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D E C I S I O N
of 9 March 2000

Case Number: T 1081/97 - 3.3.1

Application Number: 89302773.0

Publication Number: 0334590

IPC: C07D 501/20

Language of the proceedings: EN

Title of invention:
3-(Substituted)-1-carba(dethia)-3-cephems and cephalosporins and a process for production therefor

Applicant:
ELI LILLY AND COMPANY

Opponent:
-

Headword:
Tin transfer reaction/ELI LILLY

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes) - problem effectively solved by whole scope of claimed process - non obvious solution"

Decisions cited:
T 0939/92

Catchword:
-

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Case Number: T 1081/97 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 9 March 2000

Appellant: ELI LILLY AND COMPANY
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Indianapolis
Indiana 46285 (US)

Representative: Tapping, Kenneth George
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 3 June 1997 refusing European patent application No. 89 302 773.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
J. P. B. Seitz

Summary of Facts and Submissions

I. The appeal lies from the Examining Division's decision, dispatched on 3 June 1997, refusing European patent application No. 89 302 773.0, published as EP-A-0 334 590, due to lack of inventive step.

Although in the Examining Division's view the claimed process could not be deduced from the teachings of documents

(A) Palladium Reagents in Organic Synthesis, R. Heck, 1985, Academic Press, pages 2, 3, 248, 249, 293 and 294;

(B) Journal of the American Chemical Society, 106(16), 1984, 4630-4632;

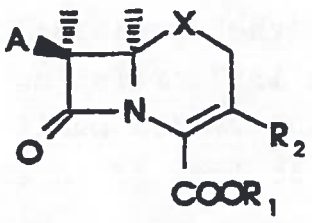
(C) Journal of the American Chemical Society, 108(11), 1986, 3033-3040; and

(D) EP-A-0 112 481,

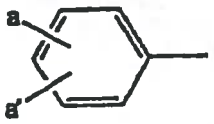
it could not establish the presence of an inventive step, since it was not shown that all claimed processes lead to the desired products.

II. The Appellant filed with telefax dated 9 October 1997 a set of claims as a main request and 5 sets of claims according to auxiliary requests 1 to 5. With telefax dated 1 March 2000 he filed a corrected set of claims headed "Main Request". The only independent claim according to the "Main Request" read:

"1. A process for preparing a compound of Formula

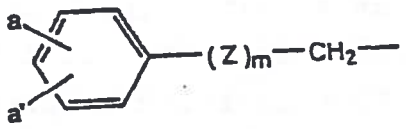


wherein A is a protected amino group or an acylamino group of the formula R(CO)NH-, and R is hydrogen; C_1-C_6 alkyl, C_1-C_6 alkyl substituted by cyano, carboxy, halogen, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, or trifluoromethylthio; a phenyl or substituted phenyl group represented by the formula



wherein a and a' independently are hydrogen, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkanoyloxy, C_1-C_4 alkyl, C_1-C_4 alkylthio, amino, mono- or di(C_1-C_4 alkyl)amino, C_1-C_4 alkanoylamino, C_1-C_4 alkylsulfonylamino, carboxy, carbamoyl, hydroxymethyl, aminomethyl, or carboxymethyl;

a group represented by the formula



wherein a and a' have the same meanings as defined above, Z is O or S, and m is 0 or 1;

a heteroarylmethyl group represented by the formula

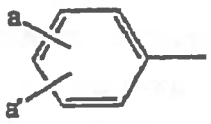
R^1-CH_2-

wherein R^1 is thienyl, furyl, benzothienyl, benzofuryl, indolyl, triazoly, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, and such heteroaryl groups substituted by amino, hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylsulfonylamino;

a substituted methyl group represented by the formula

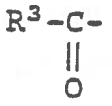
R^2-CHQ-

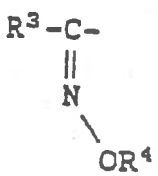
wherein R^2 is cyclohex-1,4-dienyl, or a phenyl group or substituted phenyl group represented by the formula



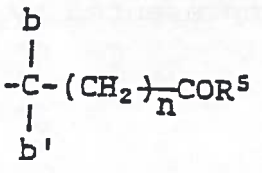
wherein a and a' have the above defined meanings, or R^2 is R^1 as defined above, and Q is hydroxy, C_1-C_4 alkanoyloxy, carboxy, sulfo, or amino;

or R is a keto group or an oximino-substituted group represented by the formulae



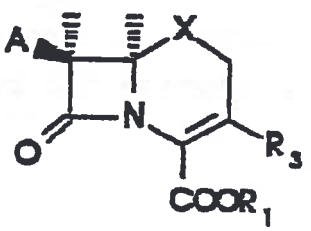


wherein R^3 is R^1 or R^2 as defined above and R^4 is hydrogen, C_1-C_4 alkyl, or a carboxy-substituted alkyl or cycloalkyl group represented by the formula



wherein n is 0, 1, 2 or 3; and wherein b and b' independently are hydrogen, or C_1-C_3 alkyl, and b and b' when taken together with the carbon to which they are bonded form a 3- to 6-membered carbocyclic ring, and R^5 is hydroxy, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

R_1 is a carboxy-protecting group or a biologically-labile ester selected from the lower alkoxymethyl groups, the α(C_1 to C_4)-alkoxyethyl groups, the 2-oxo-1,3-dioxolen-4-ylmethyl groups, the C_1 to C_3 alkylthiomethyl groups, the acyloxymethyl groups, the ethoxycarbonyl-1-methyl group, the α-acyloxy-α-substituted methyl groups, the 3-phthalidyl or 5,6-dimethylphthalidyl groups, the 1-(C_1-C_4 alkyloxycarbonyloxy)eth-1-yl groups, and the 1-(C_1 to C_4 alkylaminocarbonyloxy)eth-1-yl groups; X is sulfur or $-CH_2-$; and R_2 is methyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_1-C_6 alkyl substituted by cyano, carboxy, halogen, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio or trifluoromethylthio; C_2-C_6 alkenyl substituted by one or more halogen, hydroxy, protected hydroxy, nitro or trihalomethyl; C_2-C_6 alkynyl substituted by one or more halogen, hydroxy, protected hydroxy, nitro or trihalomethyl; phenyl; substituted phenyl; C_1-C_6 alkoxymethyl; phenyl-C_1-C_6 alkyloxymethyl; or tri (C_1-C_6)alkylsilyloxymethyl; which comprises reacting a compound or formula



wherein A, X and R_1 are as defined above, and R_3 is trifluoromethylsulfonyloxy, methanesulfonyloxy, toluenesulfonyloxy, chloro, bromo or iodo; in an inert solvent in the presence of palladium(0) and, when R_3 is trifluoromethanesulfonyloxy, methanesulfonyloxy or p-toluenesulfonyloxy, in the presence of an alkali metal halide, with a tin transfer reagent of the formula tri(C_1-C_6)alkyl-Sn-R_2 or Sn(R_2)$_4$, wherein R_2 has the same meanings as defined above."

III. The Appellant argued that, by the definitions of the process step and of the final products only those processes were embraced within the scope of Claim 1 which effectively lead to the desired final compounds.

IV. The Appellant requested that a patent be granted on the basis of the main request, filed with telefax dated 1 March 2000, or on the basis of any of the first to fifth auxiliary requests, filed with telefax dated 9 October 1997.

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

2.1 Article 123(2) EPC

Claim 1 is supported by Claims 1, 2 and 3 as filed for the Contracting States other than Greece or Spain and by the disclosures of

(i) the "biologically-labile esters" on page 14, line 24 to page 15, line 11 of the application as filed;

(ii) the substituents for the C_1 to C_6 substituted alkyl radical, the C_2 to C_6 substituted alkenyl and the C_2 to C_6 substituted alkynyl as R_2 radical listed on page 9, line 20 to page 10, line 7, and page 17, lines 1 to 4 and 20 to 23, of the application as filed.

Present Claims 2 to 10 are supported by Claims 2 and 4 to 11 respectively as filed for the Contracting States other than Greece or Spain.

Consequently, Claims 1 to 10 meet the requirement of Article 123(2) EPC.

2.2 Novelty

After examination of the cited prior art documents, the Board has reached the conclusion that the process as defined in Claims 1 to 10 is novel, since a method for preparing the final compounds according to Claim 1 with a tin transfer reagent in the presence of palladium(0) was not disclosed in any of the cited prior art documents.

Since this was not disputed, it is not necessary to give detailed reasons for this finding.

2.3 Inventive step

2.3.1 The closest prior art must be directed to the same purpose as the invention. Since the patent in suit relates to a process for preparing *inter alia* cephalosporins having a hydrocarbon radical in the 3-position and from the cited prior art only document (D)

is concerned with such process, this document serves, as the closest prior art, as a suitable starting point for evaluating the inventive merit of the invention.

Document (D) discloses on page 9, first and second full paragraph including the reaction scheme, a process for preparing a 3-vinylcarbacephalosporin of formula (VII) wherein the vinyl group is obtained by reacting the corresponding 3-formyl compound with a suitable triphenylphosphorane.

2.3.2 As it is said in the application in suit that the final compounds according to Claim 1 provide such synthetic challenges that the development of new processes is of considerable importance (see page 2, lines 9 to 11), starting from the disclosure of document (D) the problem underlying the invention must be seen in providing a further process of preparing 1-carba(dethia)-3-cephems and cephalosporins having in the 3-position a hydrocarbon radical as defined in Claim 1.

2.3.3 The application in suit claims to solve this problem by the process defined in Claim 1 (see point II above).

2.3.4 From examples 1 to 9, 12 and 13 it follows that the 3-hydrocarbon substituted 1-carba(dethia)-3-cephems and cephalosporins described therein may be effectively synthesised according to the claimed process. This has not been challenged by the Examining Division.

2.3.5 Nevertheless, in the Examining Division's view not all claimed processes would lead to the final compounds obtainable according to Claim 1, since it was known from document (A), page 2, lines 9 to 11, that Pd(0) derivatives are reactive with halides, alkyl halides, aryl halides and acids and since protecting groups may embrace any chemical functional group, such as halides.

Therefore, the **protected** amino group in radical A, the carboxy-**protecting** group in R_1 or the **protected** hydroxy group in the C_2-C_6 alkenyl or C_2-C_6 alkynyl radical in R_2 of the starting compounds according to Claim 1 might lead to side-reactions.

Furthermore, the Examining Division objected that the term "protected" embraces an unlimited number of possibilities and that it was not shown in a representative manner that all possibilities would represent a solution to the given problem, contrary to the priciple laid down in T 939/92 (OJ EPO 1996, 309).

However, it is well-known to the person skilled in the art that a protecting group is a derivative of a functional group, which is unreactive to the medium used to carry out a chemical reaction on an other functional group present in the molecule and which may subsequently be converted to the original functional group (see, for example, Introduction to Organic Chemistry, second edition, by Andrew Streitwieser, Jr. and Clayton H. Heathcock, Macmillan Publishing Co., Inc., 1981, paragraph 16.4 on pages 475 and 476). Since, consequently, the term "protecting groups" as such excludes the presence therein of any functional group which could react with the medium against which it is to be protected, the Board comes to the conclusion that in Claim 1 all three terms "protected amino", "protected hydroxy" and "protecting amino" exclude the possibility of containing a functional group which might lead to side reactions in the reactive medium according to Claim 1.

Since the said terms "protected amino", "protected hydroxy" and "protecting amino" are thus restricted by the required specific function of protecting the amino- and/or hydroxy function against the reaction medium

used in the process according to Claim 1, these terms cannot be regarded as embracing an unlimited number of possibilities as was the case in decision T 939/96, which concerned a completely different situation not comparable to the present one. In that case the Board held that a technical effect (herbicidal activity mentioned in the description) which justifies the selection of a huge group of compounds claimed as such must be one which can be fairly assumed to be produced by substantially all the selected compounds (see point 2.5.4).

2.3.6 Furthermore, the Examining Division argued that it was known from document (C), concerning palladium-catalysed coupling of vinyl triflates with organostannates, that the nature of the tin derivative can have a noticeable influence on the course of the reaction and that, therefore, the reaction with some tin derivatives would not lead to the desired compounds. Moreover, the Examining Division was of the opinion that the claimed scope for R_2 is not justified since it is not sure from the cited prior art that all substituents described in Claim 1, in particular phenyl, can be transferred to a double bond with the claimed process.

In fact, in the passage of document (C) referred to by the Examining Division, namely the first two paragraphs under "Reaction Scope" in the right-hand column on page 3035, it is disclosed that the coupling of two hindered partners tends to slow the reaction and that neither benzyltributyltin nor benzyltrimethyltin react under the conditions described therein.

However, it is also said in that paragraph that the palladium-catalysed coupling reaction with organostannates in the presence of lithium chloride is **a very general reaction** and that vinyl, alkyl, allyl

and acetylenic groups all transfer in good yields. With the exception of benzyltributyltin and benzyltrimethyltin, of which it is only said that their lack of reactivity is not understood, it does not mention any other stannate with which a radical cannot be transferred to a double bond. Since benzyl is not embraced within the scope of R_2 according to Claim 1, the disclosure of this paragraph does not dissuade a skilled person to transfer any of the substituents R_2 as defined in Claim 1 to a double bond with a palladium-catalysed coupling reaction by using the corresponding organostannate.

Therefore, in the absence of any indication that any of the R_2 substituents mentioned in the application in suit may not be introduced in a molecule by a Pd(0)-catalysed coupling reaction with an organostannate according to Claim 1, the Board has no ground to accept that with some tin derivatives the 3-hydrocarbon substituted 1-carba(dethia)-3-cephems and cephalosporins could not be synthesised.

2.3.7 The Board therefore accepts that a credible case has been put forward that the problem underlying the invention, as defined in point 2.3.2, is effectively solved by the claimed method.

2.3.8 It remains to be decided, whether, in the light of the teachings of the cited documents, a skilled person seeking to solve the above-mentioned problem would have arrived at the claimed process in an obvious way.

2.3.9 Document (D), which discloses only one process for preparing a 3-vinylcarbacephalosporin by reacting the corresponding 3-formyl compound with a suitable triphenylphosphorane, is completely silent about any other process of preparing 3-vinylcarbacephalosporins.

corresponding 3-formyl compound with a suitable triphenylphosphorane, is completely silent about any other process of preparing 3-vinylcarbacephalosporins. Therefore, the claimed process was not obviously derivable from the disclosure of document (D), taken alone.

Moreover, the Board concurs with the Examining Division that in view of the teaching of document (C) (see point 2.3.6 above) and document (B), which does not provide any information going beyond that of document (C), a skilled person would not have found any reason in the cited prior art to prepare 3-vinylcephalosporins by another process as the one described in document (D).

This was not contested by the Examining Division (see point I above).

2.3.10 Therefore, the Board comes to the conclusion that Claim 1 is not obvious in the light of the teachings of the cited prior art.

Claims 2 to 10, which represent preferred embodiments of Claim 1, derive their patentability from the same inventive concept.

3. *Auxiliary requests*

In the light of the above findings, there is no need to consider the auxiliary requests.

4. Having regard to the fact that the function of the Boards of Appeal is primarily to give a judicial decision upon the correctness of the earlier decision taken by the first instance and having regard to the fact that the description has not yet been adapted to the set of claims according to the main request, the

Board makes use of its power under Article 111(1) EPC and remits the case to the first instance for adapting the description to Claims 1 to 10 according to the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of Claims 1 to 10 according to the main request filed with telefax dated 1 March 2000 and a description yet to be adapted.

The Registrar: The Chairman:

D. Spigarelli A. Nuss