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D E C I S I O N
of 8 April 2004

Case Number: T 0948/01 - 3.3.1

Application Number: 96301421.2

Publication Number: 0729939

IPC: C07C 227/32

Language of the proceedings: EN

Title of invention:
Process for preparing optically active allophenylnorstatin derivatives, and intermediates for use therein

Applicant:
Takasago International Corporation

Opponent:
-

Headword:
Allophenylnorstatin/TAKASAGO

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no) - obvious to try with reasonable expectation of success"

Decisions cited:
T 0197/86, T 0176/89, T 0507/89, T 0694/92, T 0296/93, T 0713/97

Catchword:
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Case Number: T 0948/01 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 8 April 2004

Appellant: Takasago international Corporation
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 7 March 2001 refusing European application No. 96301421.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
S. C. Perryman

Summary of Facts and Submissions

I. The appeal lies from the Examining Division's decision, despatched on 7 March 2001, refusing European patent application No. 96301421.2, published as EP-A-0 729 939, since the then pending set of 8 claims lacked inventive step over the disclosure of documents

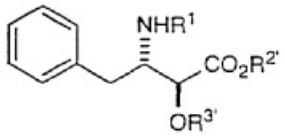
(1) EP-A-0 519 763 and

(5) J. Med. Chem., Vol. 33, 1990, pages 2707 to 2714.

In particular, the Examining Division found that document (5) represented the closest state of the art and that it could have been expected that the optically active allophenylnorstatin derivatives according to Claim 1 could be prepared following the same reaction sequence as the one known from document (1) for the preparation of the corresponding cyclohexyl compounds.

II. With telefax dated 19 July 2001 the Appellant filed an amended Claim 1, which read:

"1. A process for preparing an optically active (2S,3S)-allophenylnorstatin derivative represented by formula (I):

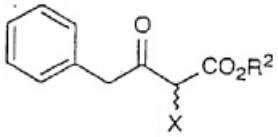


(I)

wherein R^1 represents an amino group protective group; $R^{2'}$ represents a hydrogen atom or a lower alkyl group having 1 to 6 carbon atoms; and $R^{3'}$ represents a hydrogen atom, a tri (lower alkyl) silyl group or a

(lower alkyl)diarylsilyl group; which comprises the steps of:

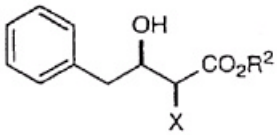
asymmetrical hydrogenating a 4-phenyl-2-halogeno-3-oxobutyric acid ester represented by the formula (III):



(III)

wherein R^2 represents a lower alkyl group having 1 to 6 carbon atoms; and X represents a halogen atom;

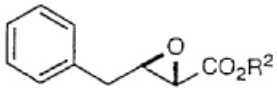
in isopropanol containing a ruthenium-phosphine complex to obtain a 4-phenyl-(2S)-halogeno-(3R)-hydroxybutyric acid ester represented by formula (IV):



(IV)

wherein R^2 and X are as defined above;

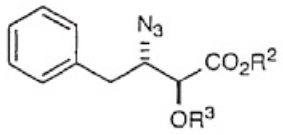
epoxidizing the ester represented by formula (IV) in the presence of a base to obtain a 4-phenyl-(2S,3R)-epoxybutyric acid ester represented by formula (V):



(V)

wherein R^2 is as defined above;

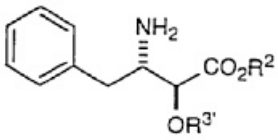
reacting the ester represented by formula (V) with a tri(lower alkyl)silylazide or a (lower alkyl)diarylsilylazide in the presence of a Lewis acid to obtain a (3S)-azido-4-phenyl-(2S)-trisubstituted silyloxybutyric acid ester represented by formula (VI):



(VI)

wherein R^2 is as defined above; and R^3 represents a hydrogen atom, a tri(lower alkyl)silyl group or a (lower alkyl)diarylsilyl group;

hydrogenolyzing the ester represented by formula (VI) to obtain a (2S,3S)-allophenylnorstatin derivative represented by formula (VII):



(VII)

wherein R^2 and $R^{3'}$ are as defined above;

protecting the amino group of the compound represented by formula (VII), and, if desired, hydrolyzing the compound before or after the amino group protection."

III. The Appellant essentially argued that the use of isopropanol as solvent in the asymmetric hydrogenation-step provides a significant and unexpected enhancement in the results obtained and that it could not have been predicted that with a ruthenium-phosphine complex an analogous stereoselectivity in the asymmetrical hydrogenation of a 4-phenyl-2-halogeno-3-oxobutyric acid ester would be obtained as in the hydrogenation of the corresponding 4-cyclohexyl-2-halogeno-3-oxobutyric acid ester.

IV. The Appellant requested that the decision be set aside and a patent be granted on the basis of Claim 1 provided by telefax of 19 July 2001 and Claims 2 to 8 underlying the contested decision.

Reasons for the Decision

1. The appeal is admissible.

2. Since the Board came to the conclusion that Claim 1 does not meet the requirement of inventive step, it is not necessary to give any reasoning as to whether the requirement of Articles 123(2) EPC and the requirement of novelty are met.

3. *Inventive step*

In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is in particular necessary to establish the closest state of the art forming the starting point, to determine in the light thereof the technical problem which the invention addresses and successfully solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

3.1 The "closest state of the art" is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common. In particular, where the background of the invention lies in difficulties encountered in known processes for preparing known compounds, the documents to be considered when determining the closest state of the art are those which describe these compounds and their preparation (T 713/97, point 4.2 of the reasons).

Since document (5), which is cited on page 2, lines 42 to 45, of the present application, is the only cited document describing the preparation of the allophenylnorstatin derivatives according to Claim 1, document (5) represents the closest state of the art, which was no longer contested.

As set out in the application in suit, document (5) effectively discloses, indeed, the syntheses of optically pure cyclohexylnorstatin and of (2S,3S)-phenylnorstatin and their isopropyl ester by oxidizing an alcohol to the corresponding aldehyde and adding hydrogen cyanide to the aldehyde (page 2709, left-hand column, second paragraph to right-hand column, last but one paragraph).

3.2 The Appellant submitted that the use of isopropanol as the solvent in the asymmetric hydrogenation-step provides an significant and unexpected enhancement, as follows from comparing the yields in example 1 for preparing (2S,3R)-2-chloro-3-hydroxy-4-phenylbutyrate in methanol or isopropanol.

However, according to the jurisprudence of the Boards of Appeal of the EPO, in order to show a superior effect, the nature of the comparison with the closest state of the art must be such that the effect is convincingly shown to have its origin in the distinguishing feature of the invention (see T 197/86 OJ EPO, 1989, 371, Reasons for the Decision 6.1.3).

However, since by comparing the yields in example 1 of the application in suit comparison has not been made with the closest state of the art, such comparison is not suitable for making any effect plausible, let alone a surprising one.

As alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the application, the said problem must rather be seen as described on page 2, lines 46 to 48, of the present application, namely that the known synthesis of (2S,3S) allophenylnorstatin derivatives, as described in document (5), raises problems due to an oxidation reaction, the use of harmful cyanide and a step of steric inversion. Furthermore, since the intermediate aldehyde is very labile and ready to racemize, it is difficult to obtain the desired compound at high optical purity.

Therefore, the Board concurs with the statement on page 2, lines 48 to 50, of the present application, that the problem to be solved consisted in providing a process for preparing (2S,3S)-allophenylnorstatin at high optical purity, easily, safely and in high yield.

3.3 The present application claims to solve this problem by the process defined in Claim 1.

3.4 The Board sees no reason to contest that this problem has successfully been solved by the process according to Claim 1.

3.5 Therefore, it remains to be decided, whether in the light of the teachings of the cited documents a skilled person seeking to solve the above-mentioned problem would have arrived at the process of Claim 1 in an obvious way or not.

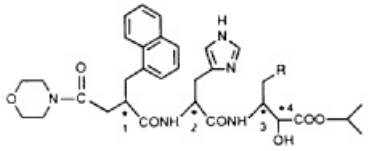
3.5.1 The problem underlying the present invention, as described in the two last paragraphs in point 3.2 above, had been recognised for the preparation of optically pure forms of cyclohexylnorstatin in document (1), which specifically refers on page 2, line 41 to the method described in document (5) and the problems encountered with such method. As solution to that problem, document (1) proposes on page 4 the same reaction sequence for the preparation of (2R,3S)-cyclohexylnorstatin as the one of Claim 1 for the preparation of (2S,3S)-allophenylnorstatin derivatives.

3.5.2 In this respect, the Appellant argued that a skilled person would not have taken document (1) into consideration, since document (1) is restricted to the preparation of optically active forms of cyclohexylnorstatin and not of phenylnorstatin. As it was stated in the first full paragraph in the left-hand column on page 2710 of document (5) that

"The side chain isopropyl group of norstatine residue in 16^7 was replaced with the larger and more hydrophobic phenyl in 17 or a cyclohexyl group in 1a. By such replacements, the potency of 1a was enhanced, while that of 17 was decreased against our expectation.",

a skilled person would have realised that the cyclohexyl in cyclohexylnorstatin may not be interchanged with phenyl without affecting the properties.

3.5.3 However, that paragraph concerns the influence of the isopropyl-, cyclohexyl- and phenyl group in the norstatin used as intermediate in the synthesis of pharmacologically active compounds of formula



on the human renin inhibitory potencies of those pharmacologically active compounds.

As the skilled person, in the present case, is not a pharmacologist interested in the effect of some drug as end-product interacting with biological systems but necessarily a chemist with organic synthesis background looking for a method of preparing optically active forms of phenylnorstatin, the content of this paragraph is irrelevant when trying to solve the problem as defined in point 3.2 above, since it does not give any indication about the chemical behaviour of the isopropyl-, cyclohexyl- and phenyl group in a chemical reaction.

The only information about the possibility of interchanging the cyclohexyl- and phenyl group in preparing norstatin bearing such group is found in the last but one paragraph in the right-hand column on page 2709 of document (5) stating that **phenyl**norstatin isopropyl ester was synthesised in a similar way to the synthesis of (2R,3S)-**cyclohexyl**norstatin. This

information clearly teaches the skilled person that in the reaction described in document (5) the desired norstatin derivative may be prepared independently of the presence of cyclohexyl or phenyl as substituent and certainly does not teach away from the possibility of interchanging cyclohexyl by phenyl.

3.5.4 Additionally, the Appellant argued that the process-sequence described in document (5) is so different from the one described in document (1), that it is virtually impossible to regard the claimed reaction-sequence as a mere modification or adaptation of the one known from document (5). In this respect reference was made to decisions T 176/89 and T 507/89.

However, the tenor of both decisions is that it is not suitable to combine the content of two documents if features in both documents are incompatible or when their teachings are mutually conflicting.

Since in the present case, document (1) proposes a solution for the problems encountered with the process described in document (5), the documents are clearly not mutually conflicting nor do they disclose incompatible features.

To the contrary, a skilled person considering the disclosure of document (5) and looking for a method of preparing (2S,3S)-allophenylnorstatin derivatives that does not have the disadvantages known to occur when following the reaction sequence described therein would have taken document (1) into consideration, since the skilled person would have realised that it contained a

pointer to the solution for the problem underlying the present invention.

3.5.5 Certainly, the problem underlying the invention according to document (1) was the provision of **(2R,3S)**-cyclohexylnorstatin. However, it clearly follows from the reaction scheme on page 4 and from the last but one paragraph on page 4 that by the enantiomeric selective hydrogenation with ruthenium-phosphine complex of the carbonyl compound, epoxidation of the formed alcohol, subsequent reaction with an azide and hydrogenolysis **(2S,3S)**-cyclohexylnorstatin is obtained with the advantages resulting therefrom in terms of optical purity, high yield, simplicity and safety. The fact that the configuration at the 2-position of the (2S,3S)- enantiomeric form may subsequently be inverted into the (2R,3S)-enantiomeric form does not affect the disclosure of the reaction sequence for preparing **(2S,3S)**-cyclohexylnorstatin.

3.5.6 The Appellant argued that, due to the different conformations of the cyclohexyl group, which has a chair form, and the phenyl group, which has a planar form, a skilled person could not predict that the ruthenium-phosphine complex would have the same stereoselectivity in the asymmetrical hydrogenation of the 2-phenyl-2-halogeno-3-oxybutyric acid ester as of the 2-cyclohexyl-2-halogeno-3-oxybutyric acid ester.

However, the correct approach in assessing inventive step is not whether a skilled person would derive from given information in the prior art a sure predictability of success, but rather whether it would be obvious to try something with a reasonable

expectation of success, which implies the ability of a skilled person to reasonably predict, on the basis of the existing knowledge, a successful conclusion of an experiment (see point 28.5 in the Reasons for the Decision of T 694/92, OJ EPO 1997, 408, and point 7.4.4 in the Reasons for the Decision of T 296/93 of 28 July 1994).

In the present case, the Appellant did not provide any evidence that the stereoselectivity of the ruthenium-phosphine complex would be so different in the asymmetrical hydrogenation of phenyl-substituted compounds and their cyclohexyl analogues that a skilled person would not have considered the reaction sequence proposed in document (1). On the contrary, document (5) suggests strongly that in the stereoselective synthesis of norstatins the phenyl group and the cyclohexyl group have an analogous behaviour and, thus, that a skilled person would indeed have every reason to look to documents, such as document (1), treating the stereoselective synthesis of norstatin having a cyclohexyl group for readily applicable methods for making the norstatin analogue with a phenyl, and thus try the asymmetric hydrogenation of 2-phenyl-2-halogeno-3-oxybutyric acid and the reaction sequence known from document (1) for the preparation of (2S,3S)-cyclohexylnorstatin ester.

3.5.7 Therefore, Claim 1 and, thus, the only request cannot be considered to meet the requirement of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin A. Nuss