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Datasheet for the decision of 28 November 2024

Case Number: T 2076/21 - 3.3.10

Application Number: 12816098.3

Publication Number: 2802562

IPC: C07C405/00, C07D307/935

Language of the proceedings: EN

Title of invention:
PROCESS FOR THE PREPARATION OF TRAVOPROST

Patent Proprietor:
EUROAPI Hungary Limited Liability Company

Opponent:
Hollatz, Christian

Headword:

Relevant legal provisions:
EPC Art. 56, 123(2), 84

Keyword:

Decisions cited:

Catchword:

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Boards of Appeal

Chambres de recours

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Case Number: T 2076/21 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 28 November 2024

Appellant: (Opponent)	Hollatz, Christian Ter Meer Steinmeister & Partner mbB Nvmphenburger Straße 4 80335 Munich (DE)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	EUROAPI Hungary Limited Liability Company To u. 1-5. 1045 Budapest (HU)
Representative:	Danubia Patent & Law Office LLC Bajcsy-Zsilinszky út 16 1051 Budapest (HU)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 22 September 2021 concerning maintenance of the European Patent No. 2802562 in amended form.**

Composition of the Board:

Chair	P. Gryczka
Members:	R. Pérez Carlón
	F. Blumer

Summary of Facts and Submissions

I. The appellant (opponent) appealed the opposition division's interlocutory decision on the maintenance of European patent No. 2 802 562 in amended form as the main request then pending, which is the main request of the respondent (patent proprietor) in appeal.

II. Notice of opposition had been filed on the ground of lack of inventive step (Article 100(a) EPC).

III. Reference is made to the following documents:

D4 EP 2 143 712 A1

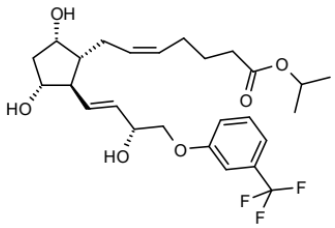
D5 C. Aswathanarayanappa *et al.*, "Diastereoselective Reduction of the Enone Intermediate of Travoprost", Organic Process Research and Development 15, 2011, 1085-7

D8 WO 93/00329

D9 US 4,638,002

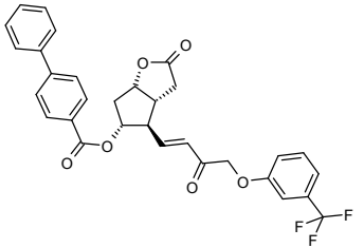
IV. Claim 1 of the main request reads as follows:

1. A process for the preparation of travoprost of formula (I).



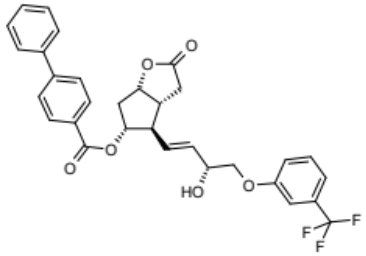
(I)

comprising that,
the compound of formula (II).



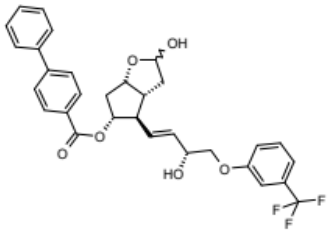
(II)

is stereoselectively reduced, wherein the selective reduction of the compound of formula (II) is carried out with a borane-type reducing agent, the resulting compound of formula (III)



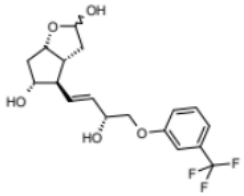
(III)

is repeatedly crystallized, the lactone group of the compound of formula (III) is reduced, the *p*-phenyl-benzoyl protecting group of the thus obtained compound of formula (IV)



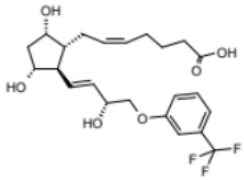
(IV)

is removed, the resulting triol of formula (V)



(V)

is if desired after crystallization transformed by Wittig reaction into the acid of formula (VI),



(VI)

which is then esterified

characterized in that the repeated crystallization is carried out in different solvents or in the mixture of them, wherein the solvents are selected from hydrocarbon, chlorinated hydrocarbon, ether, ester, ketone or alcohol-type solvents or mixtures thereof.

V. The opposition division concluded that the claims had a basis in the application as originally filed and were

clear. It also concluded that the right to priority had been validly claimed.

Document D4 was the closest prior art. The problem underlying the claimed invention was to provide a process for preparing travoprost in which the 15-epimer was substantially removed in an alternative way and in which the reduction of the lactone provided an intermediate which could be purified more easily. The claimed solution was characterised by using p-phenyl-benzoyl (PPB) as the protecting group, by recrystallising compound (III) repeatedly and by reducing the lactone in (III) before removing the PPB protecting group. The solution would not have been obvious to a skilled person and was thus inventive.

VI. The appellant's arguments were as follows.

Claim 1 of the main request included the features of claims 1 and 11 to 13 as originally filed. However, claims 11 to 13 as originally filed also required all the features of claims 2 to 10, which were not features of claim 1 of the main request. Claim 1 thus contained added subject-matter. In addition, claims 16, 17, 19, 23 and 28 of the application as originally filed only referred back to claim 1. For this reason, dependent claims 6 to 10 added matter too. As the priority document has the same content as the application as filed, the right to priority had not been validly claimed. The lack of priority right implied that two patent publications should be considered prior art for the claimed invention.

Claim 1 of the main request included the feature "alcohol-type solvent", which was not clear.

The appellant agreed with the opposition division in the choice of closest prior art (D4) and on the features characterising the claimed invention. However, the available evidence did not show an improvement over the process in D4, and the sole problem credibly solved was providing an alternative. The claimed solution would have been obvious to a skilled person and was thus not inventive.

VII. The respondent argued that the claims of the main request had the required basis and that the feature alcohol-type solvent was clear. It also argued that the priority right was validly claimed.

The respondent agreed that D4 was the closest prior art and that it did not disclose the features identified in the appealed decision. The respondent considered that the claimed process solved the problem of providing an improvement but that it was also inventive as the solution to the problem of providing an alternative process for removing the 15-epimer in the synthesis of travoprost.

VIII. The board informed the parties in a communication dated 15 April 2024 of its preliminary opinion.

IX. The appellant replied by announcing its non-attendance at the already summoned oral proceedings, which took place on 28 November 2024.

X. The parties' final requests were as follows.

The appellant requested in writing that the decision under appeal be set aside and that European patent No. 2 802 562 be revoked.

The respondent requested that the appeal be dismissed or that the patent be maintained with the claims of one of auxiliary requests 1 to 7 filed with the reply to the grounds of appeal or with the claims of one of auxiliary requests 8 and 9, filed with a letter dated 15 August 2024.

XI. At the end of the oral proceedings, the decision was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Amendments

2.1 Absent any further submission of the appellant in this respect, the board sees no reason to depart from its preliminary view that the features of claim 1 had a basis in the combination of claims 1, 2 and 11 to 13 as originally filed. This was also the opposition division's conclusion.

The appellant read the feature of claims 11 to 13, "the process as defined in claims 2-10", as requiring all features of claims 2 to 10, in combination. The board sees no reason, however, to interpret this wording other than as a typical back-reference in patent drafting.

2.2 Claims 6 to 10 have, respectively, the wording of claims 16, 17, 19, 23 and 28 of the application as originally filed, which, however, only referred back to claim 1.

Like claim 16 as originally filed, claim 6 of the main request relates to the reduction of compound (III) with diisobutylaluminium hydride (DIBAL-H). The same disclosure can be found on page 4, lines 23 and 24 of the description. No alternative is disclosed. A skilled person seeking to put the claimed invention into practice would have sought the reaction conditions for reducing compound (III) in claim 1 and found DIBAL-H as the sole reagent for this purpose. Claim 6 of the main request does not thus provide any undisclosed technical information.

Similarly, the sole conditions for removing the protecting group in claim 7 of the main request are those on page 4, lines 31 and 32.

Page 4, lines 33 and 34 discloses the purification of compound (V) by crystallisation, as required by claim 8 of the main request. No other option is provided.

Esterification of compound (VI) with isopropyl iodide, as required by claim 9, is disclosed on page 5, lines 5 and 6, and no other option can be found in the originally filed application.

Lastly, the purification of compound (I) by chromatography in claim 10 is disclosed by claim 28 as originally filed and corroborated by example 6 of the application as originally filed.

Dependent claims 6 to 10 thus have a basis in the application as originally filed.

3. **Priority**

The appellant's arguments for concluding that the right to priority was not validly claimed are the same as those in the previous point for added subject-matter. The reasoning provided there also applies. The right to priority has thus been validly claimed.

The appellant argued that the lack of priority right implied that two patent publications should be considered prior art for the claimed invention. However, it did not argue why either of them was relevant. Under these circumstances, there is no need to further elaborate on this point.

4. **Clarity**

Claim 1 of the main request contains the feature "hydrocarbon, chlorinated hydrocarbon, ether, ester, ketone or alcohol-type solvents". This feature was not in the granted claims and is open to examination for compliance with Article 84 EPC following G 3/14.

The board sees no reason to depart from its preliminary view that the feature alcohol-type solvent in claim 1 merely requires a solvent which has an alcohol group. This feature is thus clear, as concluded by the opposition division.

5. **Inventive step**

5.1 Claim 1 relates to a multi-step process for preparing travoprost (I) from a compound (II) bearing a p-phenyl-benzoyl (PPB) protecting group. The carbonyl of the enone in compound (II) is reduced with a borane-type reducing agent to yield an allylic alcohol of formula

(III), which is repeatedly recrystallised from defined solvents. The lactone group is subsequently reduced to obtain (IV); the PPB group is removed; and the resulting triol (V) is transformed by Wittig reaction into the acid (VI) which is then esterified.

5.2 Document D4 is the closest prior art. The parties agreed that D4 discloses the preparation of travoprost from a lactone compound that differs from compound (II) by having a benzoyl instead of a PPB protecting group. It was undisputed that D4 does not disclose the following features of claim 1:

- PPB as the protecting group of the hydroxy group of the lactone (see compound 20a, Example 2)
- repeated recrystallisation of the product (III), obtained by reduction with a borane-type agent, as the analogue compound in D4 is only recrystallised once (see example 3, line 17)
- reduction of the lactone group prior to deprotection of the hydroxy group

5.3 Technical problem underlying the claimed invention

The respondent saw the problem underlying the claimed invention as to provide a process for preparing travoprost where the 15-epimer is removed in an alternative way.

During the written procedure, the respondent relied on a more ambitious problem, and the appellant argued that it was not credibly solved. As the board arrived at the conclusion that the claimed subject-matter is inventive as a solution to the problem in the preceding paragraph, it is not necessary to elaborate on any of

these points.

5.4 Solution

According to the respondent, this problem is solved by the claimed process, characterised by repeated recrystallisation of a product (III) bearing a PPB protecting group.

5.5 Success of the claimed solution

According to the evidence in the patent, two recrystallisations of compound (III) allows increasing the diastereomeric excess from de=92% to de=98%.

The board expressed its doubts in its communication whether every solvent in claim 1 and every reducing media would have led to the desired separation.

The respondent argued that the success of the recrystallisation arises from the protecting group alone. According to the reply to the grounds of appeal (see last paragraph in point 4.1), the recrystallisation can be carried out in a number of other solvent systems. Absent any evidence of the contrary, the respondent's explanation is convincing.

The problem of providing a process allowing alternative removal of the 15-epimer has been thus credibly solved.

5.6 It remains to be examined whether the claimed solution would have been obvious to a skilled person in view of the prior art.

5.6.1 D4 discloses the stereoselective reduction of a compound which differs from (II) in claim 1 by having a

benzoyl protecting group (Bn) instead of a PPB group (see examples 10 and 3). The process includes a crystallisation step and leads to a de=88.7%. The product in D4 thus contains more than 10% of the undesired epimer.

D4 discloses that the 15-epimer is to be removed at a later point (see paragraph [0057]), but the examples do not explicitly address how. It could arguably have been removed in the chromatography in paragraph [0148] as the experimental data of the final compound do not hint at the presence of other diastereoisomers.

The PPB protecting group has been used in the synthesis of other prostaglandins (see, for example, Schemes 1 to 3 and Table 1 of D5). D5 discloses the reduction of (II) to yield (III) with a diastereoselectivity of de=95% (Scheme 3). The epimers were, however, separated by flash column chromatography (page 1087, right column, lines 4 to 6) and obtained as "solid", without any indication of its crystallinity. There is thus no indication in the prior art that compound (III) could be crystallised.

5.6.2 The appellant argues that compound (III) in claim 1 was expected to be crystalline as the product in D4, which only differed by lacking a phenyl group, was crystalline too. Crystalline prostaglandin intermediates similar to (III) and bearing a PPB protecting group were also prior art (example 3 of D8, example 12 of D9).

However, the crystallinity of organic compounds is not easily predictable, and the prior art lacks information on whether compound (III) forms crystals. Thus, the

appellant's argument is not convincing.

5.6.3 The appellant also argued that it would have been obvious to carry out a repeated crystallisation of compound (III). By doing so, a skilled person would have expected an enhanced diastereomeric excess and less yield.

However, this argument can only succeed if compound (III) was known to be crystalline. As this is not the case, this argument of the appellant is also not convincing.

5.6.4 The claimed process would thus not have been obvious to a skilled person seeking an alternative process for the removal of the 15-epimer in latanoprost synthesis and is thus inventive (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated