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# D E C I S I O N
## of 15 January 1996

**Case Number:** T 0378/91 - 3.3.4

**Application Number:** 83100767.9

**Publication Number:** 0084892

**IPC:** C12P 17/10

**Language of the proceedings:** EN

**Title of invention:**
Preparation of optically active cis-1,3-dibenzyl-hexahydro-1H-furo(3,4-d)imidazole-2,4-dione and its intermediates

**Patentee:**
SUMITOMO CHEMICAL COMPANY, LIMITED

**Opponent:**
Merck Patent GmbH

**Headword:**
Intermediates/SUMITOMO

**Relevant legal provisions:**
EPC Art. 56

**Keyword:**
"Inventive step (yes) - non-obvious intermediate"

**Decisions cited:**
T 0022/82, T 0163/84, T 0648/88, T 0065/82

**Catchword:**
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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0378/91 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 15 January 1996**

**Appellant:** (Opponent)
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**Representative:**
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**Respondent:** (Proprietor of the patent)
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**Representative:**
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**Decision under appeal:**
**Interlocutory decision of the Opposition Division of the European Patent Office dated 4 March 1991 concerning maintenance of European patent No. 0 084 892 in amended form.**

**Composition of the Board:**

**Chairman:** L. Galligani (Rapporteur)
**Members:** R. E. Gramaglia
S. C. Perryman

## Summary of Facts and Submissions

I. European patent No. 0 084 892 was granted on 23 December 1987 for five Contracting States with fourteen Claims based on European patent application No. 83 100 767.9.

II. Notice of opposition was filed against the European patent by the present Appellants (Opponents). Revocation of the patent to the extent of Claims 8 to 11 and 13 to 14 was requested on the ground of Article 100(a) EPC. During the procedure before the Opposition Division ten documents were relied upon by the parties. Among them the following are of relevance for the purpose of this decision (the numbering used in the decision by the Opposition Division is adhered to):

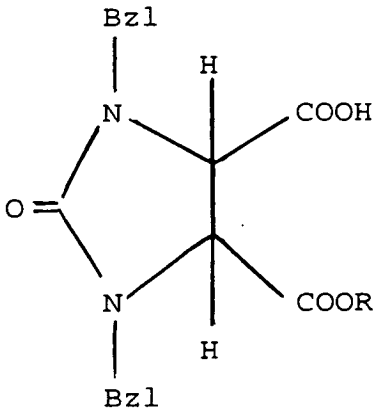
(1) US-A-2 489 233;

(3) Helv. Chim. Acta, Vol. 53, 1970, pages 991 to 999;

(5) J. Org. Chem., Vol. 47, 1982, pages 4702 to 4708.

III. The Opposition Division issued on 4 March 1991 an interlocutory decision within the meaning of Article 106(3) EPC whereby the patent was maintained on the basis of Claims 1 to 12 and 14 as granted and Claim 13 as filed on 5 July 1989 which read as follows:

" A cis-imidazolidinedicarboxylic acid monoester of the formula




(III)

wherein R is a $C_1$-$C_6$ alkyl group and Bzl represents a benzyl group in an optically active form. "

Claims 1 to 7 related to a process for preparing an optically active cis-imidazolidinedicarboxylic acid monoester of the formula (III) from a diester of formula (II), while Claims 8 to 12 related to a process for preparing an optically active cis-1,3-dibenzyl-hexahydro-1H-furo(3,4-d)imidazole-2,4-dione of formula (I) from the compound of formula (III).

Claim 14 concerned "the monoester according to claim 13, wherein the 4- and 5-positions take the 4S, 5R-configuration".

The Opposition Division, relying on document (5) as an expert's opinion, considered that the process according to Claim 8 was non-obvious in view of the fact that it was not recommended by the experts. Moreover, in its opinion, the claimed process contributed to a successful, simplified and economical overall method for

the production of the desired lactone. In the Opposition Division's view, this conclusion had also a bearing on the inventive step of Claims 13 and 14 in the light of decision T 22/82 (OJ EPO 1982, 341, especially point 7).

IV. The Appellant lodged an appeal against the decision of the Opposition Division.

V. In a communication pursuant to Article 11(2) of the rules of procedure of the Boards of Appeal, the Board expressed its preliminary opinion on the case.

VI. Oral proceedings took place on 18 December 1995 and it was announced by the Board that the final decision would be issued in writing.

During oral proceedings the Appellants withdrew their initial request for the invalidation of the decision of the Opposition Division on the ground that the said decision incorrectly rejected the opposition under Article 102(2) EPC, as well as the request for the reimbursement of the appeal fee.

The Respondents filed an auxiliary request containing only process claims 1 to 12 as granted.

VII. The Appellants submitted essentially that the skilled person, starting from the teaching of document (1), which described the preparation of a racemate of compounds of the formula (III), and having regard to the teaching of document (3), which described the resolution of a racemate of compounds of the formula (III) in which R is a $C_6$ cycloalkyl group, needed merely to conduct a simple experiment in order to confirm the feasibility of the replacement of the $C_6$ cycloalkyl group by a $C_1$-$C_6$ alkyl group. The passage on page 993 of document (3) under the heading "Spaltung von Halbestern der

Dicarbonsäuren" clearly hinted at this possibility. In the Appellants' view, the "process effect" acknowledged by the Opposition Division on the basis of decision T 22/82 (supra) could not be used to support inventive step of the intermediate products of Claims 13 and 14. In their submissions, the facts in the present case differed not only from those of the case of the quoted decision T 22/82 (supra), in which no prior art intermediate was known, but also from those of decisions T 163/84 (OJ EPO 1987, 301) and T 648/88 (OJ EPO 1991, 292). In the latter two cases the different structure of the claimed intermediate in comparison with the prior art intermediates truly influenced the overall process of which they were part. As specified in decision T 65/82 (OJ EPO 1983, 327), intermediate products could be patentable if they brought about either increased reactivity or higher yields in comparison with close-to-the-intermediate compounds or if their structure could not be readily derived from close-to-the-product compounds. In the case at issue, the advantages linked to the preparation and further processing of the intermediates rendered the said processes and the overall process inventive, but they could not be used to support the inventive step of the intermediate products because these advantages were purely of technological nature and independent from the structure of the intermediate, in particular from the nature of the R group.

VIII. The Respondents argued that, since the process of preparation of the claimed intermediate products and their further processing were regarded also by the Appellants as non-obvious having regard to the prior art, the conclusions drawn in the cases of the decisions referred to by the Appellants applied and the products per se had to be recognised as inventive. In any case, the skilled person would not have derived from document

(3) a hint at the replacement of the cyclohexyl or cholesteryl group by a $C_1$-$C_6$ alkyl group. Cyclohexanol and cholesterol were expensive products and, if their replacement by simpler alcohols could have readily been envisaged by the skilled person, this would have been indicated already in document (3).

IX. The Appellants requested that the decision under appeal be set aside and that the main request be rejected.

The Respondents requested as main request that the appeal be dismissed and as auxiliary request that the decision under appeal be set aside and that the patent be maintained on the basis of Claims 1 to 12 of the auxiliary request filed at oral proceedings on 18 December 1995.

**Reasons for the Decision**

1. The appeal is admissible.

*Extent of appeal*

2. As confirmed at oral proceedings, the Appellants no longer object to the process claims 8 to 11 as during opposition proceedings, and to this extent they do not appeal against the decision. Under these circumstances, the patentability of the said claims is not at issue here.

*Main request: Novelty*

3. Novelty of the subject-matter of Claims 13 and 14 at issue is not contested by the Appellants and the Board sees no reason to further examine this question of its own motion.

*Main request: Inventive step*

4. The closest prior art is represented by document (1) which discloses a racemate of the compound of formula (III) wherein R is an alkyl group, in particular a methyl group (cf. Example 1).

5. In the light of document (1), the underlying technical problem is the resolution of the known racemate into its optically active forms, in particular the isolation of the monoester form, wherein the 4- and 5-positions take the 4S, 5R-configuration, this being the desired configuration for the synthesis of (+)-biotin.

6. The product of Claims 13 and 14, whose isolation had not been described previously, is prepared stereospecifically by the enzymatic process of Claims 1 to 7 and is further processed (by reduction and cyclization) according to the process of Claims 8 to 11. The patentability of both these processes is no longer in dispute.

7. The claimed product is, therefore, an intermediate product of a two-step process for the preparation of a known end product [an optically active cis-1,3-dibenzyl-hexahydro-1H-furo(3,4-d)imidazole-2,4-dione of formula (I)]. As pointed out in decision T 648/88 (supra; see in particular point 8 of the Reasons), the patentability of a chemical intermediate is to be judged according to the same criterion applied to any other chemical substance,

i.e. non-obviousness of the compound having regard to the relevant prior art. In the present case, it should be decided whether the claimed chemical intermediate in question, regardless of how it was prepared and/or processed in the patent-in-suit, would have been obvious for a person skilled in the art. In particular, it should be established whether there was any incentive for the skilled person to prepare this intermediate and, should this be the case, whether the prior art taught how this could be done.

8. Half-esters of the formula (III) wherein R was an alkyl group, in particular a methyl group, were disclosed in document (1) (cf. Example 1) within the framework of the preparation of intermediates for the synthesis of biotin (cf. column 1, lines 5 to 16). The said half-esters were in the form of racemates comprising the optically active enantiomers. Thus, at least from a theoretical point of view, the skilled person was aware of the existence of the individual enantiomers in such racemates.

9. Prior art document (3) reported in detail and discussed the teaching of document (1) (cf. page 991 and scheme 1 on page 992) and pointed out that the majority of the steps of the biotin synthesis according to document (1) was carried out with racemic material and that the separation of the enantiomers was effected only at a later stage of the thiophanium salts. As an improvement to the process according of document (1), document (3) proposed to separate the enantiomers at the half-ester stage, by fractional crystallization of either the triethylamine salts of the cholesteryl half-esters or of the ephedrine salts of the cyclohexyl half-esters (cf. page 993, point 2 and scheme 3 on page 994).

10. The relevant question here is whether the skilled person, faced with the problem of the resolution of the racemate known from document (1) in its optically active forms could or would have easily carried out the resolution of the enantiomers according to any known method. In the Appellants' view, the skilled person would have readily adapted the teaching of document (3) and obtained the claimed optically active form of the half-ester of formula (III), for example, by first reacting the corresponding anhydride with a lower alkanol, such as methanol or ethanol, and then by effecting the resolution via the ephedrine salts. The feasibility of this approach is indeed confirmed by the patent-in-suit (cf. page 4, lines 10 to 21 and Examples 10 and 11).

11. In the Board's judgement, the position of the Appellants is based on ex post facto analysis because it uses the foreknowledge of the invention in order to show theoretically how, starting from document (1), the skilled person would have arrived at the products of Claims 13 and 14 by simply adapting the teaching of document (3). The Board observes that, as a matter of fact, in "real life" when dealing with the problem of improving the method of document (1), in particular the earlier resolution of the racemic material, the authors of document (3), which can reasonably be considered to represent the skilled person's thinking, relied for whatever reason on a modified reaction scheme involving cyclohexanol as the optically-inactive esterifying alcohol rather than more conventional lower alkanols such as methanol or ethanol. The skilled person was certainly aware of the fact that opening a cyclic anhydride with an alcohol to yield a half-ester would proceed more easily with a primary alcohol than with a sterically more hampered secondary one. This is shown by comparing the 3 hours needed for the reaction to occur

between the cyclic anhydride and methanol (cf. patent in suit, Example 9) or n-propanol (ibidem, Example 12) with the 10 hours or even 16 hours required for the same reaction to occur with isopropanol (ibidem, Example 11) and cyclohexanol [cf. document (3), page 998, line 6], respectively. In spite of this basic knowledge, the authors of document (3) refrained from using e.g. methanol or ethanol as a nucleophilic opening agent and turned to cyclohexanol which is a rather sterically hampered secondary alcohol. In the Board's view, this anomalous choice was possibly made in the expectation of some beneficial effect on the enantiomer resolution process. This finding does **not** support the Appellants' line of argument that the skilled person would have obviously adapted the teaching of document (3) for obtaining the half-esters of formula (III). It is only with the a posteriori knowledge of the disclosure in the patent in suit, that the Appellants now extend the specific teaching on pages 993 and 994 of document (3) so as to cover also the general teaching that a lower alkanol could serve the same purpose. No other prior art document was put forward which could suggest or render plausible the use of a lower alkanol in place of cyclohexanol as the optically-inactive esterifying alcohol in the protocol according to document (3).

12. Furthermore, it should also be taken into account that the skilled person had no real incentive or need to resolve the racemic material known from document (1) because document (3) had provided a variation of the method of said document (1) which was based on the specific reaction scheme on page 994 whereby half-esters of the formula (III) wherein R was an alkyl group, in particular a methyl group, needed not be prepared [compare in document (3) reaction scheme 1 on page 992, which outlines the synthesis of biotin according to document (1), with reaction scheme 3 on page 994].

13. No other prior art document was put forward by the Appellants to show that the separation of the claimed optically active product from the known racemate of document (1) was readily achievable by standard methods.

14. Thus, in the Board's judgement, however simple the resolution of the racemic material known from document (1) may seem a posteriori, the provision of the products of Claims 13 and 14 involved an inventive step and, consequently, the main request is allowable.

**Order**

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

The appeal is dismissed.

The Registrar: The Chairman:

L. McGarry L. Galligani