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**Datasheet for the decision  
of 22 January 2019**

**Case Number:** T 1559/15 - 3.3.10

**Application Number:** 06807907.8

**Publication Number:** 1939172

**IPC:** C07C269/04, C07C271/44,  
C07C215/50, C07C217/56

**Language of the proceedings:** EN

**Title of invention:**  
METHOD OF OBTAINING PHENYL CARBAMATES

**Patent Proprietor:**  
Interquim, S.A.

**Opponent:**  
Novartis AG

**Headword:**  
METHOD OF OBTAINING PHENYL CARBAMATES / Interquim

**Relevant legal provisions:**  
EPC Art. 56, 100(b)

**Keyword:**  
Grounds for opposition - insufficiency of disclosure (no)  
Inventive step - (yes)

**Decisions cited:**

**Catchword:**



**Beschwerdekammern**  
**Boards of Appeal**  
**Chambres de recours**

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Case Number: T 1559/15 - 3.3.10

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.10**  
**of 22 January 2019**

**Appellant:** Novartis AG  
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**Decision under appeal:** **Decision of the Opposition Division of the  
European Patent Office posted on 26 May 2015  
rejecting the opposition filed against European  
patent No. 1939172 pursuant to Article 101(2)  
EPC.**

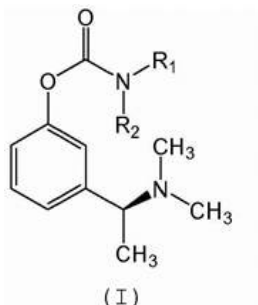
**Composition of the Board:**

**Chairman** P. Gryczka  
**Members:** J.-C. Schmid  
F. Blumer

## Summary of Facts and Submissions

I. The Appellant (Opponent) lodged an appeal against the decision of the Opposition Division rejecting the opposition against European patent No. 1 939 172, independent claims 1, 6, 12 and 19 thereof reading as follows:

"1. A method of obtaining a phenyl carbamate of general formula (I):



wherein

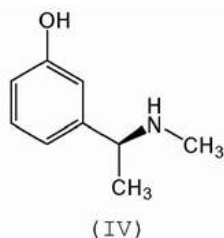
R<sub>1</sub> is C<sub>1</sub>-C<sub>5</sub> lower alkyl or benzyl; and

R<sub>2</sub> is methyl, ethyl or propyl;

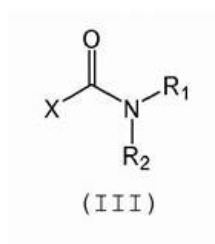
its solvates, hydrates or pharmaceutically acceptable salts,

which comprises:

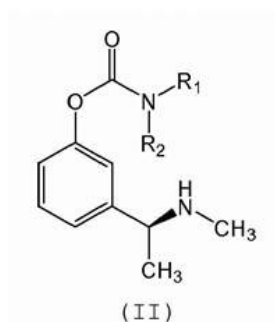
a) reacting a compound of formula (IV):



in the presence of a base, with a compound of formula (III) :



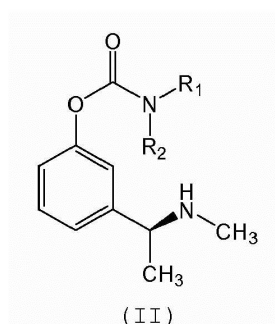
wherein  $R_1$  and  $R_2$  have the previously mentioned meanings and X is a halogen,  
to give a compound of formula (II):



wherein  $R_1$  and  $R_2$  have the previously mentioned meanings; and

b) subjecting said compound of formula (II) to a reductive amination reaction, or alternatively to a methylation reaction by reacting said compound of formula (II) with a methyl halide, to obtain the compound of formula (I)."

"6. A compound of formula (II):



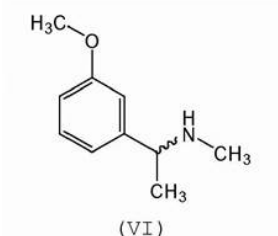
wherein

$R_1$  is  $C_1$  - $C_5$  lower alkyl or benzyl;

$R_2$  is methyl, ethyl or propyl;

and its salts. "

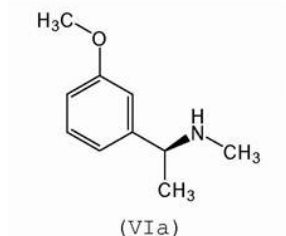
"12. A method of resolving the enantiomeric mixture of a compound of formula (VI):



which comprises:

- a) forming diastereoisomeric salts by means of reacting the corresponding enantiomers of the enantiomeric mixture with a optically active acid;
- b) recrystallizing the diastereoisomeric salts obtained in step a) in an alcohol solvent or in an alcohol solvent/water mixture to obtain a diastereoisomeric salt rich in the desired enantiomer; and
- c) obtaining the desired enantiomer by means of:
  - c.1) resuspending the diastereoisomeric salt obtained in step b) in an aqueous-organic medium;
  - c.2) neutralizing the medium using a base until reaching a pH comprised between 7 and 12; and
  - c.3) separating the organic phase and isolating the desired enantiomer in the form of a base or in the form of an acid addition salt."

"19. A compound of formula (VIa):



or a salt thereof."

Independent claims 8 and 9 contain all the features of claim 1.

II. The Appellant requested in its notice of opposition the revocation of the patent in suit in its entirety for lack of inventive step (Article 100(a) EPC) and insufficient disclosure of the invention (Article 100(b) EPC).

*Inter alia* the following documents were submitted in the opposition proceedings:

- (1) WO-A-2004/037771 and
- (3) J. Chem. Soc. 1932, 2513-2519.

According to the opposition Division the claims did not require any yield to be obtained, in particular did not require that the step of carbamoylation of the compound of formula (IV) to produce the compound of formula (II) is achieved with a yield higher than 70%. The skilled person was able to perform the carbamoylation step, for instance by following the instruction of example 4 of the patent-in-suit. The invention was therefore sufficiently disclosed.

With respect to inventive step, the Opposition Division considered that document (1) represented the closest prior art to the invention. The technical problem was seen in the provision of an alternative process for obtaining the optically resolved phenyl carbamates of formula (I). Examples 1 to 9 showed that the claimed method was a solution to this problem. None of the cited documents suggested that the compounds of formula (I) could be obtained by carbamoylation of a phenol comprising a secondary amino moiety. The subject-matter of claims 1 to 5 and 8 to 11 of the patent as granted, which were directed to methods including this step, involved therefore an inventive step. An inventive step could also be acknowledged for the subject-matter of

claims 6 and 7 of the patent as granted, since these claims were directed to the intermediate of synthesis of formula (II) obtained by the carbamoylation step.

Claims 12 to 21 of the patent as granted were directed to the optical resolution of the synthetic intermediate of formula (VI) and to the product (VIa) obtained by the process. None of the prior art documents suggested that the optical resolution could take place on the phenoxy-protected derivative as defined in claim 12. The subject-matter of these claims involved therefore an inventive step.

The Opposition Division came thus to the conclusion that the subject-matter of the claims of the patent as granted involved an inventive step.

III. With regard to sufficiency of disclosure, the sole Appellant's submission reads as follows: "As set out in paragraphs 2.1 to 2.9 of the opponent's submissions of 11th April 2013, the patent is insufficient disclosed insofar as it requires the achievement of any specific yield (alleged in paragraph [0020] of the patent, e.g. 85% to 95%) or any specific chemoselectivity (alleged e.g. in paragraph [0018] of the patent). Reaction conditions within the scope of the claims gave rise to carbamoylation (amidation) at the amine site (see paragraph 2.7 of the opponent's submissions of 11th April 2013), which rendered specific yields and chemoselectivities impossible."

With regard to inventive step, according to the Appellant, the closest prior art to the invention was document (3), which was directed to the same purpose as the patent, i.e. to providing methods of obtaining optically active phenyl carbamate with increased yield



and allowing quantitative obtainment of the (S) enantiomer. The carbamoylation reaction in document (3) did not use a carbamoyl halide. However, the reagent used in document (3) was equivalent to the carbamoyl halide.

The difference between the process of document (1) and that of claim 1 was that the carbamoylation step occurred on the compound bearing the secondary amine rather than the tertiary amine, the conversion to the tertiary amine being carried out thereafter. Starting from document (1) as the closest prior art, the objective technical problem was the provision of an alternative process for preparing optically resolved phenyl carbamates. The carbamoylation step of the claimed method could not be performed across the full scope of claim 1, since different reaction conditions, such as the number of equivalents of the base, the solvent or the number of equivalents of the carbamoyl chloride, in the carbamoylation step led to very different results in terms of yield and chemoselectivity. The technical prejudice against carrying out the carbamoylation step on the compound of formula (IV) bearing a secondary amine group, as submitted by the Respondent, was based on mischaracterization of the state of the art and had not been substantiated. Since the objective technical problem was only to provide an alternative, the question was simply whether the skilled person could, and not necessarily would, have carried out the carbamoylation step on a compound bearing a secondary amine. There was no doubt that it could have done so, since the carbamoylation reactions were well known. Thus, the process of claim 1 was obvious in view of document (1) alone.

The skilled person would have also found explicit motivation in document (3) to use a compound bearing the secondary amine in the initial steps of the synthesis of the compound of formula I, since the resolution was carried out on the  $\alpha$ -m hydroxyphenylethylmethylamine, which is the enantiomeric mixture of the compound of formula IV. The compound of formula IV was therefore an obvious starting product for the synthesis of the compounds of formula I. Therefore, the process of claim 1 was obvious over document (1) in combination with document (3).

Document (3) represented the closest prior art for claims 12 and 19 because it disclosed routes to the synthetic intermediate formula (IV). The route included a method of resolving  $\alpha$ -m hydroxyphenylethylmethylamine by reaction with an optically active acid. The difference between the subject-matter of claim 12 and the process of document (3) was that the resolution had been carried out at an earlier stage in the process on a methoxy group instead of a phenol group. The technical problem to be solved could only be seen in the provision of an alternative route for the preparing the compound of formula (IV).

Documents (1) and (3) each provided motivation for carrying out the optical resolution on the methoxy compound, which was an earlier intermediate in the synthesis of phenyl carbamates. Further, the features of the method of claim 12 were simply routine choices for the skilled person. It was also obvious to provide the compound of claim 19 as an intermediate for the preparation of the compound of formula (IV). The subject-matter of claims 12 and 19 lacked therefore an

inventive step in the light of document (3) alone, or in combination with document (1).

IV. According to the Respondent, the closest prior art to the invention regarding claims 1 to 11 was document (1), which disclosed the preparation of rivastigmine. The technical problem was the provision of an alternative method for preparing the carbamate of formula (I), including rivastigmine. It was not obvious in the light of the prior art to first carry out a carbamoylation reaction on the compound of formula (IV) which contains a secondary amine group and then to methylate the amine group to produce the compounds of formula (I). The Appellant's obviousness objection was only based on an *ex post facto* analysis explaining why the invention worked. There was no hint in the cited prior art to arrive at the claimed method or to the intermediate of formula (II) in order to provide an alternative method for preparing the compound of formula (I).

Regarding claims 12 to 21, the closest prior art to the invention was document (3). This document disclosed the preparation of the compound of formula (IV) by the optical resolution of its enantiomeric mixture. Document (1) indicated that it was desirable, but far from feasible, to perform optical resolution at an early stage of synthesis. In addition, document (3) taught that it was not easy to find an appropriate compound for the resolution step. It was therefore not obvious to carry out the optical resolution on the compound of formula (VI). It was also not obvious to provide the compound of formula (VIa), as an intermediate of synthesis, for the preparation of compound (IV). The subject-matter of claim 12 to 21 involved therefore an inventive step.

- V. The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the appeal be dismissed, or subsidiarily that the patent be maintained on the basis of one of the auxiliary requests 6, 7 or 9 filed with the letter dated 5 February 2016, or auxiliary request 10 filed with the letter dated 21 December 2018.

- VI. At the end of the oral proceedings held on 22 January 2019 the decision of the Board was announced.

### **Reasons for the Decision**

1. The appeal is admissible.

#### *Sufficiency of disclosure*

2. The Appellant submitted that the invention was insufficiently disclosed repeating arguments already put forward before the first instance, namely that the carbamoylation step could not be carried out with the required yields and chemoselectivity. These arguments were rejected by the Opposition Division in the contested decision which found that the claims did not require any yield to be obtained and that the skilled person was able to perform the contested carbamoylation step, for instance by following the instruction of example 4 of the patent-in-suit. The appellant did not provide any argument against the opposition division's reasoning.

Under these circumstances, the Board has no reason to deviate from the reasoning and conclusion of the Opposition Division that the invention is sufficiently disclosed in the patent-in-suit.

*Inventive step*

*Main request: Patent as granted*

3. *Closest prior art*

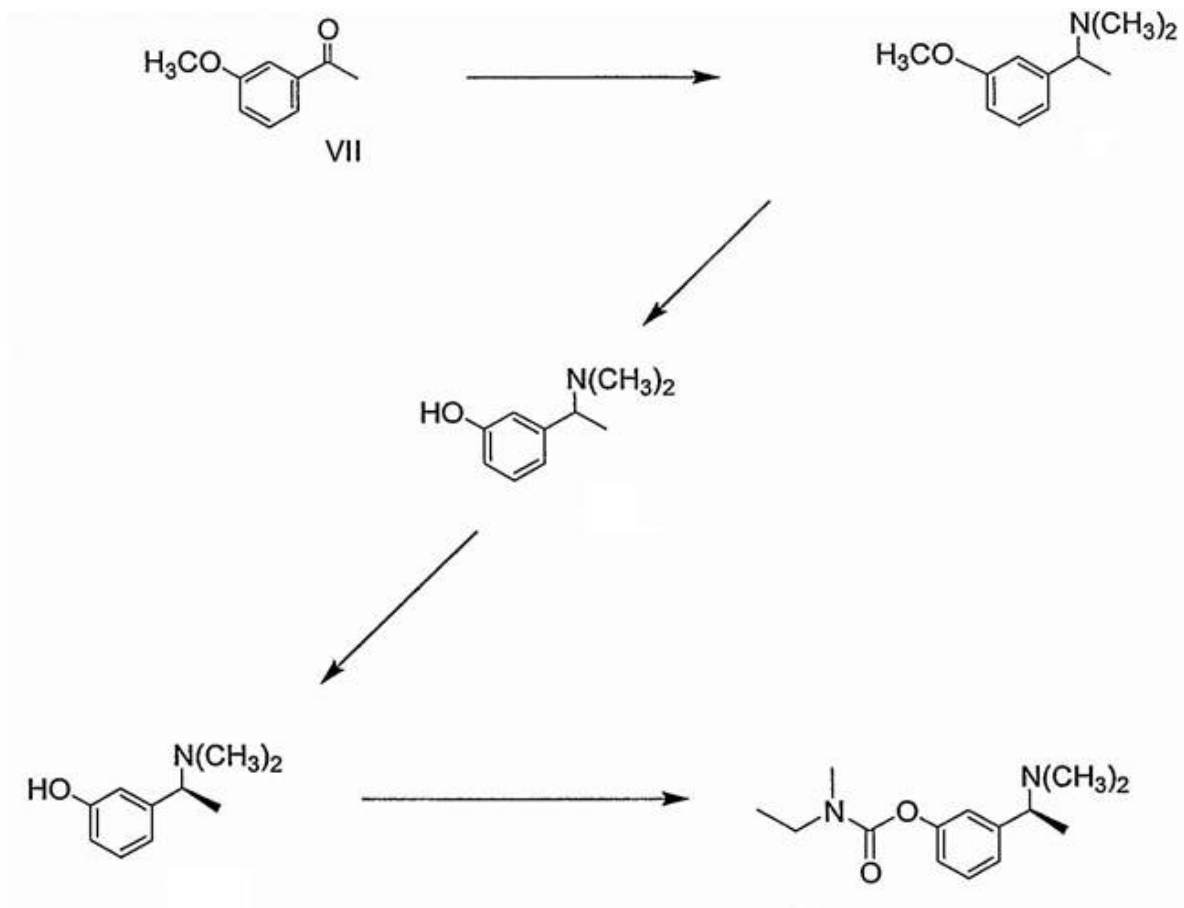
3.1 The patent-in-suit relates to the preparation of phenyl carbamates of formula I starting from 3-methoxyacetophenone (formula (VII)) via the intermediate compound of formula (IV) (see claims 8 and 9), which is a known compound (see document (3), page 2517, bottom).

Hence, one aspect of the patent-in-suit (claims 1 to 11) relates to preparing compounds of formula (I) starting from compound (IV) involving the intermediate of synthesis of formula (II) and (III) (see paragraph [0017] of the patent-in-suit). This method of synthesis is the subject-matter of claims 1 to 5. Claims 6 and 7 are directed to the intermediate of formula (II) and claims 8 to 11 to methods of obtaining a phenyl carbamate of formula (I) as in claim 1, but further comprising the steps of obtaining the intermediate of formula (IV) starting from 3-methoxyacetophenone (formula VII).

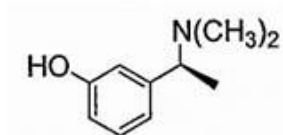
As the intermediate of synthesis of formula (IV) is known, there is another aspect of the invention (claims 12 to 21), which relates to the synthesis of this intermediate involving the optical resolution of enantiomeric mixture of formula (VI) to produce

intermediate (VIa), as depicted in scheme II in paragraph [0026] of the patent-in-suit. This aspect is the subject of claims 12 to 18 which are directed to the method of resolving the enantiomeric mixture of formula (VI) and claim 19 to 21 which are directed to the intermediate of formula (VIa).

3.2 Document (1) discloses a process for the preparation of rivastigmine, which is a carbamate of formula (I) according to the patent-in-suit, wherein R1 is ethyl and R2 is methyl) starting from 3-methoxyacetophenone (formula VII) according to the following route

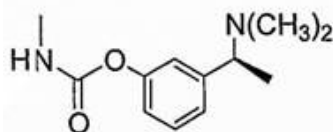


Thus, rivastigmine is obtained by reacting



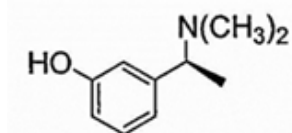
with a carbamoyl halide, which is a compound of formula III according to the patent-in-suit, wherein  $R_1$  is methyl and  $R_2$  is methyl (see claim 1).

3.3 Document (3) discloses a process for the preparation of

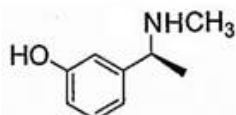


miotine having formula

by reacting

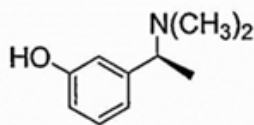


with  $O=C=NMe$ , which is not a carbamoyl halide (see page 2519, second paragraph). Furthermore, miotine is not a compound of formula (I), since  $R_1$  and  $R_2$  cannot represent hydrogen. The route of synthesis disclosed in document (3) involves the compound of



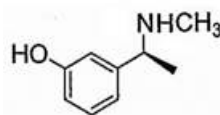
formula (IV), which is prepared by resolving the enantiomeric mixture of  $\alpha$ -*m*-methoxyphenylethylmethyl amine (see page 2517, second paragraph to page 2518, first paragraph). This enantiomeric mixture was prepared by reacting either  $\alpha$ -*m*-methoxyphenylethyl bromide or chloride with methylamine followed by demethylation of the methoxy group by hydrobromic acid (see paragraph bridging page 2513 and 2514; page 2515, last paragraph to page 2517, first paragraph).

3.4 In both documents (1) and (3), the last step for the preparation of rivastigmine and miotine, respectively,



involves the carbamylation of

In document (1) this compound is obtained by resolving its racemic mixture using an optically active acid (see claim 3; pages 10 and 11). In document (3) this compound was obtained by a reductive amination



reaction, namely by reacting (IV) with formaldehyde in methanol followed by hydrogenation in the presence of PtO<sub>2</sub> as catalyst (see paragraph bridging pages 2518 and 2519).

3.5 The Board therefore considers that document (1), which like the first aspect of the invention, aims to prepare a compound of formula (I), represents the closest prior art for the first aspect (claims 1 to 11 of the patent as granted), whereas document (3), which discloses the synthesis of the compound of formula (IV), represents the closest prior art for the second aspect of the invention (claims 12 to 21).

3.6 According to the Appellant, document (3) was also the closest prior art for claim 1 to 11, or at least equally close as document (1).

However, document (3) does not disclose any compounds of formula (I), and hence does not aim to prepare these compounds. Already for this reason, document (1) is closer to the invention than document (3) for the aspect relating to the preparation of the compounds of formula (I).



*Claim 1 to 11 - First aspect*

4. *Technical problem*

Starting from document (1) as the closest prior art, the respondent submitted that the technical problem to be solved the first aspect of the patent-in-suit was the provision of an alternative process for preparing compounds of formula (I).

*claim 1*

5. *Solution*

The proposed solution is the process of claim 1 which is characterised in that a compound of formula (IV) is carbamoylated to produce a compound of formula (II), whose amine group is then methylated.

6. *Success*

Examples 4 and 5 show that rivastigmine is obtained in a two-step process according to claim 1. First the compound of formula (IV) in the presence of a base (sodium hydride) is reacted with ethylmethylcarbamoyl chloride to give the compound a formula (II) (example 4). Then the compound of formula (II) is subjected to a reductive amination reaction to provide rivastigmine (example 5).

According to the Appellant, the problem was not solved across the whole scope of claim 1, since different reaction conditions, such as the number of equivalents of the base, the solvent or the number of equivalents of the carbamoyl chloride, in the carbamoylation step

led to very different results in terms of yield and chemoselectivity.

However, the proposed solution is not characterized by specific reaction conditions of the carbamoylation step, but is characterized by the new route of synthesis starting from compound of formula (IV) and involving the compound of formula (II) as a synthetic intermediate. Hence, the Applicant's argument relying on specific reaction conditions must be rejected.

7. *Obviousness*

According to the Appellant the solution was obvious from document (1) alone.

However, document (1) does not suggest that the compound of formula (IV) would be a suitable starting product in the preparation of compound of formula (I). Therefore, the subject-matter of claim 1 cannot be obvious in the light of document (1) alone.

The Appellant also argued that the subject-matter of claim 1 was obvious over the combination of document (1) with document (3).

The Board concurs with the Appellant's view that the skilled person faced with the problem of providing an alternative method for the preparation of compounds of formula (I) would consider the teaching of document (3) as regards the preparation of miotine, which is a close analogue of rivastigmine. Miotine differs from the compounds of formula (I) only in that it lacks an alkyl group on the carbamate moiety.

However, even by applying the teaching of document (3) to the process described of document (1), while adapting the process to the preparation of compounds of formula I, namely by replacing the isocyanate used for the carbamoylation by a compound of formula (III), the skilled person would not arrive at the process as claimed in claim 1 of the patent as granted. To arrive at the claimed process, the skilled person must further reverse the two steps of the process disclosed in document (3).

According to the Appellant, there was no reason why the skilled person would not reverse the two final steps of this process.

However, since compound (IV) has two carbamoylation-reactive functionalities, namely a secondary amine group and the hydroxyl of the phenol moiety, the skilled person would not have attempted to perform the carbamoylation step before performing the reductive amination reaction on the secondary amine group which prevents carbamoylation on the amine group.

The Appellant also argued that the relevant test for the obviousness of provision of a mere alternative was whether the skilled person could have reached the claimed solution, not whether he would have done.

However, according to the established case law, the question is not whether the skilled person could have carried out the invention, but whether he would have done so in the hope of solving the underlying technical problem - see point 5 "could-would approach", Case Law of the Boards of Appeal 8th 2016 I.D.5, page 183. So the point is not whether the skilled person could have arrived at the invention by modifying the prior art,

but rather whether, in the light of the technical problem addressed, namely in the present case in order to provide an alternative method of preparation, he would have done so because of promptings in the prior art. Once an invention exists, it can often be shown that the skilled person could have made it by modifying different elements in the prior art, but such arguments have to be disregarded as the product of *ex post facto analysis*. Accordingly, the Appellant's argument must be rejected.

8. Consequently, the Board comes to the conclusion that the subject-matter of claim 1 of the patent as granted involves an inventive step (Article 56 EPC).

*claims 2 to 11*

The subject-matter of dependent claims 2 to 5, that of independent claims 8 and 9 which although being draft as independent claims comprise all the features of claim 1, and that of dependent claims 10 and 11, involve an inventive step for the same reasons as for claim 1.

Claims 6 and 7 are directed to the compound of formula (II) obtained as a synthetic intermediate in the method of claim 1, which involves an inventive step. Thus, the subject-matter of these claims also involves an inventive step.

*Claims 12 to 21 - second aspect of the invention*

This aspect of the invention concerns the preparation of the compound of formula (IV) from the compound (VII) according to reaction scheme (II).

9. *Closest prior art*

The board considers in agreement with the Parties that document (3), which discloses the preparation of compound (IV) by resolving its enantiomeric mixture, represents the closest prior art.

10. *Technical problem*

The technical problem to be solved is the provision of an alternative method of preparation of the compound of formula (IV).

*Claims 12 to 18*

11. *Proposed solution*

The solution proposed is the method of claim 12 comprising the optical resolution of the enantiomeric mixture (VI) using an optically active acid and recrystallizing the diastereoisomeric salts in an alcohol solvent or in an alcohol solvent / water mixture.

12. *Success*

The Appellant did not contest that the problem was solved. In view of example 9 and scheme (II) of the patent-in-suit, the Board is also satisfied that the problem is solved.

13. *Obviousness*

It remains to be decided whether or not the proposed solution to the problem underlying the patent-in-suit is obvious in view of the cited prior art, i.e. whether

it is obvious to carry out the optical resolution of compound (VI) as claimed in claim 12 in order to provide a compound of formula (IV).

According to the Appellant, the proposed solution solution was obvious in the light of the last full paragraph of page 2 of document (1) which taught that for efficiency reasons the resolution step in the preparation of an optical compound should be done at an early stage.

Notwithstanding that document (1) indicates that resolution in an earlier stage of the synthesis appears, at first sight, desirable, but far from being feasible (see first full paragraph of page 3), the skilled person even seeking to resolve the enantiomeric mixture at an earlier stage of the method of preparation as disclosed in document (3) would not arrive at the subject-matter of claim 12, since the enantiomeric mixture (VI) is not included in the synthetic pathway indicated in the document (3), nor in that of the document (1).

To summarise, document (3) alone, or in combination with document (1), does not render the subject-matter of claim 12 obvious.

For these reasons, the Board concludes that the subject-matter of claim 12, and by the same token that of dependent claims 13 to 18, involves an inventive step.

*Claims 19 to 21*

14. Claim 19 is directed to the compound of formula (VIa). As indicated above, the skilled person would not have

arrived at this compound in order to find an alternative method of preparation of the compound of formula (IV). Accordingly, the subject-matter of claim 19 and for the same reason of dependent claims 20 and 21 involves an inventive step.

15. As a result, the Appellant's challenge to the lack of inventive step is rejected.

16. Auxiliary requests

Since the main request is allowable for the reasons set out above, there is no need for the Board to decide on the lower ranking auxiliary requests.

## Order

### **For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:



S. Sánchez Chiquero

P. Gryczka

Decision electronically authenticated