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(54) Titre : PROCÉDE DE PREPARATION D'ISOMERES DE SALBUTAMOL
(54) Title: PROCESS FOR PREPARING ISOMERS OF SALBUTAMOL

(57) **Abrégé/Abstract:**

A process for making optically pure (R) and (S) salbutamol comprises obtaining the (R) or (S) isomer of either salbutamol or a salbutamol precursor in substantially optically pure form by resolving a racemic or optically impure mixture of enantiomers of salbutamol or of said precursor with either (L) or (D) tartaric acid, and where necessary converting said isomer of said precursor into either (R) or (S) salbutamol respectively; then optionally converting said optically pure (R) and/or (S) salbutamol into a pharmaceutically acceptable salt.

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(54) Title: PROCESS FOR PREPARING ISOMERS OF SALBUTAMOL

(57) Abstract: A process for making optically pure (R) and (S) salbutamol comprises obtaining the (R) or (S) isomer of either salbutamol or a salbutamol precursor in substantially optically pure form by resolving a racemic or optically impure mixture of enantiomers of salbutamol or of said precursor with either (L) or (D) tartaric acid, and where necessary converting said isomer of said precursor into either (R) or (S) salbutamol respectively; then optionally converting said optically pure (R) and/or (S) salbutamol into a pharmaceutically acceptable salt.

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PROCESS FOR PREPARING ISOMERS OF SALBUTAMOL

This invention relates to an improved method of making optically pure (R) and (S) salbutamol, also known as (R) and (S) albuterol. The chemical name for salbutamol is α -[[[(1,1-dimethyl-ethyl)amino]methyl]-4-hydroxy-1,3-benzenedi-methanol.

For certain medical conditions such as asthma, the (R) isomer of salbutamol (which is laevorotatory, denoted (-) or l) is known to be very much more potent therapeutically than the dextrorotatory (S) isomer. One method of preparing the (R) and (S) isomers of salbutamol in optically pure form is disclosed in US 5,545,745. In this method, either of two precursor compounds for salbutamol is resolved using a substituted tartaric acid derivative. Specifically the resolving compound used in US 5,545,745 is chosen from (-)-di-toluoyl-L-tartaric acid, (+) -di-toluoyl-D-tartaric acid, (-)-di-benzoyl-L-tartaric acid and (+)-di-benzoyl-D-tartaric acid. Another reference (Hartley *et al*, *Journal of Medicinal Chemistry*, 1971, Vol 14, No 9, pp 895-896) describes much the same thing as US 5,545,745: the resolution is performed with either (+) or (-) di-para-toluoyl tartaric acid. A more recent publication (WO 99/42460) describes the resolution of a new ketal derivative of salbutamol (specifically 2-(N-t-butylamino)-1-(+2,2-dimethyl-1,2-benzodioxin-6-yl) ethanol). The resolution is again performed with a chiral tartaric acid derivative, such as (+) or (-) di-para-toluoyl tartaric acid or (+) or (-) di-O-benzoyl tartaric acid. Enantiomers of salbutamol can be produced if desired, via a complicated, multi-stage process involving resolution of the ketal derivative. The disadvantage of the process described in WO 99/42460 is that the enantiomeric excess of the salts obtained is low (based on the values given in the Examples). This requires additional crystallizations, thus lowering the overall yields. Further, two additional synthetic steps of ketalization and hydrolysis further reduces the economic viability of the process.

Whilst the process of US 5,545,745 is an improvement over previous methods of resolution, it nevertheless has certain disadvantages. The substituted tartaric acid derivatives employed are expensive (and not readily available) and so need to be specially prepared or bought, which adds to the overall time and cost of the process.

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These resolving compounds are generally not recovered from the process and this further contributes to the costs.

We have now found a way of substantially overcoming these problems. In particular, we have found an economical and efficient method of resolving salbutamol into its optically pure (R) and (S) isomers, which method does not require the use of expensive substituted tartaric acid derivatives.

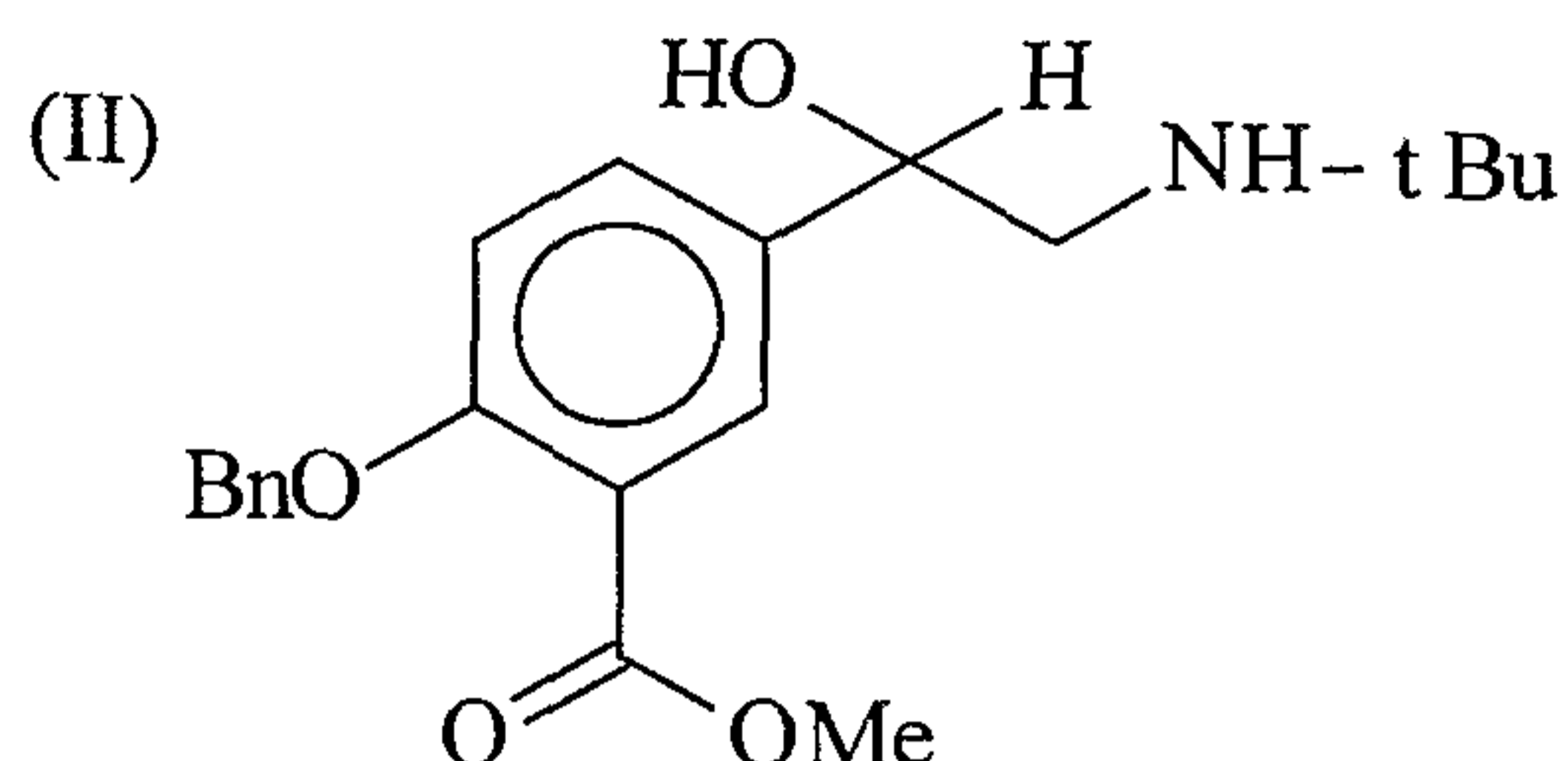
According to the present invention, there is provided a process for making optically pure (R) and/or (S) salbutamol or pharmaceutically acceptable salts thereof, which process comprises obtaining the (R) or (S) isomer of either salbutamol or a salbutamol precursor in substantially optically pure form by resolving a racemic or optically impure mixture of enantiomers of salbutamol or of said precursor with either (L) or (D) tartaric acid, and where necessary converting said isomer of said precursor into either (R) or (S) salbutamol respectively; then optionally converting said optically pure (R) and/or (S) salbutamol into a pharmaceutically acceptable salt.

Unlike the substituted tartaric acid derivatives used in US 5,545,745, (L) and (D) tartaric acid are readily available and inexpensive. They can be recovered and re-used in the process if desired, although even when they are not re-used the process is much more economical than that described in US 5,545,745.

An advantage of the present method is its general applicability to different intermediates of salbutamol. It also enables chirally pure product to be obtained in a good yield.

In a highly preferred aspect of the invention, the compound 4-benzyl albuterol (I) (α - [(1, 1 - dimethylethyl) amino] methyl] - 4 - (phenylmethoxy) - 1, 3 - benzenedimethanol) is used as the salbutamol precursor. A racemic or optically impure mixture of the compound is resolved to give the (R) and (S) isomers before conversion to the desired isomer of salbutamol takes place. 4-benzyl albuterol is readily available commercially, for example from Cipla Limited.

The precursor 4-benzyl albuterol is typically prepared, for example, from the ester intermediate methyl-5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-(phenylmethoxy)- benzoate (II).



Bn = benzyl
t Bu = tertiary butyl

This compound (II) can also, if desired, serve as the "salbutamol precursor" which is itself resolved into its (R) and (S) isomers.

We have found that the present method of resolution can be used satisfactorily to resolve racemic salbutamol (or an optically impure mixture of enantiomers of salbutamol) itself.

Thus, in a further aspect, the invention provides a process for making optically pure (R) and/or (S) salbutamol or pharmaceutically acceptable salts thereof, which process comprises resolving racemic salbutamol, or an optically impure mixture of enantiomers of salbutamol, with either (L) or (D) tartaric acid, and optionally converting said optically pure (R) and/or (S) salbutamol into a pharmaceutically acceptable salt thereof.

The present invention thus provides several ways of producing (R) and/or (S) salbutamol: by resolution at the final stage, for example on racemic salbutamol, or by resolution at an intermediate stage - for example, by resolution of the alcohol intermediate 4-benzyl albuterol or by resolution of the ester intermediate (II), methyl-5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-(phenylmethoxy)-benzoate.

We prefer to operate the process using (L) tartaric acid, since this results in the more active isomer (R) salbutamol. However, the invention encompasses the production of (S) salbutamol, in which case (D) tartaric acid is used in the resolution step.

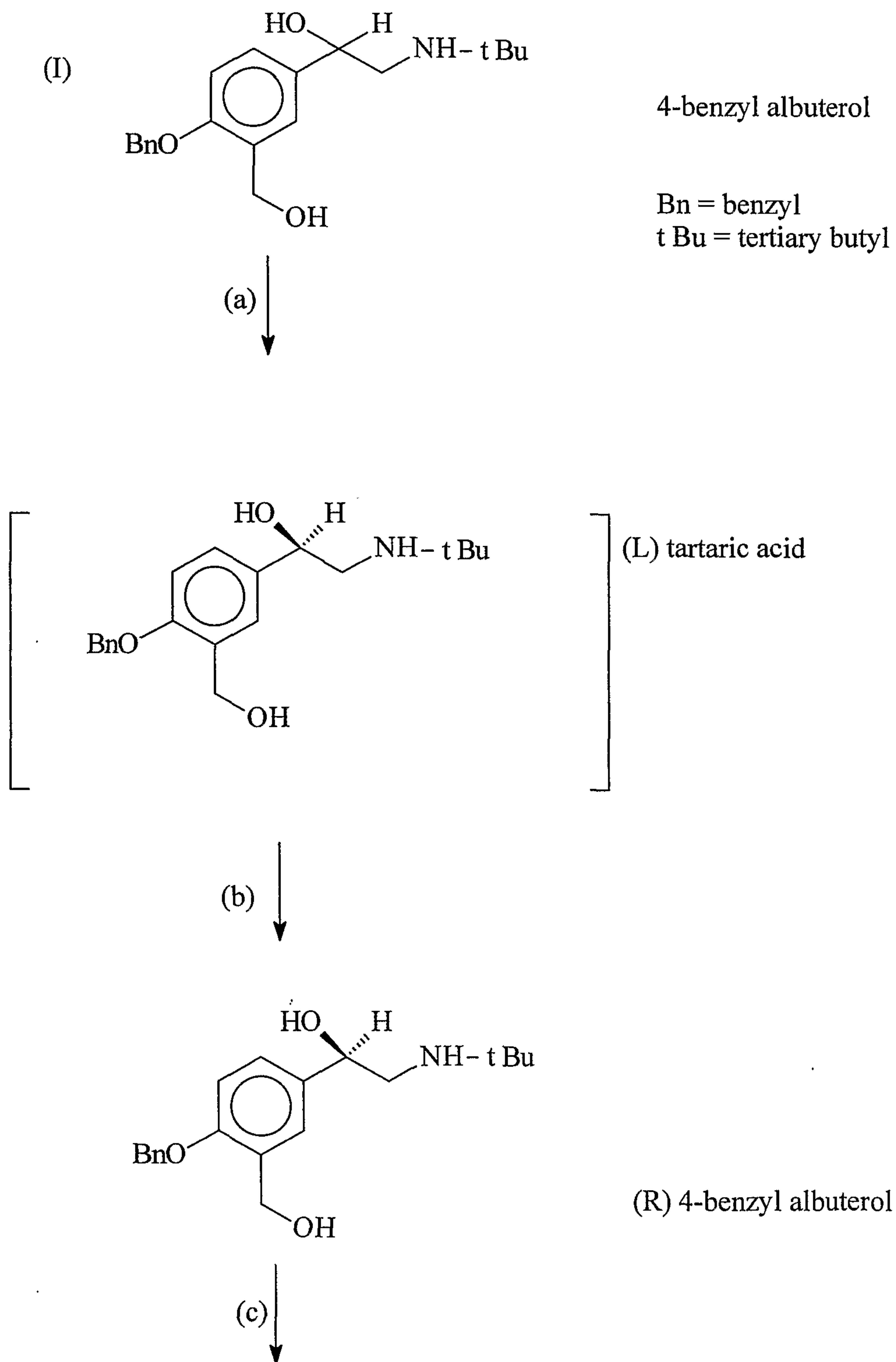
By the term "optically pure", we mean an enantiomeric excess (e.e.) (which is a measure well known in the art) of about 95% or more. The term "optically impure" refers to mixtures of enantiomers where the e.e. value is below about 95%, but where the mixture is not exactly racemic. We have found that the resolution step with (L) or

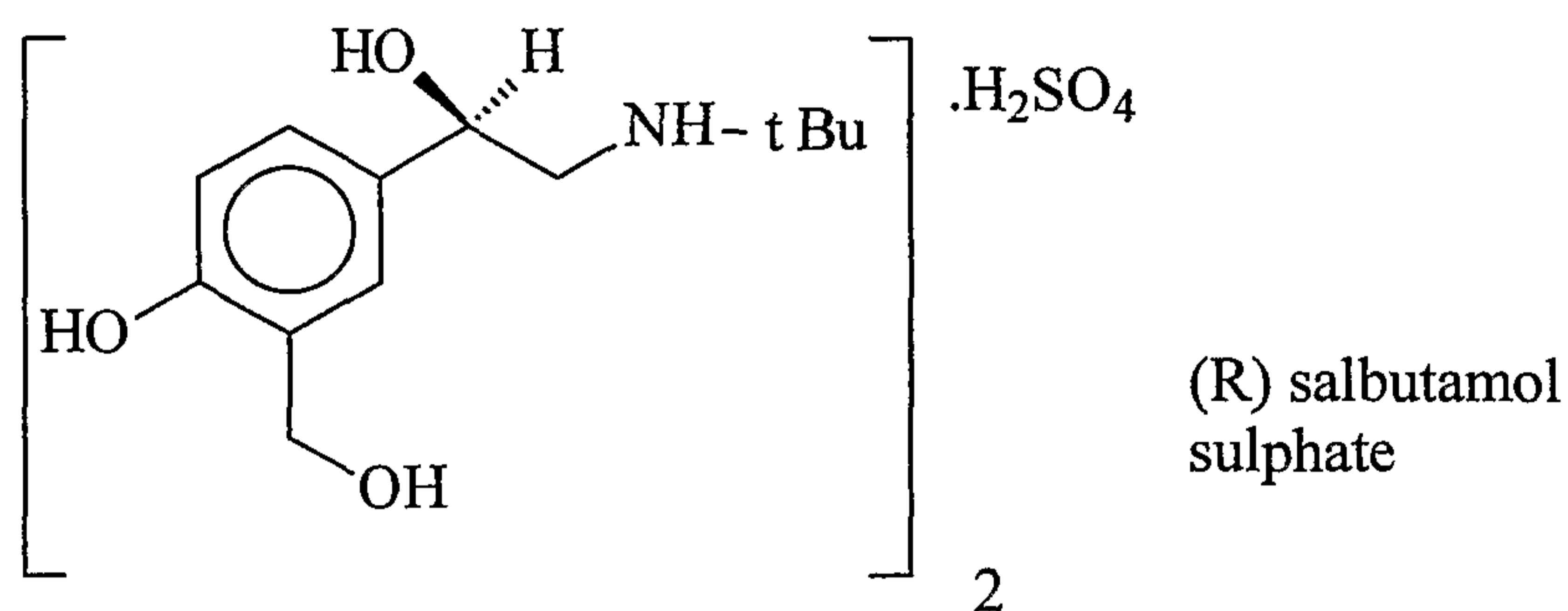
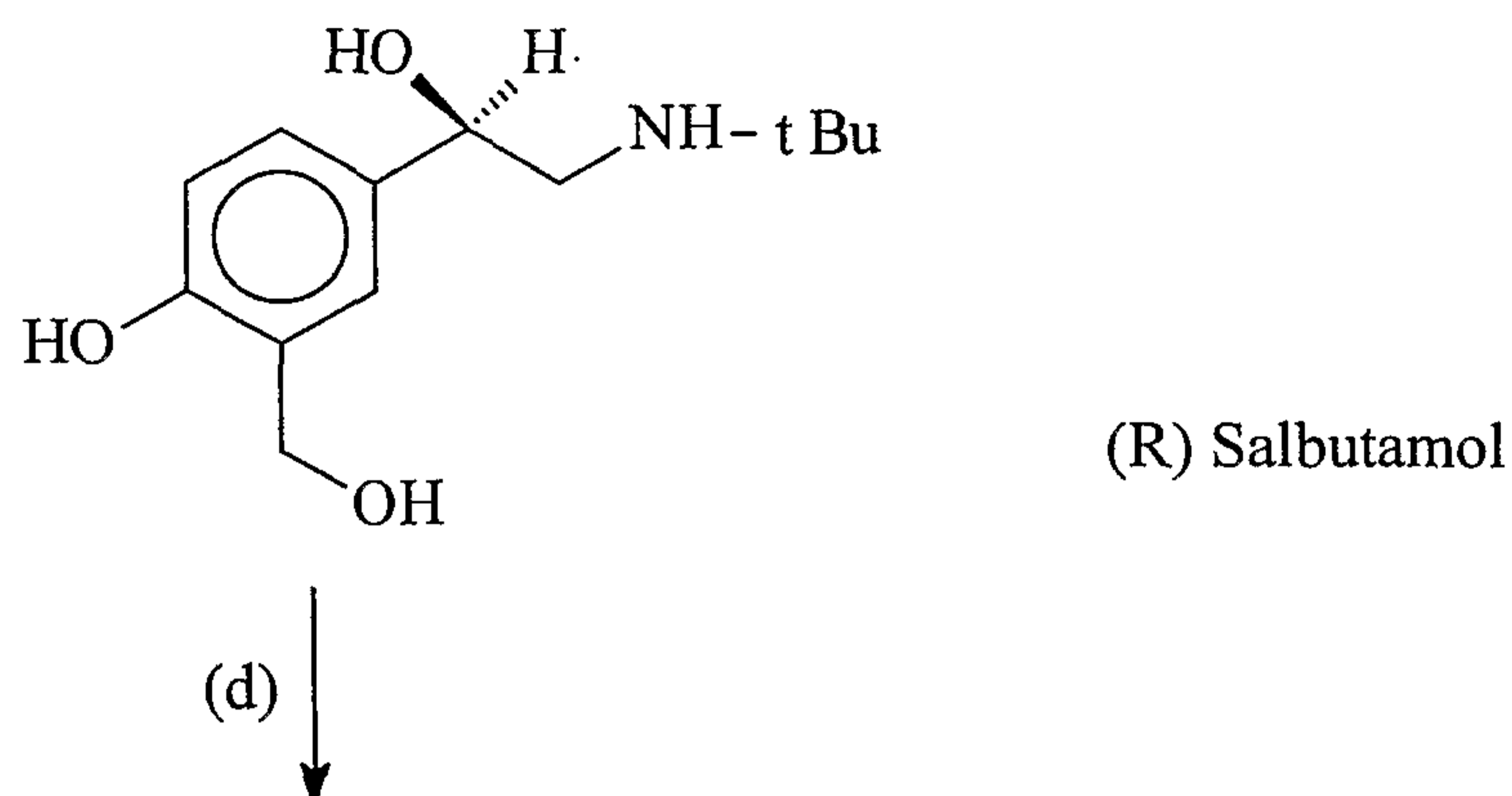
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(D) tartaric acid is very efficient, generally giving an e.e. value of 99% or more for the chosen isomer.

Operation of the process using our preferred precursor 4-benzyl albuterol is preferably carried out according to the following Scheme A below:

Scheme A





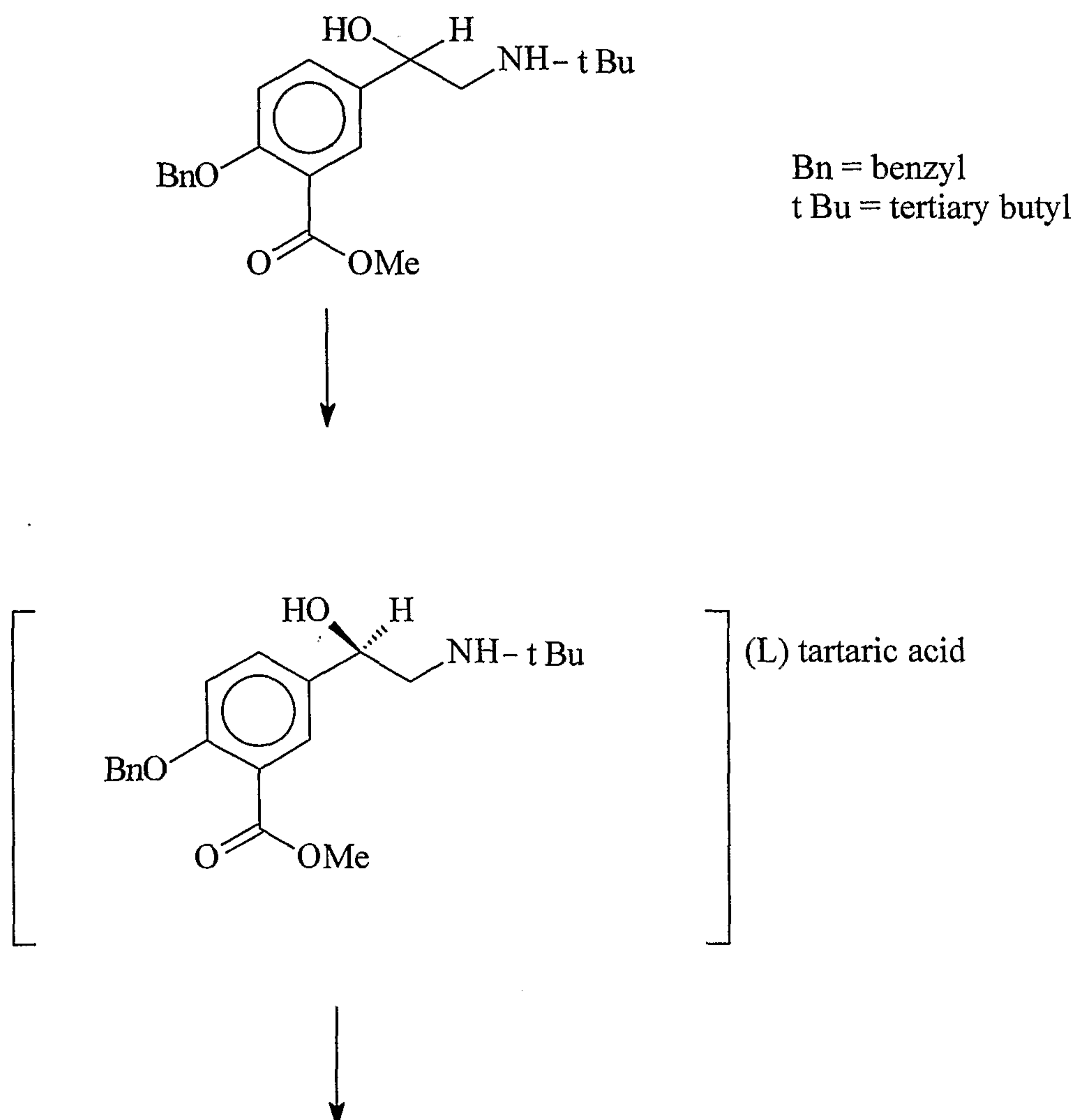
In step (a) a suspension of racemic 4-benzyl albuterol is mixed with a solution of either (L) or (D) tartaric acid (as desired) in an organic solvent. We prefer to use a solvent such as methanol, ethanol, isopropanol, acetone or ethyl acetate or a mixture of two or more thereof. The mixture is then chilled to give crystals of the (L) or (D) tartrate salt of 4-benzyl albuterol, which are then separated and purified. The yield of the chosen tartrate salt is generally above 30%, with an e.e. value of around 99%.

In step (b), the optically pure isomer of either (R) or (S) 4-benzyl albuterol is obtained from a solution (typically aqueous) of the corresponding tartrate salt. We prefer to liberate the free base from the tartrate salt by the gradual addition of alkali to the solution of the salt, for example by using sodium hydroxide or sodium carbonate. Other bases that can be used include potassium hydroxide, potassium carbonate, aqueous ammonia and sodium or potassium bicarbonate. Prolonged stirring of the alkali/salt mixture is usually necessary to precipitate the free base completely from the solution. The yield of the (R) or (S) isomer of 4-benzyl albuterol is generally 40% or more based on the quantity of racemic starting material. The e.e. value remains high, typically at 99% or more.

In step (c), (R) or (S) 4-benzyl albuterol free base is de-benzylated in order to give (R) or (S) salbutamol. This is preferably carried out by suspending the isomer of 4-benzyl albuterol in an organic solvent such as ethanol, adding a palladium on carbon catalyst and hydrogenating the suspension under pressure in a hydrogenator. The resulting optically pure isomer of salbutamol is then filtered off. If desired, a pharmaceutically acceptable salt of the free base can be obtained by the addition of an acid (for example, dilute sulphuric or hydrochloric acid) in the usual way (see step (d)).

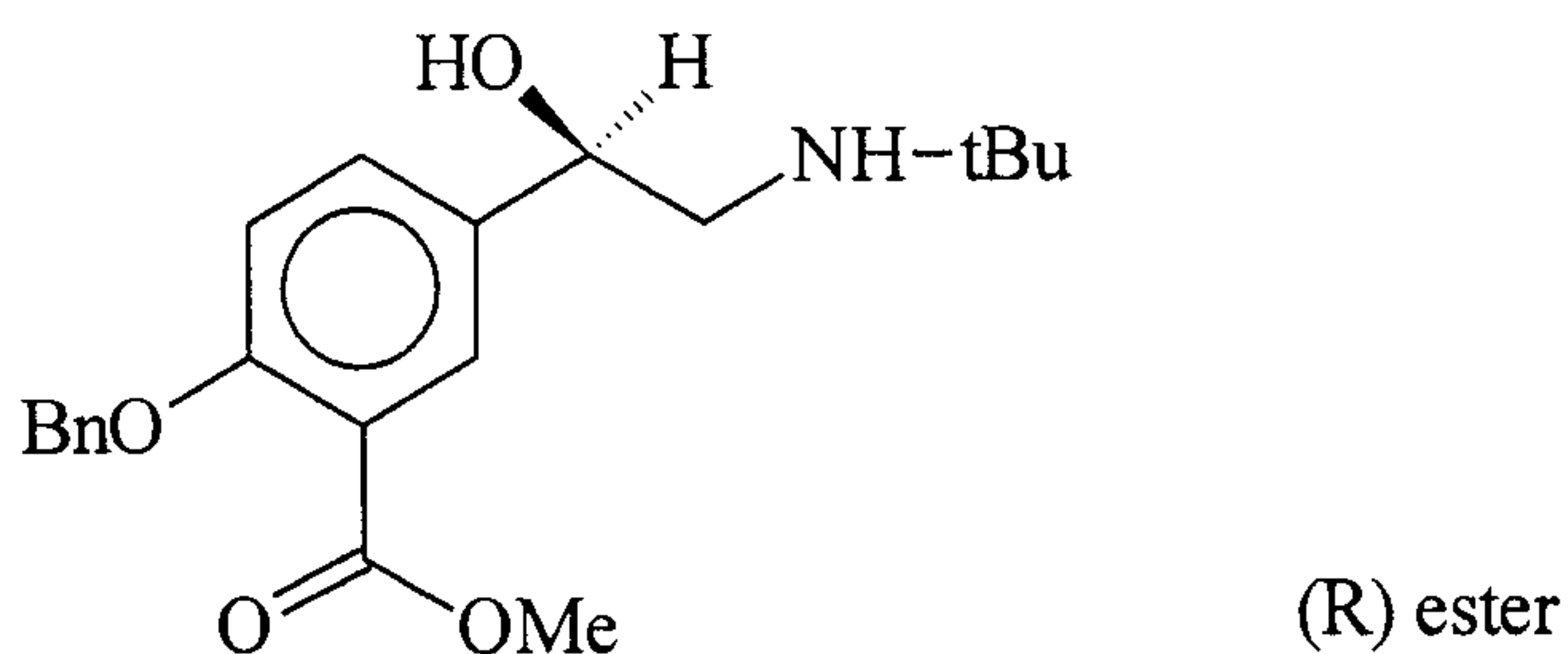
Alternatively, the resolving-step can if desired be carried out earlier in the process, for example, by resolving the ester intermediate (II). (L) or (D) tartaric acid may be used for the resolution, although preferably (L) tartaric acid is employed so as to give the (R) form of the ester. This preferred route is shown in Scheme B below.

Scheme B



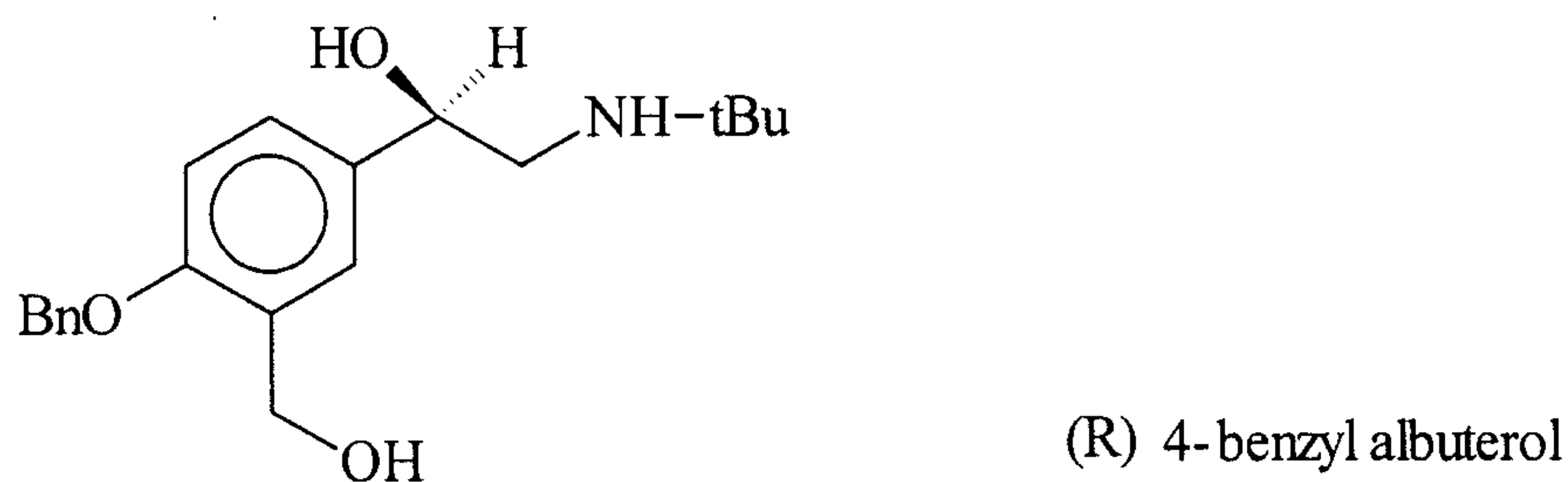
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reduction



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The reduction of the (R) isomer of the ester to (R) 4-benzyl albuterol can, for example, be carried out using lithium aluminium hydride, although any suitable reducing agent can be used. The resolution is typically carried out in the same way as that described for 4-benzyl

15

albuterol.

Other salbutamol precursors which can be usually employed in the process of the invention include derivatives of 4-benzyl albuterol in which the ring of the benzyl group is variously substituted. The benzyl group may, for

20 example, be substituted with one or more halogen atoms (such as, chlorine, fluorine or bromine) or one or more alkoxy groups such as methoxy. Other similar substitutions which have the purpose of protecting the phenolic group of the salbutamol precursor may also be used, as will be clear

25 to those skilled in the art.

In one aspect, the invention provides a process for making optically pure (R) salbutamol or a

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pharmaceutically acceptable salt thereof, which process comprises obtaining the (R) isomer of either salbutamol or a salbutamol precursor which is 4-benzyl albuterol or methyl-5-[2-[(1,1-dimethyl)amino]-1-hydroxyethyl]-2-(phenylmethoxy)-benzoate in optically pure form by resolving a racemic or optically impure mixture of enantiomers of salbutamol or of said precursor with (L) tartaric acid, and where necessary converting said isomer of said precursor into salbutamol; then optionally converting said optically pure (R) salbutamol into a pharmaceutically acceptable salt.

The following examples are intended to illustrate the invention:

Example 1

Preparation of R-4-Benzyl albuterol-L-tartrate:

Racemic 4-benzyl albuterol (100 g, 0.30 mole) is suspended in methanol (500 ml) and heated to reflux. A solution of L-tartaric acid (50 g, 0.33 mole) in methanol (150 ml) is introduced in about 15 minutes. The clear solution is then chilled to 0 to 5°C and the crystals are filtered. The wet crystals are taken up in isopropanol (300 ml) and heated to reflux, cooled to room temperature and filtered to obtain the title compound as a white solid (65 g, 45% yield, 99% e.e.).

Example 2

Preparation of R(-)-4-Benzyl albuterol:

The product from Example 1 (65 g, 0.13 mole) is dissolved in water (650 ml) and filtered over celite™ to remove insolubles. The clear filtrate is cooled to 10°C and a solution of 10% sodium hydroxide (80 ml) is slowly introduced. The sticky solid precipitated becomes free on

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prolonged stirring for 4 hours. The solid is filtered, washed with water and dried to obtain the title compound as a white solid (40 g, 40% yield based on amount of racemic compound, 99% e.e.).

5 Example 3

Preparation of R(-)Salbutamol Sulphate:

R-4-Benzyl Albuterol (10 g, 0.12 mole) is suspended in 500 ml ethanol, 5% palladium on carbon (2 g) is added and shaken in a 1 lit. Parr Hydrogenator at 30 psi for 2 hours. 10 The catalyst is filtered off and the clear filtrate is cooled to 15°C under stirring. Sulphuric acid (4.9 g, 0.05 mole) is introduced dropwise and the resulting mixture is stirred for 1 hour and filtered. The solids are washed with ethanol (20 ml) and dried at 45 to 50°C in a 15 vacuum oven to give pure R-salbutamol sulphate (30 g, 86% yield).

Example 4

Preparation of R(-)methyl-5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-(phenylmethoxy)-benzoate:

20 Racemic ester (100 g, 0.28 mole) is suspended in methanol (600 ml) and heated to reflux. A solution of L-tartaric acid (50 g, 0.33 mole) in methanol (150 ml) is introduced in about 30 minutes. The clear solution is then chilled to 0 to 5°C and the crystals are filtered. The wet crystals 25 are taken up in ethanol (400 ml) and heated to reflux, cooled to room temperature and filtered to obtain the R(-) ester- L-tartaric as a white solid. This is then dissolved in water (500 ml) and filtered over celite™ to remove insolubles. The clear filtrate is then cooled to 30 0 to 5°C and an aqueous ammonia solution is introduced so as

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to obtain a pH of 8.5 to 9. The mass is then stirred for 3 hours and the solids filtered, washed with water and dried to obtain the title compound (38 g, 38% yield based on racemic compound, 99% e.e.).

5 Example 5

Preparation of R(-)-4-benzyl albuterol using R(-) ester of Example 4:

R(-)-ester (35.8 g, 0.1 mole) is suspended in dry tetrahydrofuran (250 ml) and cooled to 0 to 5°C. Lithium
10 aluminium hydride (4 g, 0.33 mole) is introduced slowly and the reaction mass is further stirred for 3 hours. A 15% sodium sulphate (20 ml) is then introduced and the precipitate is then filtered off. The clear filtrate is then concentrated, taken up in ethyl acetate (100 ml),
15 cooled to 5°C and filtered to obtain the title compound (30 g, 91%; 99% e.e.).

Example 6

Preparation of (S)-4-benzyl albuterol-(D)-tartrate:

Racemic 4-benzyl albuterol (110 g, 0.30 mole) is suspended
20 in methanol (500 ml) and heated to reflux. A solution of (D-)tartaric acid in methanol (150 ml) is introduced in about 15 minutes. The clear solution is then chilled to 0 to 5°C and the crystals filtered. The wet crystals are taken up in isopropanol (300 ml) and heated to reflux,
25 cooled to room temperature and filtered to obtain the title compound as a white solid (65 g, 45%; 99% e.e.).

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Example 7Preparation of (S)-4-benzyl albuterol:

The product from Example 6 (65 g, 0.13 mole) is dissolved in water (650 ml) and filtered over celite™ to remove
5 insolubles. The clear filtrate is cooled to 10°C and a solution of 10% sodium hydroxide (80 ml) is slowly introduced. The solids thus

precipitated are filtered, washed with water and dried to obtain the title compound as a white solid (40 g; 40% based on racemic compound, 99% e.e.).

Example 8

Preparation of (S)- salbutamol sulphate:

(S)-4- benzyl albuterol (40 g; 0.12 mole) is suspended in 500 ml ethanol, 5% palladium on carbon (2 g) is added and shaken in a 1 litre Parr hydrogenator at 30 psi for 2 hours. The catalyst is then filtered off and the clear filtrate is cooled to 15°C. Sulphuric acid (4.9 g; 0.05 mole) is added dropwise and the resultant mixture is stirred for 1 hour and filtered. The solids are washed with ethanol (20 ml) and dried to give pure (S)-salbutamol sulphate (30 g; 86%).

Example 9

Salbutamol (100 g; 0.41 mole) is dissolved in a 1:1 mixture of ethyl acetate and methanol (500 ml) at about 70°C. To this solution is added L(+)-tartaric acid (66 g; 0.44 mole) under stirring. The contents are maintained at 70°C for 2 hours. On cooling, the tartrate salt crystallises. This is filtered and recrystallised from ethanol to give 52 g of the pure R (-) salbutamol tartrate. The salt is then suspended in methanol (200 ml) and a solution of sodium methoxide (15 g; 0.27 mole) in methanol is introduced. The precipitated solids are filtered off and the filtrate is cooled to 10°C. Sulphuric acid is added slowly to obtain a pH of the reaction mass between 4 to 4.5. The solids are filtered and dried to obtain R(-)-salbutamol sulphate (30 g).

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CLAIMS:

1. A process for making optically pure (R) salbutamol or a pharmaceutically acceptable salt thereof, which process comprises obtaining the (R) isomer of either salbutamol or a
5 salbutamol precursor which is 4-benzyl albuterol or methyl-5-[2-[(1,1-dimethyl)amino]-1-hydroxyethyl]-2-(phenylmethoxy)-benzoate in optically pure form by resolving a racemic or optically impure mixture of enantiomers of salbutamol or of said precursor with (L) tartaric acid, and
10 where necessary converting said isomer of said precursor into salbutamol; then optionally converting said optically pure (R) salbutamol into a pharmaceutically acceptable salt.
2. A process according to claim 1, wherein the resolution is carried out on racemic salbutamol or on an
15 optically impure mixture of enantiomers of salbutamol.
3. A process according to claim 1, wherein the resolution is carried out using racemic or an optically impure mixture of enantiomers of either 4-benzyl albuterol or methyl-5-[2-[(1,1-dimethyl)amino]-1-hydroxyethyl]-2-
20 (phenylmethoxy)-benzoate.
4. A process according to any one of claims 1 to 3, wherein the optical purity of the isomer of said salbutamol precursor or the optical purity of the corresponding isomer of salbutamol has a value of 95% enantiomeric excess or
25 more.
5. A process according to claim 4, wherein the optical purity has a value of 99% enantiomeric excess or more.