

X = PG₁ = boc: *Justus Liebigs Annalen der Chemie*, **1971**, 743, 57-68;



X = Fmoc, PG₁ = Ac: commercial compound of formula:

- 10 **PG₁** denotes a protective group for the alcohol functional group. boc, Fmoc and CBZ respectively denote the tert-butoxycarbonyl, 9-fluorenylmethoxycarbonyl and benzyloxycarbonyl groups. A protective group is a chemical entity which is introduced onto a molecule during a "protection" stage by modification of a chemical group, making it possible to improve the chemoselectivity of a reaction by preventing undesirable side reactions at the said chemical group, and which is released during a subsequent
- 15 "deprotection" stage. **PG₁** can, for example, be THP (tetrahydropyran), MEM (methoxyethoxymethyl), boc, trityl or acetyl (Ac).

The coupling (amidation) is advantageously carried out in the presence of an acid activator.

- 20 The term "acid activator" denotes a compound having the role of rendering the acid functional group –COOH of **P₁** or **P'₁** more reactive for the purpose of promoting the formation of an amide bond. Reference may be made, for further details with regard to acid activators, to the review *ChemFiles*, Vol. 7, No. 2, page 3, edited by Aldrich Chemical, or else to *Tetrahedron Report*, No. 672, **2004**, 60, 2447-2467, "Recent development of peptide coupling reagents in organic synthesis". EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) chloride), DCC (dicyclohexylcarbodiimide), TOTU (O-[ethoxycarbonyl]cyanomethyleneamino)-N,N,N',N'-tetramethyluronium tetrafluoroborate), HBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and N,N-carbonyldiimidazole are examples of acid activators or the anhydride of propanephosphonic acid (T3P). In the presence of the acid activator, an isolable or non-isolable intermediate may be formed which comprises an activated acid functional group of the form –COZ; for example, in the case of pivaloyl chloride, Z represents –OtBu.
- 30

The coupling can be carried out in a solvent, such as, for example, a chlorinated solvent, for example dichloromethane (DCM), an ether, for example THF, or an aromatic solvent, for example toluene, at a temperature which can be between 0°C and 20°C.

5

Stage (ii): Wittig reaction between P_2 or P'_2 and triaryl(3,4,5-trimethoxybenzyl)phosphonium halide P_3 , resulting respectively in P_4 or P'_4 . In P_3 , Ar denotes an aryl group chosen from phenyl or thienyl, optionally substituted by a (C₁-C₄)alkyl or (C₁-C₄)alkoxy group.

- 10 The Wittig reaction is carried out in a solvent in the presence of base. P_3 is obtained by the reaction of 3,4,5-trimethoxybenzyl halide with the corresponding triarylphosphine PAR_3 . Use is preferably made of a chloride or a bromide. An example of P_3 is triphenyl(3,4,5-trimethoxybenzyl)phosphonium chloride, which is described on p. 102 of *J. Fluor. Chem.*, **2003**, 123, 101–108, or else its bromide equivalent, which is described on pp. 15-16 of
- 15 **WO 02/06279**.

The solvent of this reaction can, for example, be toluene, THF, dimethylformamide (DMF), chloroform, DCM, trifluorotoluene, a mixture of these solvents or an aqueous two-phase mixture, such as, for example, the chloroform/water mixture.

20

- The base which is used is preferably a strong base, such as, for example, NaHMDS (sodium bis(trimethylsilyl)amide; CAS [1070-89-9]), KHMDS (potassium bis(trimethylsilyl)amide; CAS [40949-94-8]), sodium methoxide, sodium amide or sodium hydroxide. The base can be brought together with a phosphonium salt P_3 and then the
- 25 aldehyde P_2 or P'_2 can be run onto the phosphonium salt P_3 , which will have been brought into contact beforehand with the base. According to a preferred alternative form which makes it possible to obtain a higher yield of P_4 or P'_4 , the base is run onto the mixture formed by the aldehyde and the phosphonium salt.

- 30 The Wittig reaction can be carried out at a temperature generally of between 0°C and the reflux temperature of the solvent.

- Stage (iii):** the deprotection of P_4 or P'_4 is carried out in one or more stages and under conditions which depend on the nature of the protective groups X and, if appropriate, PG_1 . A
- 35 person skilled in the art may refer to "Greene's Protective Groups in Organic Synthesis", 4th edition, ISBN 978-0-471-69754-1, to find, if appropriate, these conditions.

Thus, for some protective groups (for example, compound **P₄** with X = boc), the deprotection can be carried out in the presence of an organic or inorganic acid AH. In this case, the deprotection results in the compound **P₅** in the salt form. For other protective groups, the deprotection can be carried out in the presence of an organic or inorganic base B. In this case, the deprotection results in the compound **P'₅** in the base form. The temperature of the deprotection reaction is preferably between 0°C and 50°C. The acid can be a strong acid, such as, for example, hydrochloric acid, which results in the hydrochloride. The base can be, for example, sodium hydroxide. It is also possible to combine an acid treatment and a basic treatment, in particular for **P'₄**, which comprises two different protective groups **X** and **PG₁**.

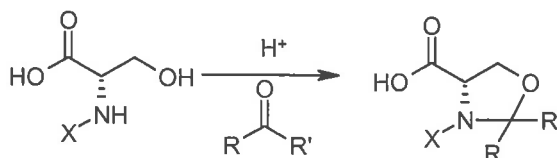
Stage (iv): if necessary, the **Z** isomer is separated from the **E** isomer by any purification technique known in organic synthesis. It can be purification by recrystallization, using as solvent a mixture comprising an alcohol and a ketone or an ester and more particularly the methyl ethyl ketone (MEK)/water mixture.

Stage (iii) or, if appropriate, (iv) can optionally be followed by an additional stage consisting in converting:

- by addition of an acid, a combretastatin in the base form (for example (II)) into combretastatin in the salt form (for example (I))
- or else, by addition of a base, the combretastatin in the salt form (for example (I)) into combretastatin in the base form (for example (II)).

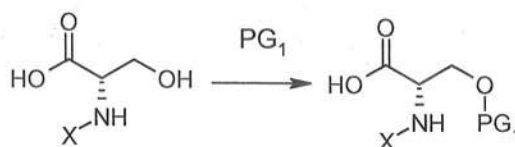
Intermediates **P₁** and **P'₁**

P₁ is obtained according to **Scheme 2** by reaction of a ketone and of a derivative of L-serine, the amine functional group of which has been protected with **X**.



Scheme 2

P'₁ is obtained by protection of the -OH functional group of a derivative of L-serine, the amine functional group of which has been protected with **X**.

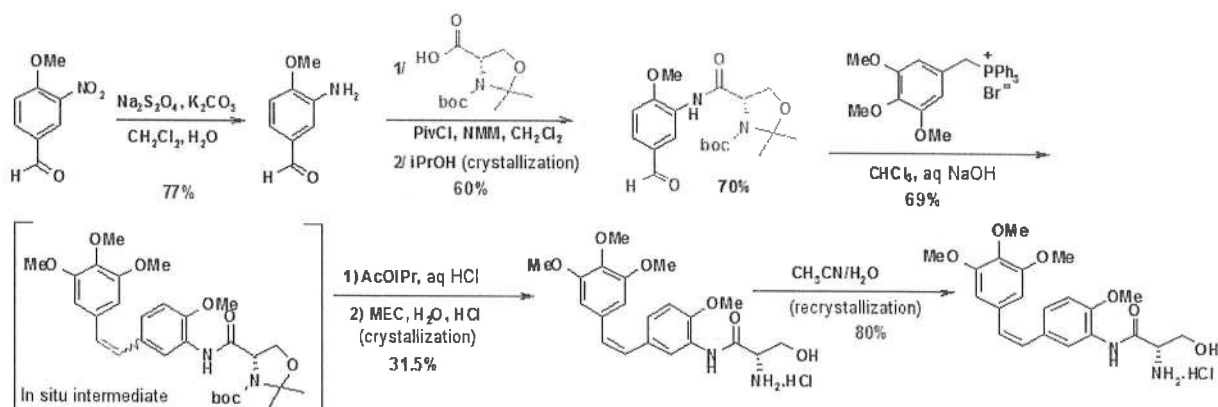


Scheme 2'

The derivative of L-serine of **Schemes 2** and **2'** can be commercially available (for example, N-boc-L-serine) or readily accessible using at least one chemical reaction known to a person skilled in the art (similar, for example, to that which makes it possible to prepare N-boc-L-serine).

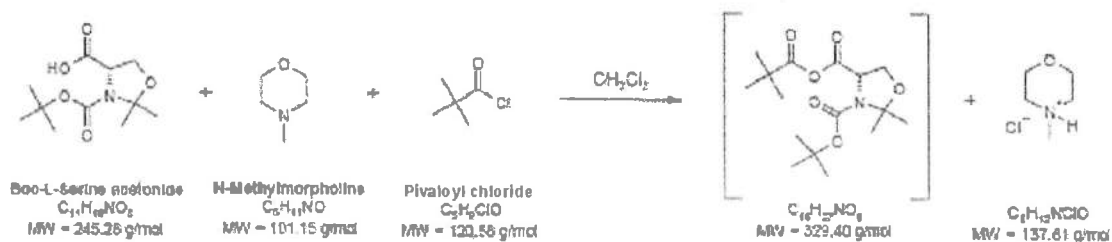
[Examples]

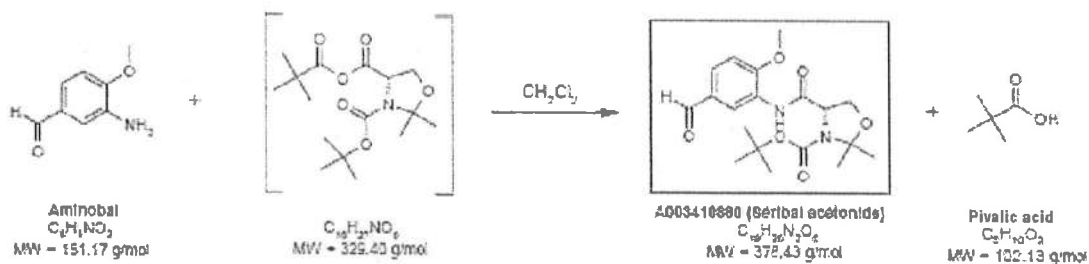
10 **Example 1:** Preparation of the hydrochloride of the compound (II)



3-Amino-4-methoxybenzaldehyde is obtained by reduction of the corresponding nitro compound according to *Tetrahedron Letters*, **1993**, 34(46), 7445-1446.

15 **Preparation of P₂ (Stage (i))**





Before being used, the reactor is freed with DCM, dried under vacuum and purged by flushing with nitrogen for 15 to 30 min, the Erlenmeyer flask is rinsed with amylene-stabilized DCM and then dried under nitrogen. 95 ml of DCM and 34.0 g of boc-L-serine acetonide are charged to the reactor, the reactor is cooled to 4-10°C and 14.3 g of N-methylmorpholine are added using a dropping funnel while maintaining the temperature at 4-10°C. The dropping funnel is rinsed with 2.5 ml of DCM. 17.1 g of pivaloyl chloride are added using a dropping funnel while maintaining the temperature at 4-10°C and the dropping funnel is rinsed with 2.5 ml of DCM. The mixture is kept stirred at 4-10°C for 2 h.

A solution of aminobal (20.0 g) in DCM (95 ml) is prepared with stirring and this solution is run into the reactor while maintaining the temperature at 4-10°C. The mixture is subsequently heated to 20°C over 1 h and is kept stirred at 20°C for a minimum of 16 h. 100 ml of demineralized water are added to the reactor at 20-25°C and the mixture is left stirring for 20 min and separated by settling. The lower organic phase comprising the product and the upper phase (predominantly aqueous) are withdrawn. The organic phase comprising the product is again charged to the reactor. 140 ml of a 1.0N aqueous sodium hydroxide solution are added. The mixture is kept stirred at 20-25°C for approximately 20 min and then allowed to separate by settling. The lower organic phase comprising the product is withdrawn. The organic phase comprising the product is again charged to the reactor. 100 ml of demineralized water are added. The mixture is kept stirred at 20-25°C for approximately 20 min and then allowed to separate by settling. The lower organic phase comprising the product is withdrawn. The organic phase comprising the product is again charged to the reactor. 100 ml of isopropanol are added.

Distillation is carried out (35 ± 5°C in the jacket) under a residual pressure of approximately 30 mbar until a residual volume of 100 ml is present in the reactor. The temperature is adjusted to 20°C and the mixture is left stirring at 20°C for 3 h. The reactor is rinsed and the cake is washed twice with a total volume of 40 ml of isopropanol. The product is dried at 40°C under a vacuum of 30 mbar. Yield of isolated product: 60%.

Wittig reaction (Stage (ii))

581 g of phosphonium salt (1.2 eq.), 350 g of the aldehyde from the preceding stage (1.0 eq.) and 3500 ml of CHCl_3 are charged to a 7 l reactor (intense yellow-brown solution). 1110 ml of a 1N NaOH solution (1.2 eq.) are added. The two-phase mixture is stirred vigorously and the solution becomes pale yellow. It is kept at approximately 20°C. 3500 ml of water are added and the mixture is stirred and separated by settling (pH of the aqueous phase 13). A 2nd washing is carried out with 3500 ml of water; the pH is then 7. Separation by settling is carried out and the yellow-orange organic phase is withdrawn (volume 4250 ml comprising 346.0 g of Z and 136.7 g of E). The Z/E ratio is 72/28 and the Z+E yield with respect to the aldehyde is 96.2%.

The solution is reintroduced into the reactor and then the CHCl_3 is distilled off under vacuum with a starting vacuum of 100 mbar and a final vacuum of 45 mbar (jacket temperature approximately 30°C). The mixture becomes syrupy. The vacuum is broken and 50 ml of CHCl_3 and 2500 ml of AcOiPr are added: a fluid solution is obtained (5250 ml). The distillation is resumed at constant volume with addition of AcOiPr. Crystals (predominantly of triphenylphosphine oxide) are formed and are filtered off. The filtrate comprising the expected product is retained for use in the following stage. Z/E ratio = 71/29. Z yield: 68.9%.

Deprotection in an acid medium (Stage (iii))

The solution from the preceding stage (3045.9 g of solution, i.e. 343.9 g of Z and 136.9 g of E) is charged. 295.2 ml of a 12N HCl solution (4 eq., with respect to the product) are added. The two-phase mixture changes from yellow to dark red. 1800 ml of water are added, the mixture is stirred for 10 min and separated by settling, and the rich aqueous phase is withdrawn. 900 ml of water are added to the organic phase. The mixture is separated by settling and the aqueous phase is withdrawn. 3714 g of orange aqueous phase are obtained (Z/E ratio = 67/33). 2700 ml of AcOiPr are added and a 10N NaOH solution is run in slowly until a pH of 10-11 is obtained. The mixture is separated by settling and the aqueous phase is withdrawn. 2700 ml of water and 11 g of NaCl are added and the mixture is vigorously stirred and then separated by settling. This whisking operation is repeated with 2700 ml of water. A yellow organic phase is recovered (2760 g) Z/E ratio = 68/32. Yield: 35%.

Recrystallization (Stage (iv))

5.27 g of the preceding product, 50 ml of water, 50 ml of AcOiPr and 1.32 ml of 30% sodium hydroxide solution are charged to a 250 ml three-necked flask. The mixture is stirred for 30 min. It is separated by settling and the aqueous phase (pH = 10) is withdrawn. Two whisking operations are carried out with water (50 ml). After the 2nd whisking operation, the pH is 7. The organic phase is evaporated to dryness (40°C, vacuum of 60 mbar) and the

residue is dried in an oven (40°C). The solid (5.49 g) is taken up in 11.2 ml of MEC, and 1.00 ml of a 12N HCl solution (density = 1.18) is added to the solution. A small amount of product is allowed to slowly crystallize. 0.36 ml of water is added and a large part of the crystallized product redissolves. 2.70 ml of MEC are then added and crystallization is again
5 allowed to take place. The mixture is stirred at ambient temperature for 5 days. The product is obtained with a Z/E ratio = 93/07. Z yield: 45%.

Example 1a: Preparation of the hydrochloride of the compound (II)

10 **Wittig reaction (Stage (ii))**

44.8 g of phosphonium salt (1.2 eq.), 27 g of the aldehyde from the preceding stage (1.0 eq.) and 270 ml of CHCl_3 are charged to a 500 ml reactor (intense yellow-brown solution). 85.6 ml of a 1N NaOH solution (1.2 eq.) are added. The two-phase mixture is stirred vigorously and the solution becomes pale yellow. It is maintained at approximately
15 20°C for approximately 4 h. 270 ml of water are added and the mixture is stirred and separated by settling (pH of the aqueous phase 13). A 2nd washing operation is carried out with 270 ml of water; the pH is then 7. The mixture is separated by settling and the yellow-orange organic phase (weight 470.4 g, comprising 26.7 g of Z and 11.2 g of E) is withdrawn. The Z/E ratio is 70/30, the Z+E ratio with respect to the aldehyde is 98% and the Z yield
20 with respect to the aldehyde is 69.0%.

The solution is reintroduced into the reactor and then a change in solvent to isopropyl acetate is carried out under reduced pressure (45 to 100 mbar at 30°C approximately). At the end of the operation, the residual volume is adjusted to 203 ml. Crystals are formed,
25 which crystals are filtered off and washed with isopropyl acetate. The filtrate, comprising the reaction product, is used as is in the following stage. Z/E ratio = 70/30. Z yield: 69.0%.

Deprotection in acidic medium (Stage (iii))

The solution from the preceding stage (248.0 g of solution, i.e. 26.7 g of Z and 11.2 g of E)
30 is charged to a 500 ml reactor. 23.3 ml of a 12N HCl solution (4 eq. with respect to the product) are added. The two-phase mixture changes from yellow to dark red. The mixture is kept stirred at 20°C for approximately 5 h. 137 ml of water are added, the mixture is stirred for 10 min and separated by settling, and the rich aqueous phase is withdrawn. 69 ml of water are added to the organic phase. The mixture is separated by settling and the aqueous
35 phase is withdrawn. 283.6 g of orange aqueous phase are obtained (Z/E ratio = 66/34). 206 ml of AcOiPr are added and a 10N NaOH solution is slowly run in until a pH of 10-11 is obtained. The mixture is separated by settling and the aqueous phase is withdrawn. 206 ml of water and 2.1 g of NaCl are added and the mixture is vigorously stirred and then

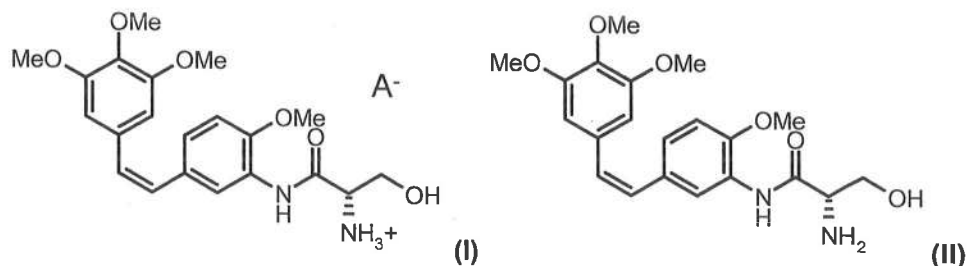
separated by settling. This operation is repeated a second time. A yellow organic phase is recovered and is brought to dryness (35.0 g, Z/E ratio = 66/34). This residue is taken up in 108.3 g of MEC. A solution is obtained. 5.82 ml of 12N HCl and 2.75 ml of water are successively added. Initiation is subsequently carried out by the addition of 75 mg of pure Z isomer. The mixture is kept stirred at 20°C for 24 h and then the slurry obtained is filtered. The cake is pulled as dry as possible and then dried in an oven (50°C, 60 mbar). 7.15 g of a fine beige powder are thus obtained: Z yield: 31.5%, Z/E ratio = 95.9/4.1.

Recrystallization (Stage (iv))

- 488 mg of compound (I) (Z/E = 93.5/6.5), 0.115 ml of water and 268 ml of acetonitrile are charged to a 5 ml round-bottomed flask. The mixture is heated to 35°C, stirred until a solution is obtained and then cooled to 20°C. Initiation is carried out at this temperature with 3 mg of the pure Z isomer. The mixture is kept stirred for 30 min and then 3.44 ml of acetonitrile are run in over approximately 2 h. The mixture is subsequently kept stirred at 20°C for 18 h and filtered. The cake obtained is dried in an oven (50°C, 60 mbar). 367 mg of the expected product are thus obtained with a Z/E ratio of 99.65/0.35, i.e. a yield of 80%.

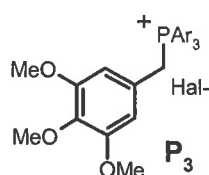
CLAIMS

1. Process for the preparation of a combretastatin derivative of formula (I) or (II):



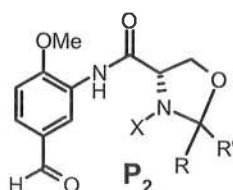
A^- denoting the anion associated with an acid AH, comprising the following stages:

- triaryl(3,4,5-trimethoxybenzyl)phosphonium halide P_3



in which Ar denotes an aryl group chosen from phenyl or thienyl, optionally substituted by a (C_1-C_4) alkyl, (C_1-C_4) alkoxy or halogen group, is reacted, in the presence of a base, with:

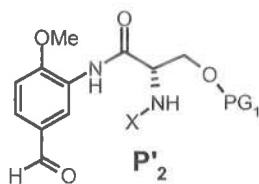
- P_2 of formula:



in which R and R' represent:

- each a (C_1-C_4) alkyl group;
- or else R represents a phenyl group optionally substituted by a (C_1-C_4) alkoxy group and R' represents a hydrogen atom;
- or else R and R' form, together with the carbon atom to which they are connected, a (C_3-C_7) cycloalkyl group;

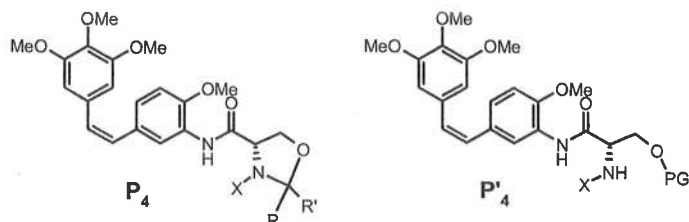
- or else P'_2 of formula:



in which PG_1 represents a protective group for the alcohol functional group,

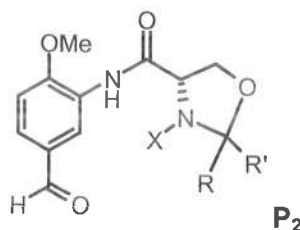
X representing boc, Fmoc or CBZ,

so as to respectively obtain the compound **P₄** or **P'₄**:



5

- then, during a deprotection stage in the presence of an acid and/or of a base, the compound of formula **P₄** or **P'₄** results, after an optional purification stage, in the compound of formula (I) or (II).
- 10 2. Process according to Claim 1, in which **R** and **R'** both represent a methyl group or form, together with the carbon atom to which they are connected, the cyclohexyl group.
 3. Process according to Claim 1 or 2, in which **X** represents boc.
 - 15 4. Process according to Claim 1 to Claim 3, in which **PG₁** represents one of the following protective groups: THP (tetrahydropyran), MEM (methoxyethoxymethyl), boc, trityl or acetyl (Ac).
 5. Process according to Claim 1 to Claim 4, in which **Ar** represents the phenyl or thienyl group, optionally substituted by a (C₁-C₄)alkyl or (C₁-C₄)alkoxy group.
 - 20 6. Process according to one of Claims 1 to 5, in which **A⁻** denotes Cl⁻.
 7. Compound of formula **P₂**:



25

in which **R** and **R'** represent:

- each a (C₁-C₄)alkyl group;
- or else **R** represents a phenyl group optionally substituted by a (C₁-C₄)alkoxy group and **R'** represents a hydrogen atom;

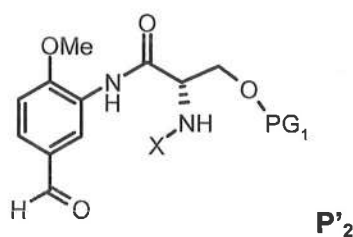
o or else **R** and **R'** form, together with the carbon atom to which they are connected, a (C₃-C₇)cycloalkyl group;
and **X** represents boc, Fmoc or CBZ.

5 8. Compound according to Claim 7, in which **X** represents boc.

9. Compound according to Claim 8, in which **R** and **R'** both represent a methyl group or else **R** and **R'** form, together with the carbon atom to which they are connected, the cyclohexyl group.

10

10. Compound of formula **P'₂**:



in which **PG₁** represents a protective group for the alcohol functional group and **X** represents boc, Fmoc or CBZ.

15

11. Compound according to Claim 10, in which **PG₁** represents THP (tetrahydropyran), MEM (methoxyethoxymethyl), boc, trityl or acetyl (Ac).

20

12. Use of a compound according to Claim 7 to Claim 11 as intermediate in the preparation of a compound of formula (I) or (II) as defined in Claim 1.