BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

A		B		C	X

File Number: T 181/91 - 3.3.1

Application No.: 87 101 461.9

Publication No.: 0 233 543

Title of invention: Process for preparing cholesta-1,5,7-trien-3-ol

Classification: C07J 9/00

D E C I S I O N
of 18 August 1992

Applicant: Nisshin Flour Milling Co., Ltd.

Headword: Steroid/NISSHIN

EPC Art. 56

Keyword: "Inventive step (no) - obvious alternatives"

Case Number : T 181/91 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 18 August 1991

Appellant : NISSHIN FLOUR MILLING CO., LTD.
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Decision under appeal : Decision of Examining Division of the European Patent Office dated 17 September 1990 refusing European patent application No. 87 101 461.9 pursuant to Article 97(1) EPC.

Composition of the Board :

Chairman : K.J.A. Jahn
Members : R.K. Spangenberg
J.A. Stephens-Ofner

Summary of Facts and Submissions

I. The appeal was filed on 17 November 1990, accompanied by the payment of the appropriate fee, and lies from the decision of the Examining Division of the EPO dated 17 September 1990 refusing European patent application No. 87 101 461.9, corresponding to EP-A-233 543.

II. The decision under appeal was based upon Claim 1 received on 15 August 1989 relating to a process for preparing cholesta-1,5,7-trien-3-ol.

The Examining Division concluded that the claimed subject-matter did not involve an inventive step having regard to the following documents:

D1 = EP-A-O 045 884 and

D3 = FIESER & FIESER Reagents for Organic Synthesis, Vol. 1 (1967), 524-527.

The technical problem underlying the application was seen to be the preparation of cholesta-1,5,7-trien-3-ol, an important intermediate for the synthesis of 1α-hydroxyvitamin D3, in high yields. The key step of the process proposed as the solution of this problem was the acylation of cholesta-1,4,6-triene-3-one with isopropenyl acetate in an acid catalysed reaction. However, a comparable reaction was already recommended in D1 as an improved general synthethic route to 1,5,7-tri-unsaturated-3-hydroxy-steroids. Although the examples of this reference described the use of acetic anhydride or acetyl chloride in the presence of pyridine as acylating agents, the use of other sufficiently electrophilic acylating agents such as isopropenyl acetate was also disclosed. According to common general knowledge, which was summarised in D3, it was obvious to carry out the

acetylation with this reagent in the presence of an acid catalyst.

III. In the statement of grounds of appeal, received on 25 January 1991, the Appellant argued that it was previously thought necessary to prepare cholesta-1,5,7-trien-3-ol starting from cholesta-1,4,6-trien-3-one by isomerization, as indicated in the application (see EP-A-233 543, page 2, lines 10 to 17). This isomeriation process being disclosed in

D4 = C. Kaneko et al., Tetrahedron 30(1974), 2701 ff and

D5 = Guest et al., J. Chem. Soc., Perkin I,1979, 1695 ff.

used a base-catalysed rearrangement of cholesta-1,4,6-trien-3-one and only furnished small yields.

On the other hand, in the Appellant's submission, D1 neither described the preparation of cholesta-1,5,7-trien-3-ol nor the use of cholesta-1,4,6-trien-3-one as a starting material therefor. For this reason, Claim 1 was reworded as follows:

"A process for preparing cholesta-1,5,7-trien-3-ol starting from cholesta-1,4,6-trien-3-one, characterized in that the cholesta-1,4,6-trien-3-one is reacted with isopropenyl acetate in the presence of an acid catalyst to form cholesta-1,3,5,7-tetraen-3-yl acetate, and reducing the same."

During oral proceedings, which took place on 18 August 1992, the Appellant's attention was drawn to Example II of D1, which described the preparation of cholesta-1,5,7-trien-3-ol starting from cholesta-1,4,6-trien-3-one by the steps of acetylation with acetyl chloride in the presence of pyridine and subsequent reduction with

calciumborohydride. In the Appellant's opinion this example was not the closest state of the art, essentially because it taught the control of acidity. Moreover, since in the field of steroid chemistry it was not easily possible to transfer the teaching from one document to another, the Appellant could see no pointer in that document towards the claimed solution of the present technical problem. Since D3 only illustrated the enol acetylation of steorids which were structurally different from the starting compound of the present application, it could not suggest the present process either.

During oral proceedings the Appellant submitted an amended Claim 1 by way of auxiliary request, the amendment consisting in the limitation of the acid catalyst to paratoluenesulfonic acid and in that the reaction be performed in the absence of a solvent or in the presence of butyl acetate. He submitted that the process including these features gave unexpectedly higher yields of the desired product than the acylation in the presence of other acids such as methanesulfonic acid or potassium acid sulfate and other solvents such as toluene.

IV. The Appellant requested that the decision under appeal be set aside and the patent be granted on the basis of Claim 1 as submitted together with the statement of grounds of appeal or on the basis of Claim 1 submitted during oral proceedings.

V. At the end of oral proceedings the decision of the Board to dismiss the appeal was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Main request

2.1 No objection under Article 123(2) EPC arises against the present Claim 1, since it differs from Claim 1 as filed only in that it is drafted in the two-part form.

2.2 The novelty of the claimed subject-matter has been acknowledged in the decision under appeal, since the acylation of cholesta-1,4,6-trien-3-one with isopropenyl acetate was regarded as being neither disclosed in D1 nor in D3. In the light of the disclosure in D1, Example II (page 20), and the reference to isopropenylacetate as another possible acetylating agent on page 13, line 22, novelty can only be acknowledged if the presence of an acid is not unambiguously implied by the disclosure of D1. Such implication may exist here in view of the relevant common general knowledge, as represented by D3. However, since D3 does not expressly state that it is not possible to perform acetylations with isopropenylacetate in the absence of an acid catalyst, so that doubts remain in this respect, the claimed process may be regarded as novel.

2.3 The Board cannot agree with the Appellant's opinion that D4 and D5 represented the closest state of the art, since D1 discloses to control acid. D4 and D5 both relate to the preparation of cholesta-1,5,7-trien-3-ol via cholesta-1,5,7-trien-3-one which ketone is prepared by a low-yield isomerisation of cholesta-1,4,6-trien-3-one, and subsequent reduction with $Ca(BH_4)_2$ (see D4, page 2702, right-hand column, lines 10 to 16 and page 2704, left-hand column, the paragraph headed "Preparation of cholesta-1,5,7-trien-3ß-ol (3) from compound 1", and D5, page 1696, right-hand column, the paragraph headed "Cholesta-1,5,7-trien-3ß-ol (3)"), i.e. these documents disclose the preparation of the desired compound by a quite different sequence of reaction steps. Therefore, in the Board's judgment, it is inappropriate to regard this older state of the art as the one closest to the claimed process.

Moreover, this state of the art does not require the presence of an acid. This feature, therefore, cannot form part of the technical problem, but is an element of the solution (see T 229/85, OJ EPO 1987, 237).

Thus, in the Board's judgment, the process of Example II of D1 (see page 20), steps (C) and (D) represents the closest state of the art. In step (C) the acetylation of cholesta-1,4,6-trien-3-one is performed with an excess of acetyl chloride and acetic anhydride in the presence of pyridine. The yield is 84%. The product of this step is then reduced with $Ca(BH_4)_2$ to cholesta-1,5,7-trien-3-ol (90% yield). The overall yield of these two steps therefore is about 75 %.

2.4 In respect of this state of the art, the technical problem underlying the application can be seen in providing a further process for preparing cholesta-1,5,7-trien-3-ol from cholesta-1,4,6,-trien-3-one in a yield comparable with that provided by the processes according to D1.

2.5 Having regard to the yields reported in D1 and the yields obtained according to the examples of the application (about 60 to 66%), the stated problem can be regarded as being solved.

2.6 The proposed solution consists in modifying the acetylation step in the reaction sequence disclosed in D1 by replacing the acetylating agent, viz. acetyl chloride and acetic anhydride in the presence of pyridine, by isopropenylacetate in the presence of an acid.

2.7 For modification of the process disclosed in Example II, D1 already suggests to use acylating agents other than acetyl chloride and acetic anhydride (see page 13, lines 19 to 28). One of the alternatives mentioned is isopropenylacetate. However, it is not mentioned there

that isopropenylacetate should be used in the presence of an acid. Further, the Board is unable to accept the Appellant's submission that it follows from the disclosure on page 13, lines 19 to 25 in combination with page 5, lines 20 to 23 as well as Claims 10 and 12 that acidic reaction conditions must not be applied. On the contrary, on page 5 it is only stated that it is necessary to buffer against acid if the reaction is carried out where acid sensitive groups are present in the molecule, which is not the case in the reaction under consideration, and on page 13, paragraph 4, it is expressly stated that the reaction can be carried out with or without pyridine, which controls acidity. Therefore, in the Board's judgment, in the light of the disclosure in D1, the presence of pyridine in the process of Example II is in no way mandatory. This finding is not in contradiction to the fact that in Claims 10 to 12 of D1 the process of Example II is claimed as a preferred embodiment of the general process of Claim 8, because the disclosure of D1 is in no way limited to the said specific embodiment. Therefore, the existence of these claims cannot support the Appellant's submission either.

This finding is further confirmed by the reference to an earlier process on page 4 of D1 (see the second step in the reaction scheme) and by D3, both references providing additional examples of the preparation of steroid-3-enolacetates from the corresponding ketone by reaction with isopropenylacetate in the presence of an acid catalyst.

With respect to this state of the art, the Board cannot agree with the Appellant's unsupported submission that there was no pointer to using these reaction conditions for modifying the process of Example II of D1, because it was not readily possible to transfer the teaching of one document to another one in the field of the complicated

steroid chemistry. In the Board's judgment, a person skilled in the art would not normally expect, in the absence of any evidence to the contrary, that a reaction which is described in a textbook, such as D3, as being generally applicable in the technical field of steroid chemistry, would not give the promised result. Therefore, the Board is satisfied that in the present circumstances the skilled person would have expected that the replacement of the acetylating agent acetyl chloride/acetic anhydride in the presence of pyridine by isopropenyl acetate in the presence of an acid would not result in a significant change in the yield of the reaction.

2.8 Thus, the claimed process does not involve an inventive step as required by Art. 56 EPC and the main request must therefore fail.

3. Auxiliary request

3.1 The additional technical features contained in the present Claim 1 find their basis in Examples 1 and 2 as filed. The requirement of Art. 123(2) EPC is therefore met.

3.2 The Board is satisfied that the combination of technical features now claimed is not disclosed in any of the cited documents. The claimed subject-matter is therefore novel.

3.3 In respect of inventive step, the Appellant submitted that the technical problem underlying the process now claimed should not only be seen in providing an alternative to the process disclosed in D1, but also in optimising the preparation of cholesta-1,5,7-trien-3-ol in the presence of an acid. With reference to Examples 1 and 2 of the present application on the one hand and Examples 3 and 4 on the other hand, he pointed out that an inventive

selection was necessary in order to obtain improved yields.

3.4 In the Board's judgment, the technical problem must normally be formulated by starting from the state of the art as it exists and not, as the Appellant now suggests, on the basis of a process which does not belong to the state of the art but is only rendered obvious by it (see e.g. T 181/82; OJ EPO 1984, 401). Therefore, the Board cannot accept the Appellant's arguments so that the closest state of the art with respect to the process now claimed remains the process of Example II of D1.

3.5 Since the Appellant did not rely upon any additional advantage of the process now claimed in respect of this closest state of the art, the technical problem underlying the process of the main request remains unchanged and it is also clear from points 2.3 to 2.5 above that the Board is satisfied that it has been effectively solved by the combination of technical features contained in the present Claim 1.

3.6 It therefore only remains to be examined whether the state of the art provided a suggestion to consider the technical features of the present Claim 1, which are not already contained in Claim 1 of the main request, with a view to solving the present technical problem. The result of this examination is that such a suggestion is provided by D3, which, under the headings "Isopropenyl acetate"..."Enol acetylation" contains the following information:

"It is the enol acetate of acetone and in the presence of a catalytic amount of sulfuric acid or paratoluenesulfonic acid it reacts with a higher ketone to give the higher enol acetate and acetone, which is removed by distillation to displace the equilibrium. The reaction is usually

carried out with either benzene or excess reagent as solvent."

Furthermore, in the light of Example 1 of the application under consideration the expression "in the absence of a solvent" now contained in Claim 1 must be construed to include the reaction in the presence of excess isopropenyl acetate as a solvent.

Therefore, the present Claim 1 includes one of the possibilities expressly mentioned in D3 as being the normal way of performing acetylations with isopropenyl acetate (see also the reaction (3) to (4) on page 525), which a person skilled in the art would inevitably consider if he wishes to follow the suggestion of D1, page 13 (see point 2.7 above) and to use isopropenyl acetate as acetylating agent.

3.7 In the Board's judgment, the subject-matter of dependent Claims 2 to 8 as far as it is not incorporated in the present Claim 1 and is still claimed, i.e. substantially that of Claims 3 and 7, does not involve an inventive step either. Since the Appellant did not submit any specific arguments in this respect, no detailed reasons need to be given for this finding.

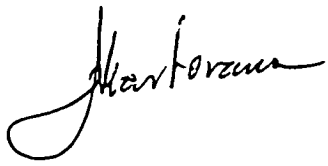
3.8 Thus, the process according to the auxiliary request does not involve an inventive step and this request must also fail.

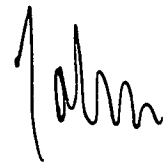
Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:





P. Martorana A. Jahn