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D E C I S I O N
of 6 November 2001

Case Number: T 0219/98 - 3.3.1

Application Number: 93303947.1

Publication Number: 0573184

IPC: C07C 255/20

Language of the proceedings: EN

Title of invention:
t-Butyl (R)-(-)-4-Cyano-3-hydroxybutyrate and process for its preparation

Patentee:
Takasago International Corporation

Opponent:
LONZA AG

Headword:
t-Butyl (R)-(-)-4-Cyano-3-hydroxybutyrate/TAKASAGO

Relevant legal provisions:
EPC Art. 123(2)(3), 54(3)(4), 158(1)(2)

Keyword:
"Main request and auxiliary request I: novelty (no) - no "twofold" selection - purity level not a distinguishing feature"
"Auxiliary requests II, III, IV: support by the application as filed (no) - inadmissible generalization of an example"

Decisions cited:
G 0001/92, T 0012/81, T 0201/83, T 0007/86, T 0077/87, T 0296/87, T 0279/89, T 0666/89, T 0990/96, T 0728/98, T 0941/98

Catchword:
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Case Number: T 0219/98 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 6 November 2001

Appellant: (Opponent)
LONZA AG
CH-3945 Gampel/Wallis (CH)

Representative:
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 5 February 1998 concerning maintenance of European patent No. 0 573 184 in amended form.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. F. Ranguis
R. T. Menapace

Summary of Facts and Submissions

I. The Appellant (Opponent) lodged an appeal against the interlocutory decision of the Opposition Division to maintain the European patent No. 0 573 184 (European patent application No. 93 303 947.1) in the form as amended (auxiliary request filed before the Opposition Division) pursuant to Article 102(3)a) EPC.

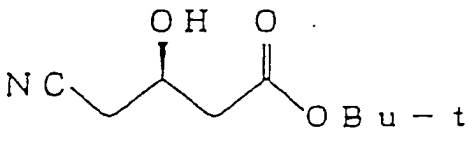
II. The opposition sought revocation of the patent in suit *inter alia* on the ground that its subject matter lacked novelty in view of the prior non-published international patent application

(1) WO-A-93 07 115 (European patent application EP-A-0 6 43 689)

under Articles 54(3)(4) and 158(1)(2) EPC.

III. The patent as maintained by the Opposition Division comprised eight claims, independent Claims 1, 2 and 3 reading as follows:

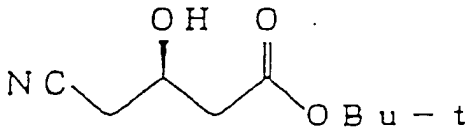
"1. t-Butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I):



(I)

having an optical purity of at least 92% ee and wherein Bu-t represents a t-butyl group."

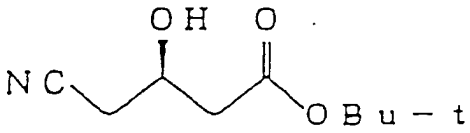
"2. t-Butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I):



(I)

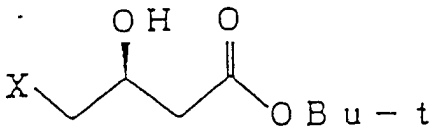
having an optical purity of at least 99% ee and wherein Bu-t represents a t-butyl group."

"3. A process for preparing t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I):



(I)

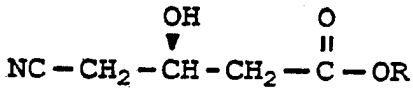
having an optical purity of at least 92% ee and wherein Bu-t represents a t-butyl group, comprising reacting a t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate represented by formula (II):



(II)

wherein Bu-t is as defined above; and X represents a chlorine atom or a bromine atom, with sodium cyanide or potassium cyanide."

IV. The reasons for the decision were, in particular, that Claims 1 and 2 of the amended set of claims (cf. point III above) met the requirements of Article 54(3) and (4) EPC in view of document (1). In its decision, the Opposition Division held that the (3R)-4-cyano-3-hydroxybutyric acid esters of formula (II):

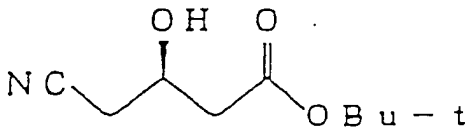


wherein R is alkyl of from one to ten carbon atoms, allyl or benzyl, the term "alkyl" meaning "a straight or branched hydrocarbon radical including, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, secondary butyl, isobutyl, tertiary butyl ... and the like" (cf. page 5, lines 21 to 27) was not novelty destroying for the claims of the patent given that the esters of formula (II) were intermediates for the preparation of (5R)-1,1-dimethylethyl 6-cyano-5-hydroxy-3-oxo-hexanoate and it would have been immediately apparent to the person skilled in the art that the t-butoxy group, which was, as it was well known, a very poor leaving group, could not have been singled out to yield the end-product. It followed that the person skilled in the art would not have seriously contemplated the claimed t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I) in present Claim 1. Furthermore, insofar as the disclosure of document (1) related to the t-butoxy esters it could be regarded as an erroneous disclosure.

V. At the oral proceedings which took place on 6 November 2001, the Respondent (Proprietor of the patent), in addition to the main request, namely the set of claims as maintained (cf. point III above), submitted four sets of claims as auxiliary requests I, II, III and IV. The text of the claim of each request relevant in the context of this decision is quoted below.

(a) Auxiliary request I

"1. t-Butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I):

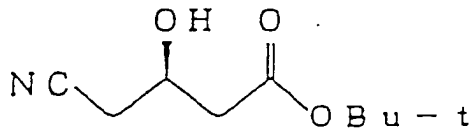


(I)

having an optical purity of at least 99% ee and wherein Bu-t represents a t-butyl group."

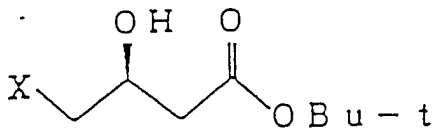
(b) Auxiliary request II

"3. A process for preparing t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I):



(I)

having an optical purity of at least 99% ee and wherein Bu-t represents a t-butyl group, comprising reacting a t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate represented by formula (II):

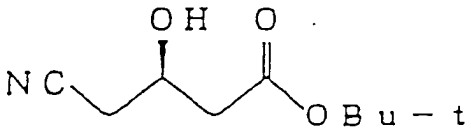


(II)

wherein Bu-t is as defined above; and X represents a chlorine atom or a bromine atom, with sodium cyanide or potassium cyanide."

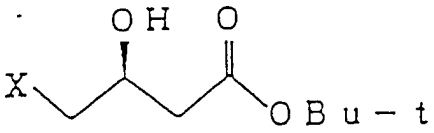
(c) Auxiliary request III

"3. A process for preparing t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I):



(I)

wherein Bu-t represents a t-butyl group, comprising:
(i) reacting a t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate represented by formula (II):

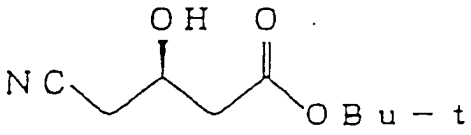


(II)

wherein Bu-t is as defined above; and X represents a chlorine atom or a bromine atom, with sodium cyanide or potassium cyanide, to form a crude product having an optical purity of at least 92% ee; and
(ii) purifying said crude product by recrystallisation."

(d) Auxiliary request IV

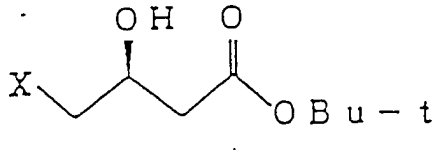
"3. A process for preparing t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I):



(I)

wherein Bu-t represents a t-butyl group, comprising:

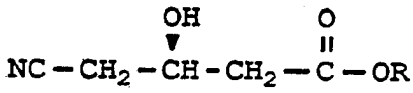
(i) reacting a t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate represented by formula (II):



(II)

wherein Bu-t is as defined above; and X represents a chlorine atom or a bromine atom, with sodium cyanide or potassium cyanide, to form a crude product; and
(ii) purifying said crude product by recrystallisation to at least 99% ee."

VI. The Appellant contested the reasons for the decision of the Opposition Division and disputed, first, that the subject matter of Claim 2 of the main request was novel over document (1) under Article 54(3) and (4) EPC. In this context, he argued that the specific disclosure of a chemical compound was not only to be acknowledged when this chemical compound was expressly cited or described in an example but also when there was a pointer to its individual configuration. In the present case, the carbon in position -3 of the compound of formula:

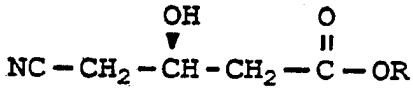


had the same chiral configuration (R). The radical R could be an alkyl group having one to ten carbon atoms and the tertiary butyl group was expressly designated. It followed that the t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate was explicitly disclosed in that document. Furthermore, a level of purity of at least 99% ee was achieved by a recrystallisation step, a conventional method of purification, and therefore, could not establish novelty for the claimed compound.

Furthermore, the subject matter of Claims 3 of the auxiliary requests II, III and IV extended beyond the content of the application as filed since it was an inadmissible generalization of the process disclosed in Example 1 of this application.

VII. Regarding the novelty of either Claim 2 of the main request or Claim 1 of the first auxiliary request, the Respondent disputed that document (1) disclosed the claimed compound t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate represented by formula (I) (cf. point III above).

Document (1) disclosed the production of (5R)-1,1-dimethyl 6-cyano-5-hydroxy-3-oxo-hexanoate, a key intermediate in the preparation of certain structurally complex pharmaceuticals. This compound was obtained through a reaction involving (3R)-4-cyano-3-hydroxybutyric acid esters of formula:



wherein R could be alkyl of from one to ten carbon atoms, allyl or benzyl. It was true that document (1) mentioned in a non-exhaustive list ("and the like") the t-butyl group. However, such a citation could not amount to a direct and unambiguous disclosure of the compound t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate for the following reasons:

- The experiments submitted in the course of the opposition proceedings showed that the (3R)-4-cyano-3-hydroxybutyric acid n-butyl ester could successfully be used to make the eventual desired

hexanoate, whereas the corresponding (3R)-4-cyano-3-hydroxybutyric acid t-butyl ester failed. As the document (1) was concerned with the production of (5R)-1,1-dimethyl 6-cyano-5-hydroxy-3-oxo-hexanoate, the person skilled in the art would not have seriously contemplated using R = t-butyl in view of the earlier decision T 666/89. Alternatively, the mention of R = t-butyl could only be regarded as an erroneous and therefore non novelty-destroying disclosure as established in the decision T 77/87.

- Furthermore, choosing R = t-butyl resulted from an arbitrary selection among a great number of possibilities since the definition alkyl from one to ten atom carbon atoms embraced seventy-five radicals, whereas only R = n-butyl was exemplified. The claimed compound fulfilled, therefore, the conditions for novelty established by the decision T 279/89 and it was only with the benefit of hindsight that t-butyl could have been considered.

- It had also to be pointed out that the (3R)-4-cyano-3-hydroxybutyric acid n-butyl ester was a liquid which could not be recrystallised, whereas the (3R)-4-cyano-3-hydroxybutyric acid t-butyl ester being a solid could be obtained with an increased purity by recrystallisation. The level of purity of at least 99% ee was, therefore, another distinguishing feature since this step was not and could not be described in document (1) given the liquid state of the (3R)-4-cyano-3-hydroxybutyric acid n-butyl ester.

Regarding the compliance of Claim 3 of each auxiliary request II, III and IV with Article 123(2) EPC, the person skilled in the art would have derived without undue burden the claimed subject matter from Example 1 of the application as filed.

VIII. The Appellant requested that the decision under appeal be set aside and that the European patent be revoked or, in the event that one of the Respondent's auxiliary requests would be held allowable, remittal of the case to the first instance.

The Respondent requested that the appeal be dismissed (main request) or that the patent be maintained on the basis of the one of the sets of claims filed as auxiliary requests I to IV during the Oral Proceedings.

IX. At the end of the Oral Proceedings the decision of the Board was announced orally.

Reasons for the Decision

1. The appeal is admissible.

Main request and auxiliary request I

2. *Rule 57a EPC*

Claim 2 of the main request and Claim 1 of the auxiliary request I differs from Claim 1 as granted in that the feature "having an optical purity of at least 99% ee" was added. This feature is designed to overcome a ground of opposition, namely absence of novelty. Therefore, that amendment can be admitted under

Rule 57a EPC.

3. *Article 123(2) and (3) EPC*

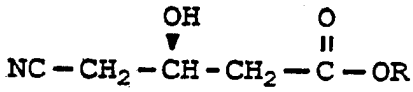
The Board is satisfied that Claim 2 of the main request and Claim 1 of the auxiliary request I are not amended in such a way that they contain subject matter which extends beyond the application as filed. This amendment indeed finds support in the disclosure of the application as filed (cf. page 4, lines 17 to 20 and Example 1, page 9, line 24 to page 10, line 3).

Those claims are not amended as to extend the protection conferred, either.

4. *Novelty - Article 54(3) and (4) EPC*

4.1 Document (1) is comprised in the state of the art under Article 54(3) and (4) EPC in conjunction with Article 158(1) and (2) EPC. This was not contested by the Respondent.

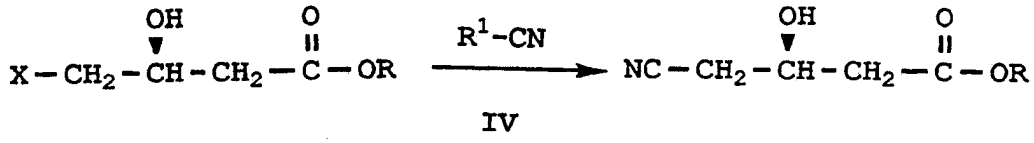
4.2 Document (1) discloses (3R)-4-cyano-3-hydroxybutyric acid esters of formula (II):



wherein R is alkyl of from one to ten carbon atoms, allyl or benzyl, the term "alkyl" meaning "a straight or branched hydrocarbon radical including, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, secondary butyl, isobutyl, tertiary butyl ... and the like" (cf. page 5, lines 21 to 27). It is not disputed, in that respect, that the carbon in position -3 is in the

chiral configuration (R).

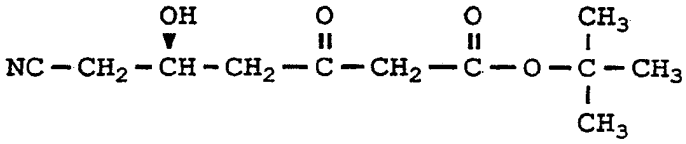
A process for preparing compounds of formula (II) is outlined in the following scheme:



(cf. page 7),

wherein X is a leaving group such as halogen, R is as defined above and R^1 is tetraalkylammonium, silver, copper (I), copper (II), an alkali metal or an alkaline earth metal. The reaction is carried out in a solvent at about 0°C to about the reflux temperature of the solvent (cf. page 8, lines 1 to 22).

The compound of formula (II) is said to yield the desired hexanoate of formula (I)



through a subsequent reaction (cf. scheme on page 7).

4.3 On that basis, the question to be decided is whether the individual t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate compound having an optical purity of at least 99% ee has been made available to the public by that disclosure. The Board holds, in accordance with the consistent jurisprudence of the Boards of Appeal, that the novelty of such an individual chemical compound falling under the scope of a general formula can only be denied if there is an unambiguous pointer

to its individual configuration in the form of a technical teaching (cf. T 941/98, point 5.1; and T 296/87, OJ EPO 1990, 195, points 6.1 and 6.4 of the reasons). It is thus not sufficient that the compound in question belongs conceptually to a disclosed class of possible compounds, if there is no pointer to the individual member.

4.4 The Respondent, first, argued that the person skilled in the art would not have considered the (3R)-4-cyano-3-hydroxybutyric acid esters wherein R is "t-butyl" (cf. point 4.2 above) since its transformation in a compound of formula (I) failed (cf. point VII above). However, such an argument fails to recognize that the purpose of Article 54(1) EPC is to prevent the state of the art being patented. Article 54(2) EPC defines the state of the art as comprising everything made available to the public before the date of filing in any way. As set out in the decision G 1/92 (OJ EPO 1993, 277, in particular point 2.1 of the reasons), any element of subjectivity must be excluded in applying the concept of novelty as defined in Article 54(1) and (2) EPC. In particular, the Enlarged Board pointed out (in point 3 of the reasons) that the **extrinsic** characteristics, which are only revealed when the product is exposed to interaction with specifically chosen outside conditions, e.g., reactants or the like, in order to provide a particular effect or result **point beyond** the product *per se*. The Board, therefore, concludes that the argumentation of the Respondent based on a characteristic which is extrinsic to the compound, namely its further transformation, does not address the novelty issue to be decided.

4.5 The Respondent also argued that the (3R)-4-cyano-3-

hydroxybutyric acid esters wherein R is "t-butyl" (cf. point 4.2 above) could only be regarded as an erroneous and therefore non novelty-destroying disclosure as established in the decision T 77/87 since its transformation in a compound of formula (I) failed (cf. point VII above). However, the Board observes that the situation which prevailed in the decision T 77/87 was quite different since, in that case, the Proprietor of the patent had shown that an error had occured in the published abstract of a document leading to a substantial inconsistency with the disclosure of the original document (the ratio of 30/50 for vinylidene chloride / vinyl chloride had been wrongly inverted). This error concerned an intrinsic property of the claimed composition. Therefore, in that case, the disclosure of the prior document was erroneous in respect of an aspect affecting the novelty of the claimed composition *per se.* In the present case, the Respondent did not adduce any convincing evidence for his contention; rather its sole argument amounted, in fact, to revert to what was previously presented but not accepted by the Board (cf. point 4.4 above) given that even a proven error related to an extrinsic property of a product is not decisive for establishing the disclosure of the said product. Again the Respondent's argument does not address the issue to be decided. The question whether the **subsequent** transformation of the compound of formula (II) in a compound of formula (I) can be achieved by the indicated route is not relevant for deciding whether or not the ester of formula (II) wherein R is "t-butyl" is disclosed in document (1).

4.6 The Board concludes, therefore, that the radical "t-butyl" stands for one possible meaning of R in the

definition of the compound of formula (II) disclosed in document (1).

4.7 It remains to be decided whether the novelty of the claimed compound can be nonetheless acknowledged on the basis of a still undisclosed individualization. According to established jurisprudence of the Boards of Appeal a document disclosing polysubstituted chemical compounds does not qualify for a specific disclosure of an individual compound if the individual compound can only be derived from the generic disclosure by selecting one substituent from each of two or more lists of substituents (cf. decisions T 12/81, OJ EPO 1982, 296, point 13 of the reasons; T 7/86, OJ EPO 1988, 381, point 5.1 of the reasons). In applying this principle to the present case, the Board observes that once the skilled reader has turned his attention to the explicitly disclosed "t-butyl" radical as one of the meanings for the radical R, the t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate emerges clearly and unambiguously from the disclosure of document (1). Thus, the compound does not result from a "twofold/multifold" choice or selection required to confer novelty to the particular election of a compound within a generic formula. In that context, the decisions T 279/89 and T 666/89 which deal with the novelty issue of a claimed subject-matter in relation to the prior art where there is an overlap of numerical ranges or where there is a selection out of a broad numerical range, are not relevant. Furthermore, in the present case, the unambiguous pointer to the t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate is in the form of a technical teaching since document (1) describes a detailed method for obtaining the said compound (cf. in particular, page 8, line 1 to page 10, line 21).

In conclusion, the disclosure of document (1) points unambiguously to the individual compound t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate in Claim 1 of the patent in suit.

4.8 The Respondent also alleged that the distinctly different feature of the claimed t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate was the level of purity, i.e. at least 99% ee. However, the level of purity of a low molecular chemical compound, as a rule, cannot entail novelty since conventional methods for its purification are common general knowledge. Thus, a document disclosing such a chemical compound normally makes available this compound to the public within the meaning of Article 54 EPC in any level of purity (cf. T 990/96, OJ EPO 1998, 489, point 7 of the reasons and T 728/98, OJ EPO 2001, 319, point 6.4 of the reasons). No evidence was submitted from which the Board could conclude that in the present case an exceptional situation exists which would justify a different conclusion (cf. T 990/96, loc cit., point 8 of the reasons). The fact that the claimed product may exist in solid form which makes it purifiable by recrystallisation, whereas other esters such as the n-butyl ester only exist in liquid form, is not reflected in the features of the claims at issue (cf. Claim 2 of the main request or Claim 1 of the auxiliary request I) and, furthermore, is only an additional parameter for defining the said ester without giving rise to a different chemical product.

4.9 For the above reasons Claim 2 of the main request and Claim 1 of the auxiliary request I lack novelty over document (1), so that the patent in suit cannot be maintained in the form as submitted in those requests.

Auxiliary requests II, III and IV

5. *Rule 57a EPC*

Independent Claims 3 of the auxiliary requests II, III and IV differ from Claim 3 as granted in that the feature related to the level of optical purity, either 92% ee or 99% depending on the requests, has been added (cf. point V, b), c), d) above). Those respective features are designed to overcome a ground of opposition, namely absence of novelty. Therefore, that amendment can be admitted under Rule 57a EPC.

6. *Article 123(2) EPC*

6.1 All Claims 3 of the last three auxiliary requests have in common the technical feature according to which a t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate having an optical purity of at least 92% ee or at least 99% ee (with or without recrystallisation), depending on the claims, is obtained from a t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate of formula (II).

6.2 The sole concrete indication for the quantification of the level of enantiomeric purity can be found in Example 1. The Board observes nevertheless that in this example the t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate having an optical purity of, either 92% ee or 99% ee or more, is obtained from a t-butyl (S)-(-)-4-chloro-3-hydroxybutyrate having **an optical purity of 92% ee** (cf. page 9, line 5 of the application as filed). In that respect, the subject matter of Claim 3 of each request amounts to the combination of:

- the general disclosure referring merely to the

reaction starting from any t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate, namely without any optical purity being mentioned at all (cf. page 5, lines 1 to 11 of the application as filed), with

- the particular optical purity value(s) for the t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate as indicated above (cf. point 6.1).

6.3 The generalisation of a feature from an example is considered to be allowable in accordance with decision T 201/83 (OJ EPO 1984, 481, point 12 of the reasons) provided that the person skilled in the art could have readily recognised this feature as not so closely associated with the other features of the example as to determine the effect of that embodiment of the invention as a whole in an unique manner and to a significant degree.

6.4 In the present situation, it cannot be derived from Example 1 that for **any level of optical purity** of t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate, a t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate having an optical purity of, either 92% ee or 99% ee or more, is necessarily obtained. By contrast, as shown by Example 1 (cf. page 4, lines 9 to 45 of the patent in suit), the optical purity of the t-butyl (R)-(-)-4-cyano-3-hydroxybutyrate is **directly related** to the optical purity of the starting t-butyl (S)-(-)-4-halogeno-3-hydroxybutyrate. It follows from the above that the subject matter of Claim 3 of each request amounts to an inadmissible generalization of the Example 1. For this reason, the amendments contravene Article 123(2) EPC.

6.5 Consequently, the auxiliary requests II, III and IV must fail.

7. As none of the requests submitted by the Respondent meets the requirements of the EPC, the patent in suit must be revoked. Therefore, there is no need to deal with the auxiliary request of the Appellant.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin A. Nuss