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Datasheet for the decision of 9 September 2021

Case Number: T 1089/15 - 3.3.02

Application Number: 05748485.9

Publication Number: 1752460

IPC: C07D501/60, C07D501/04

Language of the proceedings: EN

Title of invention:
3-ALKENYLCEPHEM COMPOUNDS AND PROCESS FOR PRODUCTION THEREOF

Patent Proprietor:
Otsuka Chemical Co., Ltd.

Opponent:
Stötter, Gerd

Headword:

Relevant legal provisions:
EPC Art. 56, 83, 123(2)

Keyword:
Inventive step - (yes)
Sufficiency of disclosure - (yes)
Amendments - allowable (yes)

Decisions cited:
T 0022/82, T 0648/88, T 0019/90, T 0435/91, T 0190/99, T 0579/00, T 0318/02, T 1023/02, T 1063/06, T 0480/11, T 0544/12

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 1089/15 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 9 September 2021

Appellant: (Opponent)	Stötter, Gerd Bamberger Strasse 49 01187 Dresden (DE)
Representative:	Kailuweit & Uhlemann Patentanwälte Partnerschaft mbB Bamberger Straße 49 01187 Dresden (DE)
Respondent: (Patent Proprietor)	Otsuka Chemical Co., Ltd. 2-27, Otedori 3-chome, Chuo-ku Osaka-shi, Osaka 540-0021 (JP)
Representative:	Held, Stephan Meissner Bolte Patentanwälte Rechtsanwälte Partnerschaft mbB Widenmayerstraße 47 80538 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 1 April 2015 rejecting the opposition filed against European patent No. 1752460 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. Maremonti
Members:	P. O'Sullivan
	R. Romandini

Summary of Facts and Submissions

I. The appeal of the opponent (hereinafter appellant) lies from the decision of the opposition division to reject the opposition against European patent 1 752 460.

II. The patent was opposed under Article 100(a) (lack of inventive step), (b) and (c) EPC.

III. The following documents were among those cited during opposition proceedings:

D2: EP 0 658 558 A1;
D3: EP 1 016 665 A1;
D7: Giulletti & Bernardo, Crystallization - Science and Technology Chapter 14: *Crystallization by Antisolvent Addition and Cooling*, 383-384;
D8: "The HPLC Solvent Guide, 2nd Edition", Wiley-lnterscience, 2002;
D9: Latscha et al., "*Chemie - Datensammlung: Laborhilfen für Studium und Praxis*", 1990, Springer-Verlag, 248-249;
D10: Organische Chemie, Vollhardt & Schore, Eds., 4. Auflage 2005, 1110-1111;
D11: EP 0 009 008 A2;
D12: EP 0 059 683 A2;
D13: Hosny et al., Asian J. Pharm. Clin. Res. 2014, 7(1), 145-150;
D14: "*Inorganic Acids*" - Sigma-Aldrich online catalogue;
D15: "*Acids-Inorganic*" - Loba Chemie online catalogue.

Furthermore, during appeal proceedings, the parties referred to experiments filed by the patent proprietor (hereinafter respondent) during opposition proceedings, denoted in the following as:

D22: Experimental Data filed by the respondent with the letter dated 8 November 2013

IV. With the statement setting out the grounds of appeal the appellant submitted the following documents:

D16: Sakagami et al., The Journal of Antibiotics 1990, 8:1047-1050;
D17: Atsumi, Journal of Synthetic Organic Chemistry, Japan 2002, 2:155-161;
D18: Sakagami et al., Chemical and Pharmaceutical Bulletin 1991, 39(9) 2433-2436;
D19: Falbe and Bauer, Eds. 1985, Carbonsäuren und Carbonsäurederivate, 223-226;

D20: Vollhardt and Schore, Eds., 2005, Organische Chemie, 392, 393, 990-992, 1060;
D21: Greenberg et al., Eds., 2002, The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science, 85-87.

V. In its reply to the statement of grounds of appeal, the respondent rebutted the arguments of the appellant and submitted that the subject-matter claimed in the patent as granted met the requirements of the EPC.

VI. With a communication pursuant to Article 15(1) RPBA, the board set out the preliminary opinion that the

grounds for opposition invoked by the appellant did not prejudice the maintenance of the patent as granted.

VII. The appellant replied to the board's communication and contested the board's preliminary opinion as regards inventive step.

VIII. Oral proceedings by videoconference were held on 9 September 2021.

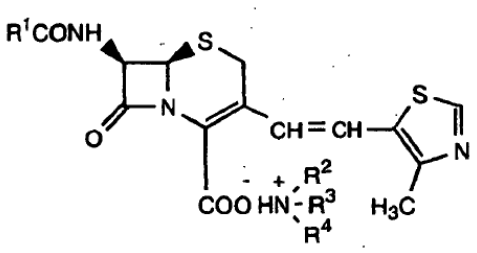
IX. Requests relevant to the present decision

The appellant requested that the contested decision be set aside and the patent be revoked in its entirety.

The respondent requested as its main request dismissal of the appeal, i.e. maintenance of the patent as granted.

X. Independent claims 1, 3, 4, 5 and 6 of the main request read as follows:

"*1. A 3-alkenylcephem compound of the formula (1)*

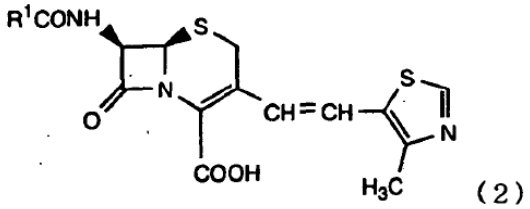


(1)

wherein R^1 is benzyl or phenoxymethyl, R^2, R^3 and R^4 are alike or different and are each a hydrogen atom, C_{1-10} alkyl, C_{4-8} cycloalkyl or aryl C_{1-3} alkyl substituted or unsubstituted with C_{1-4} alkyl, R^2 and R^3, when taken together, form a group

$-(CH_2)_1X_m(CH_2)_n-$ substituted or unsubstituted with C_{1-4} alkyl at an optional position, X is an oxygen atom or group $-N(R^5)-$, 1 is 0 to 3, m is 0 or 1, n is an integer of 2 to 4, R^5 is a hydrogen atom or C_{1-4} alkyl.

3. A process for preparing a 3-alkenylcephem compound of the formula (1) ***characterized by*** *reacting an amine compound of the formula (3) with a 3-alkenylcephem compound of the formula (2)*



(2)

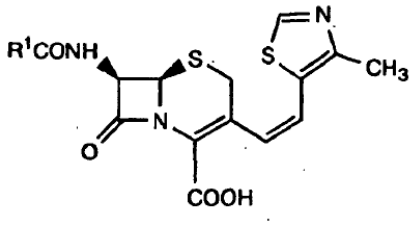
wherein R^1 is the same as above

(3)

wherein R^2, R^3 and R^4 are the same as above.

4. A process for preparing a 3-alkenylcephem compound of the formula (2) which is improved in the content of a 3-(Z)-alkenylcephem compound of the formula (2a), the process being ***characterized by*** *adding at least one of organic solvents including alcohols, ethers, aliphatic hydrocarbons, alicyclic ketones and aliphatic ketones to a solution of a 3-alkenylcephem compound of the formula (1) in water or in a solvent mixture of water and at least one organic solvent selected from among alcohols, aliphatic ketones, esters, amides and nitriles for crystallization to obtain a solution or suspension of a 3-alkenylcephem compound of the formula (1) which is improved in the content of a 3-(Z)-alkenylcephem compound of the formula (1a), and*

adjusting the solution or suspension to a pH of 0.5 to 4



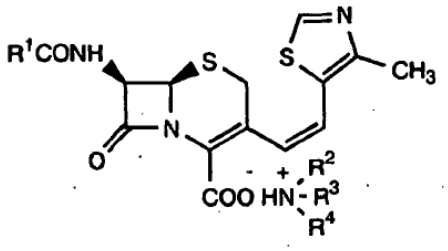
(2 a)

wherein R^1 is the same as above.

5. A process for preparing a 3-alkenylcephem compound of the formula (1) which is improved in the content of a 3-(Z)-alkenylcephem compound of the formula (1a), the process being ***characterized by*** *adding at least one of organic solvents including alcohols, ethers, aliphatic hydrocarbons, alicyclic ketones and aliphatic ketones to a solution of a 3-alkenylcephem compound of the formula (1) in water or in a solvent mixture of water and at least one organic solvent selected from among alcohols, aliphatic ketones, esters, amides and nitriles to crystallize the 3-alkenylcephem compound of the formula (1).*

6. A process for preparing a 3-alkenylcephem compound of the formula (2) which is improved in the content of a 3-(Z)-alkenylcephem compound of the formula (2a), the process being ***characterized by*** *adjusting a solution or suspension of a 3-alkenylcephem compound of the formula (1) which is improved in the content of a 3-(Z)-alkenylcephem compound of the formula (1a) to a pH of 0.5 to 4."*

In the above, the compound of formula 1a corresponds to the *Z*-isomer of the compound of formula 1, i.e.



(1 a)

wherein R^1, R^2, R^3 and R^4 are the same as defined above.

XI. The arguments of the appellant insofar as relevant to the present decision, may be summarised as follows:

Main request

Articles 100(a) and 56 EPC

D2 represented the closest prior art. The compound of formula (1) of claim 1 at issue was distinguished from the compound of formula II in D2 in that the amino group (H_2N-) in the 7-position is protected (with the moiety -COR^1). The compound of formula (1) of claim 1 was merely a known compound with a new protecting group, and revealed no special effects or properties. The alleged technical effect, the increased yield of Z-isomer from the selective crystallisation, could not be attributed to the distinguishing feature, but rather to differences in the respective processes in the solvents used, the temperature, the reaction period, and whether the mixture was stirred, all of which could have a significant impact on the yield obtained. Even if said effect were to be recognised, and the objective technical problem formulated accordingly, the solution provided in claim 1 was obvious in view of D2 in combination with D3 or with D16 or D18.

Sufficiency of disclosure - Article 100(b) EPC

The invention defined in the claims as granted was not sufficiently disclosed. This was *inter alia* due to the breadth of the contested claims compared to the examples. Specifically, in terms of the possible solvent combinations (some of which were unstable), the variation possible in definition of the amine (3) in the claims (some of which would not work), and the fact that not all mineral acids were suitable to perform the method claimed.

Amendments - Article 100(c) EPC

Claims 9, 20 and 21 comprised subject-matter which was not derivable from the application as filed, in contravention of Article 123(2) EPC.

XII. The arguments of the respondent insofar as relevant to the present decision, may be summarised as follows:

Main request

Articles 100(a) and 56 EPC

The subject-matter of the granted claims involved an inventive step starting at D2 as closest prior art. Claim 1 was distinguished from the compound of formula II in D2 in that the amino group (H_2N-) in the 7-position is protected (with $-COR^1$). The technical effect of an increased yield of Z-isomer in the selective crystallisation underlying claim 1 was demonstrated in the examples, in particular in a comparison of example 3 of the patent with comparative example 2 of D22. The technical problem was the

provision of a 3-alkenylcephem compound which allows an increase in the overall yield of the Z-isomer. The solution to the problem, the compound of claim 1, involved an inventive step.

Sufficiency of disclosure - Article 100(b) EPC

The invention defined in the claims as granted was sufficiently disclosed. The appellant's arguments were based on mere allegation without substantiation.

Amendments - Article 100(c) EPC

Claims 9, 20 and 21 did not comprise subject-matter which was not derivable from the application as filed, and thus the ground under Article 100(c) did not prejudice the maintenance of the patent as granted.

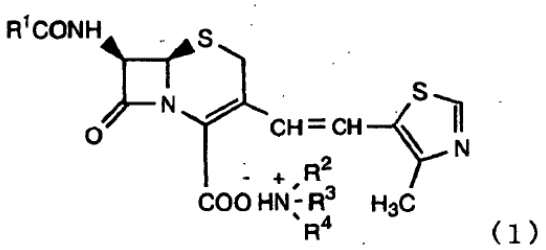
Reasons for the Decision

Main request (patent as granted)

1. Inventive step - Articles 100(a) and 56 EPC

Independent Claim 1

Claim 1 is directed to a 3-alkenylcephem compound of formula (1)

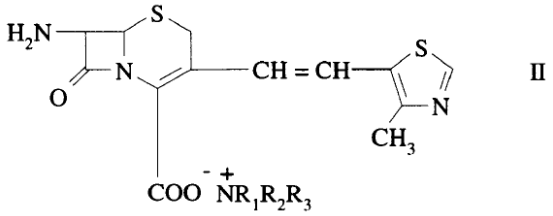


(1)

According to the patent (e.g. paragraph [0007]), compound (1) is useful as an intermediate in a process for preparing cefditoren pivoxil (of formula (4), paragraph [0002]), widely used as an antibacterial agent. The configuration of the alkenyl group in cefditoren pivoxil is Z. It was therefore important to diminish to the greatest possible extent the presence of the E-isomer. Thus, attempts had been made (in the prior art) to improve the Z-isomer content of process intermediates (patent, paragraph [0003]).

1.1 Closest prior art & distinguishing feature

1.1.1 Both parties were of the opinion that patent document D2 represented the closest prior art. The board agrees with this assessment. Similarly to the contested patent, D2 discloses a method for depleting the content of the E-isomer in an E,Z mixture of a compound of formula II



II

by selective crystallisation (D2, page 3, lines 41-46).

1.1.2 The parties also agreed that the compound of formula (1) of claim 1 at issue was distinguished from the compound of formula II in D2 in that the amino group (H_2N-) in the 7-position is protected with an R^1CO- moiety, i.e. an amide group with R^1 selected from benzyl or phenoxymethyl (c.f. contested claim 1). The board shares this view.

1.1.3 Although the subject-matter of claim 1 concerns only the compound of formula (1), its utility is relevant for the assessment of inventive step. With the exception of the above-mentioned difference, the compounds of formulae (1) and II in the patent and D2 respectively are used in an identical manner to improve the Z-isomer content of the desired product. Specifically, the carboxylic acid amine salt of formulae (1) and II respectively is prepared by reacting the carboxylic acid with an appropriate amine, and the desired Z-isomer is selectively crystallised from the reaction mixture (patent, claims 3 and 5; D2, example 2, first step). The amine salt is then transformed back to the carboxylic acid by treatment with acid (patent, claim 6; D2, example 2, second step).

1.2 Problem solved

1.2.1 According to the patent, the crystallisation process of the prior art (JP1995-188250 A, a family member of D2) did not provide a satisfactory yield of the desired amine salt, depleted in the E-isomer (patent, paragraphs [0004] and [0005]). In contrast, according to the patent, the use of an amine salt compound having an amide structure in the 7-position (i.e. of formula (1), above) improved the yield of the desired compound and improved the Z-isomer content (patent, paragraph [0010]).

1.2.2 According to established case law, alleged advantages to which a patent proprietor merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step. It

must therefore be determined whether the evidence on file is sufficient to support the alleged effect of improved Z-isomer yield.

1.2.3 D2 is silent with regard to the yield obtained according to the examples thereof. According to the respondent, the improved yield was evident from a comparison of the examples of the patent with comparative example 1 of the patent and comparative example 2 of D22, both of which concerned the preparation and selective crystallisation of a compound of formula II of D2.

1.2.4 The board is of the following view. Comparative example 2, filed with the respondent's experiments D22, details the preparation and crystallisation of the 7-amino amine salt corresponding to the compound of formula II of D2. It is reported that the Z-isomer product was isolated in 59.2% yield. In contrast, the corresponding step according to [procedure 1] in the examples of the patent provided the corresponding amino-protected product of formula (1) of claim 1 in yields ranging from 96.4 (example 2) to 99.3% (example 1). Comparative example 2 of D22 is best compared with procedure 1 of example 3 of the patent (paragraphs [0058] and [0059]). Both procedures involved the formation of the dicyclohexylamine salt, and were performed using the same solvent mixture (water/acetone). Furthermore, acetone (as the antisolvent) is employed in both examples to induce crystallisation. The process of example 3 of the patent however provided the desired amine salt in above 95.7% yield (see the combined yield provided in example 3 for [Procedure 1] and [Procedure 2] (the conversion of the amine salt back to the acid]: the yield for [procedure 1] in isolation was not stated; patent, page 10, line 53).

1.2.5 The appellant argued that the evidence on file was insufficient to attribute the improvement in the overall yield of the Z-isomer to the distinguishing feature of the compound of formula (1) of claim 1 as set out above. In particular, the respective processes differed in several aspects. More specifically, there were differences in the solvents used, the temperature, the reaction period, and whether the mixture was stirred, all of which could have had a significant impact on the yield obtained.

The respondent conceded that there were slight differences between the respective procedures, but argued that these were not sufficient to cast doubt on the validity of the comparison, in particular in view of the large improvement in yield demonstrated.

1.2.6 The board agrees with the respondent, in particular with regard to the comparison of example 3 of the patent and comparative example 2 of D22 as addressed above. These examples concern the preparation of a salt with the same amine as the cation, and employ the same solvent system for the preparation of said salt, as well as for the subsequent crystallisation. They differ in the following aspects:

(a) the E-isomer content of the starting material in comparative example 2 was 0.85%, while the initial E-isomer content in example 3 of the patent was 10.0%.

(b) in comparative example 2, the 7-amino starting material was suspended in the solvent mixture; in example 3 the starting material was dissolved.

(c) in comparative example 2 the temperature of addition of dicyclohexylamine to the suspension is not stated; in example 3, the solution was cooled to not higher than 5°C before addition of dicyclohexylamine.

(d) after addition of dicyclohexylamine:

in comparative example 2 the suspension was stirred until crystals separated out from a transparent solution subsequently formed; the reaction mixture stood at room temperature for 15 minutes, after which it was cooled in an ice bath and thereafter, acetone was added to the mixture. After stirring for two hours, the resulting crystals were filtered;

in example 3, the reaction mixture was stirred for 2 hours and thereafter stirred at 10°C for 30 minutes. Acetone was added to the resulting reaction mixture, and the crystals separating out were filtered off.

The board is of the following view.

Aspect (a) was identified by the appellant, and it was argued that examples with large differences in E- to Z-isomer ratios in the starting material could not be compared with each other. However, the board sees no technical reason why the yields in the respective examples could not be compared on this basis. The yield provided both for example 3 of the patent and for comparative example 2 is that for the Z-isomer, which for the skilled person is simply to be calculated on the basis of the amount of Z-isomer present in the starting material.

Although identifying aspect (b), the appellant did not offer any explanation as to how it could negatively affect the yield in comparative example 2 relative to example 3 of the patent. Independently of whether the starting material was suspended or dissolved, there was no argument from the appellant according to which the desired salt was not formed. Indeed, despite starting with a suspension in comparative example 2, after addition of dicyclohexylamine, "a transparent solution subsequently formed" (D22, page 2, line 19). Thus the resultant salt in both comparative example 2 and example 3 of the patent was in solution before the selective crystallisation took place.

Similarly, the board sees no technical reason why aspect (c) could negatively affect the outcome of comparative example 2. Even if it were assumed that the addition of dicyclohexylamine were carried out at room temperature according to comparative example 2 (since in this regard the example is silent), there is no reason to suspect that the desired salt was not formed as a result of this difference, nor is there any reason to suspect undesirable side reactions which could explain the lower yield obtained in comparative example 2.

Regarding aspect (d), while there are differences in the manner in which the respective selective crystallisation was performed, this is in some respect unsurprising. Indeed, the amine salts being subjected to crystallisation are not identical, but differ at the 7-position as set out above. As such, said compounds would be expected to have different properties in particular in terms of polarity and solubility and as a consequence, crystallise under different conditions. If

however one were to insist on identifying potential consequences on the basis of the differences outlined in aspect (d), it would rather be expected that the yield in example 3 would be lower than that of comparative example 2. Specifically, the steps of cooling in an ice bath and stirring for 2 hours disclosed in comparative example 2 would, if anything, be expected to positively affect the extent of crystal formation. Specifically, at a lower temperature, a substance would be expected to have lower solubility in a given solvent, and thus crystallise to a greater extent than at a higher temperature. Instead however, a lower Z-isomer yield of 59.2% was obtained in comparative example 2.

In consequence, the differences between example 3 of the patent and comparative example 2 of D22 are not sufficient to cast any doubt on the origin of the large improvement in yield obtained, namely from 59.2% yield (comparative example 2) to above 95.7% yield according to example 3 of the patent. The improved yield of the Z-isomer can therefore be attributed to the distinguishing feature outlined above.

1.2.7 The appellant argued that even if an improved Z-isomer yield were recognised on the basis of the comparison between example 3 of the patent and comparative example 2, it was not credible that such an effect would be achieved across the whole claimed scope.

The board disagrees. In the absence of any experimental evidence to the contrary, the appellant's argument has to be regarded merely as an allegation. The board sees no reason to doubt that the effect demonstrated in example 3 of the patent is credible across the entire scope of claim 1.

1.2.8 The effect of the differentiating feature with respect to D2 is therefore that it permits an improvement in overall yield of the desired Z-isomer product (1a) (patent, structure in claim 2), and ultimately the corresponding Z-carboxylic acid (2a) (patent, structure in claim 4).

1.2.9 Therefore, the objective technical problem facing the skilled person is how to modify the disclosure in D2 so as to improve the yield of the Z-isomer of a 3-alkenylcephem compound useful in the preparation of the desired cefditoren pivoxil end product (referred to more generally as cephalosporin end products in D2, page 2, lines 13-15).

1.3 Obviousness

1.3.1 The solution to the above problem is the provision of the compound of formula (1) of claim 1. According to established case law, a new intermediate chemical product (such as the compound of formula (1)) may be held to be patentable on the grounds that its preparation took place in connection with inventive further processing or in the course of an inventive complete processing (e.g. T 22/82, reasons, 7; T 648/88, reasons, 8). Thus, a chemical compound can involve an inventive step irrespective of whether it itself has an unexpected technical effect, or whether its effect is linked to the improvement in a complete processing, as is the case for the improvement in Z-isomer yield directly attributable to the intermediate compound (1) of claim 1, as set out above.

1.3.2 The appellant was of the view that even if the effect of increased Z-isomer yield were to be accepted,

obtaining it was not surprising. The skilled person would have looked to the disclosure in D3 for the solution, and thereby would have arrived at the subject-matter of claim 1 without exercising inventive step. Specifically, starting from the process of D2 and performing a selective crystallisation of compound II (page 4) it would have been obvious to the skilled person that the unprotected amino group in the 7-position was a source of potential side-reactions and responsible for the low yield of Z-isomer obtained. It was consequently an obvious step for the skilled person to choose to protect said amino group. To choose the appropriate protecting group the skilled person would have referred to D3, since the aim thereof was also to obtain the Z-isomer of a 3-alkenylcephem compound in high yield and purity. Moreover, D3 referred to D2 in paragraph [0009]. In the synthetic steps of D3 (paragraph [0006]), the amino group is protected. The preferred amino-protecting groups (D3, paragraph [0020]) include those employed in the compound of formula (1) of claim 1 at issue, namely R^1CO- where R^1 is selected from benzyl or phenoxymethyl. D3 thus provided the skilled person with clear guidance to prepare and selectively crystallise the protected 7-amino compound of formula (1) of claim 1 at issue with a view to solving the problem.

1.3.3 The board disagrees with this view. In particular, the board sees no technical reason why the skilled person would have expected protection of the amino group in the 7-position of compound II of D2 to improve the Z-isomer yield. The board agrees with the arguments of the respondent according to which protecting groups are commonly used to protect functional groups in reactions involving chemical bond formation. However, in the selective crystallisation process disclosed in D2, no

chemical bonds are formed. Rather, the process involves salt formation to form compound II by treatment with an amine and subsequent selective crystallisation. Therefore, the skilled person would not expect the 7-amino group in compound II of D2 to require protection in this manipulation.

1.3.4 D3 is also concerned with the selective preparation of Z-isomers of carboxylic acids similar to those of the present patent (paragraph [0016]). However the aim of D3 is to overcome the drawbacks of the prior art according to which the isolation of the desired Z-isomer requires additional and complicated steps and provides unsatisfactory yield (D3, paragraph [0013]). This aim is achieved in D3 by the provision of specific Wittig reaction conditions which allow improved selectivity towards the desired Z-isomer along with enhanced yield (paragraph [0015]). The Z-isomer selectivity according to D3 is such that no further purification steps such as recrystallisation or chromatography are required to remove the E-isomer (D3, paragraph [0029]).

1.3.5 Thus, D3 teaches the skilled person to achieve the selective formation of the Z-isomer in a specifically optimised Wittig reaction which selectively installs the relevant double bond in the desired Z-configuration, and thereby teaches away from any process involving "additional and complicated steps" such as those disclosed in the prior art, *inter alia* in document D2, cited in paragraph [0009] of D3 and stated to involve recrystallisation and chromatography. Thus, although as noted by the appellant, D3 discloses compounds similar to those of claim 1 at issue comprising protected amines (D3, page 4, structure H; paragraph [0020]), there is no teaching nor incentive

therein for the skilled person to modify the disclosure in D2 by specifically selecting a compound comprising said protecting groups in isolation as a solution to the above-mentioned problem, while ignoring the central teaching of D3.

1.3.6 Furthermore, the appellant submitted that documents D16-D18, filed with the statement of grounds of appeal, served as proof that the use of a phenylacetyl protecting group in the 7-amino position in the preparation of the compounds of interest was common general knowledge (D16, scheme 1, compound 4; D17, table 1; D18, chart 1). In particular, it was argued that D2 could also be combined with D16 or D18 in order to arrive at the subject-matter of claim 1 (letter of 17 March 2020, page 3, fifth paragraph). However, similarly as for D3, the fact that said protecting groups are known in similar systems is irrelevant to the question of whether employing them would have been obvious to the skilled person specifically seeking a solution to the objective technical problem as set out above. There is no indication in any of D16, D17 or D18 that said problem could be solved by providing a compound of formula (1) of claim 1.

Finally, the appellant submitted that the compound of formula (1) of claim 1 was merely a known compound with a new protecting group, and revealed no special effects or properties. The protection afforded to such a product claim was not justified by an increase in the yield of the Z-isomer. To support its position, the appellant cited decisions T 579/00 and T 318/02.

The board disagrees. Firstly, the argument that a compound may not involve an inventive step by virtue of it merely representing a protected analogue of a known

compound is not consistent with the problem-solution approach employed at the EPO to assess inventive step. According to this approach, the question of obviousness may only be addressed once the objective technical problem has been formulated, which in turn must take place after the distinguishing feature/s over the closest prior art, and the technical effect thereof have been identified. Furthermore, it is incorrect to state that compound (1) of claim 1 has no technical effect. As set out above, the "effect" of the compound of formula (1) of claim 1 is linked to the improvement in a process, namely the improvement in Z-isomer yield after crystallisation. The situation in the above decisions cited by the appellant contrasts with the present case in that a technical effect was not acknowledged for the claimed compounds. Specifically, in T 579/00, the claimed compounds differed from the known compounds in the presence of known protecting groups. The objective technical problem was the provision of further glycine derivatives for the preparation of PNA and PNA/DNA hybrids (reasons, 7.2). Since no technical effect had been demonstrated, inventive step was denied (reasons, 7.5.1). Similarly, in T 318/02, the alleged effect of the claimed compounds was not considered successfully achieved (reasons, 2.4.2), and the solution to the objective technical problem, the provision of further compounds useful for solid phase peptide synthesis, was found to lack inventive step (reasons 2.7.4).

1.3.7 In view of the foregoing, the subject-matter of claim 1 therefore involve an inventive step (Article 56 EPC).

1.4 Further independent claims

1.4.1 During oral proceedings, after announcing the conclusion that the subject-matter of claim 1 involved an inventive step, the board provided the preliminary view that since independent process claims 3, 4, 5 and 6 all involved the use of the compound of formula (1) in further processing, they also appeared to involve an inventive step for the same reasons as claim 1. The appellant did not provide any further counter-arguments in this regard.

Independent claim 3 is directed to a process for preparing the compound of formula (1) of claim 1 by reacting an amine compound of the formula (3) with a 3-alkenylcephem compound of the formula (2) (supra). It is well established that a process is patentable if it provides a novel and inventive product. Therefore, since the compound of formula (1) involves an inventive step, the same applies to its process of manufacture according to claim 3.

Similarly, independent claim 4 (supra) concerns the crystallisation of the compound (1) of claim 1 and subsequent reconversion to the carboxylic acid (2a), improved in the content of the Z-isomer. Since this process involves the inventive compound (1) of claim 1, the subject-matter of claim 4 also involves an inventive step.

Independent claim 5 (supra) is directed to the first step of claim 4, namely the selective crystallisation of the compound of formula (1) of claim 1. Hence, the subject-matter of claim 5 involves an inventive step for the same reason as that of claim 4.

Independent claim 6 (supra) is directed to the second step of claim 4, namely the conversion of compound (1a) (which corresponds to compound (1) of claim 1, enriched in the Z-isomer) to the carboxylic acid (2), enriched in the Z-isomer of formula (2a). Since compound (1) of claim 1 involves an inventive step, it follows that the same applies to the further processing of compound (1) (to a subsequent intermediate in the sequence leading to the desired 3-alkenylcephem compounds) according to claim 6. Hence, the subject-matter of claim 6 involves an inventive step.

1.5 It follows from the foregoing that the ground for opposition under Article 100(a) in combination with Article 56 EPC does not prejudice the maintenance of the patent as granted.

2. Sufficiency of disclosure - Article 100(b) EPC

2.1 According to the appellant, the invention as defined in the claims as granted was not sufficiently disclosed in the contested patent. With reference to documents D7-D15 and D19-D21 it argued *inter alia* that insufficiency of disclosure arose since

- the process claims (claims 4, 5, 13, 14, 16-18) and the patent in suit offered the skilled person a huge range of possible solvent combinations, examples of which were provided only for water/ acetone as the first solvent and acetone (examples of the patent), n-hexane or diisopropyl ether (examples filed with D22) as the second solvent;

- the definition of amine (3) in the claims (claims 1-6, 8-11, 13-21) allowed a huge variation in possible substituents and coupling patterns for R^2,

R^3 and R^4; more bulky steric residues falling within these definitions did not allow the invention to work;

- despite the specification in claims 19 and 20 that a mineral acid should be used in the adjustment of the pH recited in the claims (claims 4, 6, 19-21), not all mineral acids were suitable to perform the method claimed, and only hydrochloric acid was exemplified;

- certain solvent combinations were not stable under the reaction conditions (claim 4, 6, 19-21);

- certain organic solvents underwent undesired side reactions with the carboxylic acid group of the compound (2) (claims 4, 6, 19-21).

2.2 The board finds the appellant's arguments unconvincing for the following reasons.

2.3 The question that arises with regard to sufficiency of disclosure is whether the contested patent contains sufficient guidance to allow the skilled person, using his common general knowledge at the priority date of the patent, to select those process embodiments that lead to the desired product (T 435/91, reasons, 2.2.1; T 1063/06, reasons, 5; T 544/12, reasons, 4.2).

2.4 In this respect a reasonable amount of trial and error may be acceptable. This presupposes, however, that sufficient information is available that leads the skilled person directly towards success through the evaluation of initial failures (T 480/11, reasons, 3.4; T 544/12, reasons, 4.8).

2.5 Accordingly, in the present case, the question is not whether certain specific combinations of solvent, amine, or mineral acid recited in the claims will fail to provide the desired product. Rather it is whether the skilled person, using common general knowledge and the information provided in the patent, is able to prepare the compound of claim 1, and carry out the processes of claims 3, 4, 5 and 6 without undue burden. With respect to solvents for example, the appellant himself refers to the principle of antisolvent crystallisation as set out in D7 (page 383, final paragraph). In view of this general knowledge, there is no reason to suspect that the skilled person would have been unable to select an appropriate solvent combination allowing the desired crystallisation to take place.

This view is also not altered by the disclosures in documents D19, D20 and D21, filed by the appellant as evidence of the common general knowledge concerning the stability of esters, amides and nitriles under acidic conditions. Specifically, the appellant argued that those documents were evidence that not all solvents were chemically stable at a pH of 0.5 to 4 (recited in independent claims 4 and 6), and would therefore degrade, leading to both contamination of the desired crystalline product, and side reactions during the claimed processes. Even if these arguments were to be accepted, there is no reason to doubt that the skilled person, using common general knowledge and the guidance provided in the description, would be capable of preparing the compound of claim 1, and carrying out the processes of claims 3, 4, 5 and 6 without undue burden, if necessary by avoiding specific solvents or solvent combinations.

2.6 In view of the examples in the patent as well as the guidelines provided in the description, the board is convinced that the skilled person, without undue burden, is capable of carrying out the invention as defined in the claims as granted.

2.7 Finally, according to established case law of the Boards of Appeal, a successful objection of lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts, that the invention cannot be carried out by the skilled person (e.g. T 19/90, OJ 1990, 476, reasons, 3.3). In the present case, the appellant has not filed any evidence in support of its case and relied in its arguments on mere allegation.

2.8 The view outlined above was expressed by the board in the communication pursuant to Article 15(1) RPBA sent in preparation for oral proceedings. This view was not contested by the appellant in its reply to the board's communication (VII supra). Also at the oral proceedings, the appellant merely referred to its written submissions, and thereby chose not to submit counter-arguments against the position expressed by the board in said communication.

2.9 In consequence, the ground for opposition under Article 100(b) EPC does not prejudice the maintenance of the patent as granted.

3. Amendments - Article 100(c) EPC

3.1 The appellant submitted that claims 9, 20 and 21 comprised subject-matter which was not derivable from the application as filed. In the application as filed said claims were worded as independent claims, but were

amended during examination with the addition of back references to claims 3 (claim 9) and claim 6 (claims 20 and 21). The result of the added back references in claim 9 was that the step of reacting the amine (3) with the compound of formula (2), being repeated in claim 9 although already being performed according to claim 3, was consequently performed twice. Similarly, claims 20 and 21 contained a repetition of the step of adjusting the pH of a solution or suspension of the compound of formula (1) to obtain a compound of the formula (2), which was already performed according to claim 6. Since the repetition of said steps according to claims 9, 20 and 21 was not disclosed in the application as filed, subject-matter had been added.

3.2 In this regard the board agrees with the position of the respondent. When considering the language of a claim, the skilled person should rule out interpretations which are illogical or do not make technical sense (see e.g. T 0190/99, reasons, 2.4; T 1023/02, reasons, 7). The patent must be understood by a mind willing to understand, not a mind desirous of misunderstanding (*ibidem*). In the present case, it appears clear from the claims as filed as well as the description as a whole that originally filed claims 9, 20 and 21, despite lacking a reference to the independent claims upon which they now depend, in fact concerned the same subject-matter and the same steps. They cannot therefore be understood to include embodiments whereby the step in question is merely repeated. Thus the addition of a back reference in claims 9, 20 and 21 to independent claims 3 and 6 could at most amount to a lack of clarity but not to an addition of subject-matter within the meaning of Article 123(2) EPC.

Similarly to that set out above with regard to sufficiency of disclosure, the view outlined above was expressed by the board in the communication pursuant to Article 15(1) RPBA sent in preparation for oral proceedings. This view was not contested by the appellant in its reply to the board's communication (VII supra). Also at the oral proceedings, the appellant merely referred to its written submissions, and thereby chose not to submit counter-arguments against the position expressed by the board in said communication.

3.3 Consequently, the ground for opposition under Article 100(c) EPC does not prejudice the maintenance of the patent as granted.

4. Conclusion

None of the grounds for opposition prejudice the maintenance of the patent as granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. Maremonti

Decision electronically authenticated