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Datasheet for the decision of 11 December 2012

Case Number: T 0979/10 - 3.3.01

Application Number: 04026903.7

Publication Number: 1533305

IPC: C07D 257/04

Language of the proceedings: EN

Title of invention:
A process for the preparation of valsartan and intermediates thereof

Patentee:
Dipharma Francis S.r.l.

Opponent:
Novartis AG

Headword:
Oxazolidinone ring opening/DIPHARMA

Relevant legal provisions:
EPC Art. 83, 56

Keyword:
"Main request: sufficiency of disclosure (yes); inventive step (yes) - non obvious alternative"

Decisions cited:
T 0516/99, T 0422/99

Catchword:
-

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Case Number: T 0979/10 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 11 December 2012

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 13 April 2010 concerning maintenance of European patent No. 1533305 in amended form.

Composition of the Board:

Chairman: P. Ranguis
Members: G. Seufert
C.-P. Brandt

Summary of Facts and Submissions

I. The Appellant (Opponent) lodged an appeal against the interlocutory decision of the Opposition Division on the amended form in which European patent No. 1 533 305 could be maintained.

II. In this decision the following numbering will be used to refer to the documents:

(1) US 5,399,578

(9) R. M. Freidinger et al., J. Org. Chem., vol. 48, 1983, pages 77-81

(13) Experimental reproduction of patent examples for valsartan API: N-Trityl valsartan benzyl ester by Ulrich Onken dated 25 January 2010

(14) Th. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons New York, 1981, pages vii, ix-xiii, 184-186, 232, 233, 249, 250, 293, 294, 323, 324, 327, 328

(16) D. Seebach and A. Fadel, Helvetia Chimica Acta, vol. 68, 1985, pages 1243-1250

(18) Th. W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, 1991, pages 266-267

(19) R. M. Williams, Synthesis of Optically Active α-Amino Acids, 1989, Pergamon Press Oxford, pages 62, 69, 77-83, 131

(20) J. N. Kinkel, Helvetica Chimica Acta, vol. 74, 1991, pages 1622-1635

(22) Reaction scheme: Comparison of Reactions between document (1) and the patent in suit

(24) Judgement of the Norwegian Appeal Court delivered on 23 October 2012 and its English translation (24T) (hereafter the "Norwegian decision")

(25) Expert Opinion Actavis Valsartan Process by Prof. A. G. M. Barrett including exhibits A-W

(26) Report from court-appointed experts Larsen and Svendsen dated 10 March 2010, translation from Norwegian

(27) Interim Judgement of the Helsinki District court dated 3 April 2012 and its English translation (27T) (hereafter the "Finnish decision").

III. Opposition was filed requesting revocation of the patent in suit in its entirety on the grounds of lack of inventive step, insufficiency of disclosure and extension beyond the content of the application as originally filed (Articles 100(a), (b) and (c) EPC).

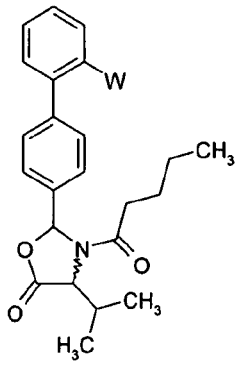
IV. The decision of the Opposition Division was based on the main request, initially filed as first auxiliary request with letter of 25 January 2010.

The Opposition Division held that

- the provisions of Articles 123(2) and (3) EPC were met,
- the invention was sufficiently disclosed,
- the subject-matter involved an inventive step, since no clear teaching could be derived from the prior art that would have led the skilled person to modify the processes according to document (1) to arrive at the claimed subject-matter.

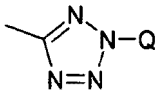
V. Independent claims 1, 11 and 12 of the main request underlying the contested decision read as follows:

"1. A process for the preparation of valsartan, or a pharmaceutically acceptable salt thereof, which comprises opening the oxazolidinone ring in a compound having formula (II),



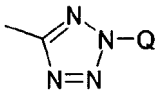
(II)

wherein W is a



group in which Q is a protective group; or W is a CN group, and

a) when W is a

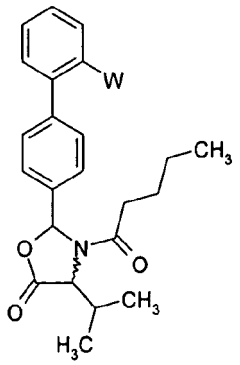


group, removing the protecting group Q; or

b) when W is a -CN group, converting it to a 5-tetrazolyl group;

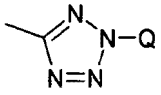
and, if desired, transforming the resulting valsartan into a pharmaceutically acceptable salt."

"11. A compound having formula (II),



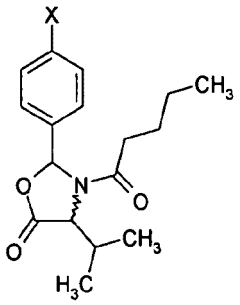
(II)

wherein W is a



group in which Q is a protecting group as defined in claim 3; or W is a -CN group."

"12. A compound of formula (III)



(III)

wherein X is a leaving group selected from a halogen atom or a hydroxy group activated through esterification; a $-B(R_1R_2)$ group wherein R_1 and R_2, which can be the same or different, are halogen, hydroxy or C_1-C_4 alkoxy; a lithium or copper atom or a halogenated metal."

VI. In its statement of grounds of appeal the Appellant contested sufficiency of disclosure and inventive step. In support of its arguments, further documents, amongst

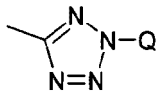
them additional pages of documents (14) and (19), were submitted.

VII. With letter of 10 January 2011 the Respondent (Patent Proprietor) defended the maintenance of the patent in suit on the basis of the main request underlying the decision under appeal, and filed first and second auxiliary requests. In addition, documents (25) and (26) were submitted in support of its arguments concerning inventive step.

VIII. With letter of 9 November 2012 the Appellant submitted document (24) and its translation into English (24T). With regard to the Respondent's first and second auxiliary requests, additional objections under Articles 123(2) and 54 EPC were raised.

IX. In reply to the Appellant's newly raised objections, the Respondent with letter of 4 December 2012 filed revised first and second auxiliary requests and submitted document (27) and its translation into English (27T).

The first auxiliary request differs from the main request in that the substituent W in formula (II) in independent claims 1 and 10 (corresponding to independent claim 11 of the main request) is limited to the following group:



In independent claim 11 the feature "or an isomer thereof" was deleted.

The second auxiliary request differs from the first auxiliary request in that independent claim 1 includes two specific reaction sequences for the preparation of compound (II) and, consequently, for valsartan.

X. The arguments of the Appellant, to the extent that they are relevant for the present decision, can be summarised as follows:

- Admissibility of documents

Document (13) was relevant with regard to the issue of the alleged improvements in yield and purity and should be admitted into the appeal proceedings. The Norwegian decision was provided in support of the Appellant's arguments and for the Board's information. It had been filed as soon as possible and dealt with issues which were also relevant in the present case. It should therefore be admitted into the proceedings. On the other hand, document (27/27T) filed by the Respondent could have been filed earlier. The Appellant had not had an adequate opportunity to comment. It would also have been necessary to provide the extensive documentation referred to therein. Accordingly, it should not be admitted.

- Sufficiency of disclosure

The claimed subject-matter was much broader than that enabled, for basically two reasons: the undefined stereochemistry in compounds (II), (III) and (VI) and the unspecific ring opening. Firstly, although claimed, the patent in suit did not contain any information on

how to realise a process in which the (R)-form of compound (II) was to be transformed into the (S)-form of valsartan. Secondly, the claimed process covered ring openings at five different sites, but only one particular ring opening was disclosed in the patent. Other ring openings would not yield valsartan or the valsartan basic structure. The patent in suit failed to provide adequate guidance as to how the skilled person could obtain valsartan from compounds which were the result of these other ring openings.

- Inventive step

Document (1) was the closest state of the art. In the light of this document, and in view of the fact that no comparative data was present which could demonstrate any specific technical effects or advantages as alleged in paragraph [0005] of the patent, the problem to be solved was the provision of an alternative method for the preparation of valsartan. The alleged reduction in the number of steps for the preparation of compound (II) as well as the alleged reduction in waste material, was equally without merit, since claim 1 was not limited to a particular way of preparing compound (II) and Prof. Barrett's opinion concerning superior atom economy was based on a specific commercial process involving a reaction sequence which was not disclosed in the patent.

The claimed subject-matter was not inventive in view of document (1), in particular example 54, and the skilled person's general knowledge as reflected in documents (18) or (19). The skilled person seeking to provide an alternative process for valsartan would have

looked for an alternative protected intermediate of the benzyl ester of example 54 and to this end would have consulted standard literature relating to protective groups, like document (18). There, oxazolidinones were disclosed as suitable protective groups. Their preparation involved the formation of a substituted imine followed by cyclisation with an acyl chloride. Applying the teaching of document (18) to the substituted imine intermediates mentioned in column 21 of document (1) would have led the skilled person directly to the oxazolidinone of formula (II). Document (1) also taught that hydrogenolysis was a suitable method to set valsartan free from its protected precursor. Due to the structural similarity with the benzyl ester of example 54 of document (1), it would have been obvious to the skilled person that hydrogenolysis was also a proper way to open the ring in such a way as to yield valsartan. This was also confirmed by document (20).

The claimed subject-matter was also not inventive in view of document (19), which described the same concept as document (18). In addition, it explicitly taught that hydrogenation as disclosed in example 54 of document (1) was a suitable method for ring opening at a position which would be required for valsartan. Moreover, document (19) referred to document (9), disclosing ring opening of oxazolidinones via ionic hydrogenolysis. The method in document (9) was generally applicable and led to N-substituted amino acids, similar to valsartan, which could be considered as N-substituted valine.

Finally, the claimed subject matter was not inventive in view of document (1) as it was merely based on an exchange in the sequence of reaction steps. Document (1) taught the reduction of an imine followed by an acylation step. According to the patent in suit an imine was first acylated followed by a reduction step. The motive to reverse the steps was provided by the well-known technique of using oxazolidinones as synthesis intermediates in the preparation of substituted amino acids reflected in document (19).

The oxazolidinone (II) of claim 11 being the starting material in the obvious process of claim 1 was likewise obvious, as well as the oxazolidinone (III) of claim 12. The latter was the precursor of the obvious compound (II) into which it was transformed according to standard procedures.

XI. The arguments of the Respondent, to the extent that they are relevant for the decision, can be summarised as follows:

- Admissibility of documents

Document (13) was not relevant. Its comparison was flawed, as it did not contain a proper reproduction of the prior-art example. It had been rightly rejected by the Opposition Division and should not be admitted into the appeal proceedings. The Norwegian and Finnish decisions merely provided background information and were not binding on the Board. The Finnish decision, which came to a different conclusion than the Norwegian decision, had been filed mainly in response to the Appellant's filing of the Norwegian decision.

- Sufficiency of disclosure

A simple comparison between the structure of formula (II) and the structure of valsartan showed that the Appellant's interpretation with respect to the various ring openings allegedly encompassed by claim 1 was neither reasonable nor technically sensible. The skilled person immediately understood which bond had to be cleaved in order to obtain valsartan and would not consider any other ring opening reactions. The Appellant's second assertion that the claim covered the reaction of the (R)-form of compound (II) to the (S)-configuration of valsartan was equally flawed and again ignored a reasonable and technical sensible interpretation of claim 1 by the skilled person.

- Inventive step

Document (1) was considered to represent the closest prior art. In the light of this document the problem to be solved was the provision of an economically advantageous process for the manufacturing of valsartan. The problem was solved by the claimed process, which allowed the use of a final intermediate that was easier to synthesize than the final intermediate in document (1) and which also produced less waste material.

The claimed subject-matter was not obvious in view of the prior art. The combination of document (1) with documents (18) or (19) was based on hindsight and misinterpretation of the skilled person's common general knowledge. Document (1) described different processes

for the preparation of valsartan and related compounds. The final hydrogenation step in example 54 was employed only in connection with the cleavage of the protective benzyl group. This did not justify the conclusion that hydrogenolysis by hydrogenation was a suitable and well-known final reaction step in the preparation of valsartan. Nor did it provide the skilled person with an incentive to look for hydrogenation reactions which had no link whatsoever with the removal of the particular benzyl protective group. Furthermore, starting from example 54 the skilled person looking for an alternative to the benzyl ester of example 54 had no motive for selecting oxazolidinones. The final intermediate in example 54 was a tertiary amine derivative and for the preparation of oxazolidinone according to document (18) a primary amine was required. Nor did this document disclose ring opening by hydrogenation. It was also clear from document (18) that the oxazolidinone served as a mere temporary protective group to be eliminated once protection was no longer required. Such a removal of the protective group was not done in the present invention. Document (19) was concerned with α-alkylation of amino acids, something that was not done and not required in the patent in suit. Moreover, document (19) failed to disclose hydrogenolysis for splitting one bond in the oxazolidinone ring to provide an intermediate, but only mentioned hydrogenolysis to obtain the initial free amino acid and carboxyl group. This was completely different from the claimed reaction. The statement on page 79 of document (19) concerning hydrogenolysis was mere speculation and presented no reproducible teaching. Document (9) was found only by considering document (19), which due to its different purpose the skilled person would not have done in the first place.

Secondly, it was concerned with differently protected compounds and the transferability of its results to the presently claimed oxazolidinone was speculative. The only document that disclosed ring opening via hydrogenation as in example 54 of document (1) was document (20), which was a very specific paper. It did not form part of the skilled person's general knowledge and could have been found only with hindsight.

Concerning the reversal of steps, the reaction sequence allegedly describing the disclosure in document (1) could not be found in that document. Furthermore, starting from a compound with an unprotected carboxylic acid group completely ignored the starting point for the assessment of inventive step, namely the hydrogenation in example 54, which allegedly motivated the skilled person to look for an alternative synthesis involving hydrogenation. Hydrogenation was necessary only to remove the protecting group. Without the presence of a protective group, hydrogenation was not necessary. A combination of example 54 with the alleged reaction sequence was thus not even possible.

As claim 1 was inventive, so were the compounds of claims 11 and 12.

XII. The Appellant requested that

- the decision under appeal be set aside and that the patent be revoked in its entirety,
- document (13) be admitted into the proceedings
- the first and second auxiliary requests, filed with letter of 4 December 2012, and the Finnish decision not be admitted into the proceedings

XIII. The Respondent requested that

- the appeal be dismissed or, as an auxiliary measure, that the patent be maintained on the basis of the first or second auxiliary requests filed with letter of 4 December 2012,
- the Norwegian decision and document (13) not be admitted into the proceedings.

XIV. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible

2. Admission of the documents (24/24T), (27/27T) and (13)

2.1 The Norwegian decision (court of appeal; documents (24/24T)) was submitted by the Appellant in response to the Respondent's submission of document (25), namely the expert opinion by Prof. Barrett prepared for litigation in Norway relating to the Norwegian counter-part of document (1), and document (26), a report from (district) court-appointed experts. The decision was filed as soon as possible after its delivery in support of the Appellant's arguments with respect to obviousness of the invention. Hence, the Board saw no reason not to admit documents (24/24T).

2.2 The Finnish decision (documents (27/27T)) was filed by the Respondent in response to the Appellant's filing of the Norwegian decision, in particular to highlight that the Finnish court had come to a different conclusion

with respect to obviousness. As the Board had decided to admit the Appellant's document (24/24T), it was appropriate and in accordance with proper procedure also to admit documents (27/27T).

2.3 The Opposition Division's decision not to admit document (13) into the proceedings, because it was not considered to be of *prima facie* relevance, was challenged by the Appellant. After a brief discussion at the beginning of the oral proceedings, the Appellant declared that it did not insist on the admission of document (13), if yield and purity were not decisive issues in the assessment of inventive step. The Board decided to postpone its decision on the admissibility of document (13) and to come back to this issue, if necessary, in the discussion of inventive step.

Since the question of purity or yield was in fact not relevant for the outcome of the present decision (see point 5 below), there was no need to decide on whether or not the Board should overrule the Opposition Division's decision and admit document (13) into the appeal proceedings.

Main request

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

3.1 The Opposition Division decided that the amendments in the main request were supported by claims 1-9, 11 and 12 and page 4, lines 19-27. The provisions of Article 123(2) and (3) EPC were considered to be met. This was not disputed by the Appellant and the Board

sees no reason to deviate from the findings of the Opposition Division.

4. Sufficiency of disclosure

4.1 Claim 1 of the main request refers to a process for the preparation of valsartan, or a pharmaceutically acceptable salt thereof, which comprises ring opening of the oxazolidinone compound of formula (II) and

a) if the variable W is a protected tetrazolyl, removing the protective group or

b) if W is a cyano group, converting it into a tetrazolyl group and,

if desired, transforming the **resulting** valsartan into a pharmaceutically acceptable salt (emphasis added by the Board).

4.2 The Appellant based its objection of insufficient disclosure on two reasons:

4.2.1 Firstly, the Appellant submitted that claim 1 was not limited to a specific ring opening of the oxazolidinone, but rather covered any conceivable ring opening. In view of the open language of the claim ("comprises") there was also no reason to assume that the ring opening should yield the basic structure of valsartan or valsartan itself. The ring opening may be followed by various further steps ultimately resulting in valsartan.

According to the Appellant, there were five different sites in compound (II) at which ring opening could occur. Processes with a ring opening at each of these sites were covered by claim 1, but only one particular

ring opening was described in the patent in suit. Ring opening reactions at different sites of the oxazolidinone were known in the art, for example the hydrolytic ring opening as shown in document (19) (scheme 81, reaction of the compounds 383 or 385 to the compounds 384 or 386). However, the patent in suit failed to provide adequate guidance as to how the skilled person could arrive at the target compound valsartan from compounds resulting from a ring opening other than that described in the patent in suit.

4.2.2 Secondly, the Appellant argued that the process as claimed was directed to the preparation of valsartan, which had (S)-configuration in the valine moiety. In the starting material of formula (II) the stereochemistry was undefined, as indicated by the wiggly line. Consequently, claim 1 also covered a process starting from compound (II) having (R)-configuration to obtain valsartan with its (S)-configuration. The patent in suit provided no information as to how the skilled person could put such a process into practice.

4.3 The Board does not share the Appellant's interpretation of claim 1.

4.3.1 Although no specific ring opening is indicated in claim 1, it is immediately evident for the skilled person reading claim 1 that in order to obtain the basic structure of valsartan from a compound of formula (II) there is only one possible ring opening to be considered, namely the cleavage of the bond between the oxygen atom of the oxazolidinone ring and the carbon atom between the ring oxygen and the ring

nitrogen atom. This ring opening naturally suggests itself, taking into account the structure of valsartan and the structure of compound (II). Moreover, the Board is convinced that, in view of the wording of claim 1, in particular the use of the word "**resulting** valsartan", the skilled person understands this claim as one directed to a process where the combination of the ring opening of compound (II) and, depending on the substituent W present in that compound, the conversion of W into the required substituent are the last steps in a process leading to the target compound valsartan. In other words the ring opening reaction and the respective conversions form a reaction sequence directly **resulting** in the formation of valsartan. It follows that a hydrolytic ring opening, contrary to the assertion of the Appellant, is not encompassed by present claim 1. Such a reaction removes the biphenyl moiety from compound (II) and by converting W, which is attached to the biphenyl moiety, into the required tetrazolyl group **results** in a tetrazolyl substituted biphenylaldehyde and the acylated amino acid educt, rather than valsartan. Such a destructive ring opening reaction resulting in slightly modified starting materials makes no technical sense and would not be considered by a person skilled in the art.

Even if one takes into account the possibility that a ring opening reaction at a different position may be envisaged, the specification of the patent does not mention such a possibility at all. It is concerned only with a ring opening reaction as mentioned above, leading directly to valsartan or the valsartan basic structure. In the context of the teaching of the patent, the skilled person would therefore not

interpret the ring opening reaction in the manner advocated by the Appellant.

4.3.2 Concerning the Appellant's second objection the Board concurs with the Opposition Division that this objection relates to lack of clarity due to inconsistent use of terminology, rather than to insufficiency of disclosure.

On page 2 of the patent in suit the structure of valsartan and its chemical name are given. It is immediately apparent to any skilled reader that there is an inconsistency between name and structure. While the name defines valsartan as N-(oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-**L-valine** (L-valine has (S)-configuration), i.e. a compound with a defined stereochemistry, the corresponding formula shows a wiggly line, meaning that the stereochemistry in the valine moiety is undefined. The same inconsistency can be identified for compounds (II), (III) or (VI), which according to the patent in suit are prepared from **L-valine** (paragraphs [0016], [0018], [0020] and [0021]), but nevertheless show a wiggly line in their structure.

Thus, either the wiggly line in the valsartan on page 2 is a mistake, perpetuated throughout the patent in suit, including claim 1, which is identical to present claim 1, or the name mentioned on page 2 is incorrect and the patent refers to racemic valsartan or to valsartan with an undefined stereochemistry.

Since it was uncontested by both parties that the name valsartan refers to a compound with (S)-configuration,

the Board is convinced that the skilled person would have identified the wiggly line in the desired product **as well as** in the intermediates as incorrect. The Appellant's interpretation that claim 1 encompasses a process starting from compound (II) having (R)-configuration, but yielding (S)-configured valsartan can therefore not be followed.

The Board also concurs with the Opposition Division's decision that the feature objected to is not open to an objection under Article 84 EPC, since it was already present in the claims as granted and since Article 84 EPC is not a ground for opposition.

4.4 In the light of the interpretation of claim 1 adopted by the Board, the Appellant's arguments that the patent in suit fails to provide sufficient disclosure for an allegedly "vast majority of embodiments", in support of which it cited the decisions T 516/99 and T 422/99, must fail.

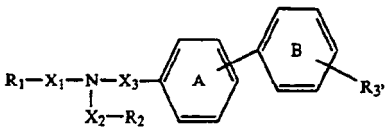
The Board concurs with the Opposition Division that, based on the examples as well as the information provided in the description of the patent in suit (paragraphs [0010] to [0013], [0016] to [0021]), the skilled person is provided with sufficient guidance to be able to choose suitable reagents and reaction conditions for the preparation of valsartan. Hence, the requirement of Article 100(b) EPC is fulfilled.

5. Inventive step

5.1 The Board considers in agreement with both parties and the Opposition Division that document (1) represents

the closest state of the art, and, hence, takes it as the starting point for the assessment of inventive step.

5.2 Document (1) describes biphenyl compounds of the general formula (I)



and methods for their preparation (column 1, lines 6-40, column 14, line 36 - column 26, line 4). Claim 3 of document (1) is directed to the compound valsartan and examples 16, 37 and 54 describe its preparation.

Example 16 describes the reductive amination of 2'-cyanobiphenyl-4-carbaldehyde with L-valine methyl ester hydrochloride to yield N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester. This compound is acylated with valeryl chloride followed by the conversion of the cyano group into the tetrazolyl group. Example 37 discloses an analogous process using (L)-valine benzyl ester toluene sulfonic acid salt as starting material. In the last step of example 37 the benzyl group is removed via hydrogenation.

In example 54 (L)-valine benzyl ester tosylate is alkylated with 4-bromomethyl-2'cyanobiphenyl. The product obtained is then acylated, followed by the conversion of the cyano group into the tetrazolyl group, analogous to the steps in example 16, and in a final step the benzyl group is removed via hydrogenation to yield valsartan.

5.3 According to the patent in suit, the problem to be solved in view of document (1) is the provision of an

improved industrial process for the preparation of valsartan, which reduces costs, avoids the conversion of the cyano group in one of the last synthetic steps, and avoids the use of highly toxic butyltin derivatives.

5.4 However, the patent in suit does not contain any evidence of improved cost-effectiveness in the presently claimed process vis-à-vis document (1). Nor is the conversion of cyano in the last synthesis step avoided. According to claim 1 of the present main request, the substituent W can be cyano, which is converted after hydrogenolysis into the tetrazolyl group to yield the final product valsartan. Furthermore, since claim 1 is not restricted to specific reaction conditions, the use of highly toxic butyltin derivatives for the conversion of the cyano group is not excluded.

5.5 The Respondent also argued that the claimed process was economically advantageous in that the intermediate (II) could be obtained in a more straightforward way requiring fewer synthesis steps. Additionally, the claimed process showed superior atom economy. In support of the latter, the Respondent referred to the expert opinion of Prof. Barrett (document (25)), in particular to page 17.

5.6 However, claim 1 is directed to a process using compound (II) as starting material. It leaves the question of its preparation entirely open. The Respondent's arguments with regard to any advantages linked to the preparation of compound (II) are therefore without merit. Concerning the alleged superiority in atom economy, the Board notes that Prof.

Barrett compares the last step of a specific process (QSSA process), in which ring opening of a compound of formula (II) with an **unprotected** tetrazolyl group takes place, with the last step of example 54 of document (1), in which the benzyl group is removed from valsartan benzyl ester, resulting in the formation of toluene. Since the last step according to the QSSA process yielded valsartan without producing toluene as "waste material", Prof. Barrett considered the atom economy of the QSSA process to be superior to that of the process of document (1).

5.7 According to claim 1 of the present main request, the starting material for the ring opening reaction is compound (II) where the variable W is a **protected** tetrazolyl group. Prof. Barrett's analysis is not concerned with such a process. The use of a compound of formula (II) with W equal to a protected tetrazolyl group as starting material requires deprotection, which may occur during the ring opening reaction, yielding valsartan **and** the compound resulting from the splitting off of the protective group as "waste material". Thus, no advantages concerning the avoidance of "waste material" compared to example 54 of document (1) are apparent.

This conclusion is not altered by the Respondent's reference to the description of document (1) which mentions an N-protected tetrazolyl group as a possible substituent. The statement in column 15, lines 14-15 mentions a number of possible substituents for the variable Z_1, amongst them N-protected tetrazolyl, in the general and very broadly defined compound (II) of document (1). No specific process which could validly

be compared with the presently claimed process is described in this context. Thus, any statement with regard to an improvement in atom economy is mere speculation. Nor is there a convincing reason for the skilled person to consider a combination of the disclosure in column 15 with example 54. Since, according to this example, protection of the tetrazolyl group is not required for the successful hydrogenation of the benzyl ester, the skilled person has no reason to consider the addition of such a superfluous protection step.

5.8 Since the alleged advantages have not been adequately demonstrated, they cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step. In the light of document (1), the Board, in accordance with the Opposition Division and the Appellant, therefore sees the problem to be solved in the provision of an alternative process for the production of valsartan.

5.9 As the solution to this problem, the patent in suit proposes ring opening of an oxazolidinone compound of formula (II) followed by the transformation of the group W into the tetrazolyl group of valsartan. In view of the examples provided in the patent in suit, the Board is satisfied that the problem has been successfully solved.

5.10 It then remains to be decided whether the proposed solution is obvious.

According to the Appellant, the claimed process was obvious in view of document (1), in particular

example 54, in combination with either document (18) or (19), both reflecting common general knowledge.

5.11 The Appellant argued that the last step of example 54 of document (1) already pointed to hydrogenolyis as a very suitable final step in a reaction sequence leading to the target compound valsartan. According to the Appellant, taking this clear teaching as a starting point the skilled person faced with the problem of providing an alternative process for the preparation of valsartan would therefore have looked for an alternative synthesis involving a hydrogenation reaction as the last step. In particular, he would have considered an approach starting from an alternative protected final intermediate, while retaining the hydrogenation reaction of the prior-art example. To this end the skilled person would have consulted document (18), a well-known standard textbook on protective groups. In view of example 54, where the protective group was an ester, he would have focused his attention on alternative ester protective groups and in particular on those described in the context of the preparation of amino acids, since the starting compound in document (1) was an amino acid, namely valine, and valsartan could be considered as a substituted amino acid. Document (18) contained in the chapter "protection for the carboxyl group" a section called "miscellaneous esters". In this section, on page 267, oxazolidinones were mentioned as suitable protective groups for the carboxylic acid group in amino acids. These were formed via the reaction of the amino acid with an aldehyde leading to a substituted imine (or Schiff base). Addition of benzoyl chloride to the imine resulted in the formation of an oxazolidinone.

According to the Appellant, the general applicability of this reaction was easily recognisable for the skilled person and was furthermore confirmed by document (16), to which document (18) referred as the original paper (page 267, second reference below the reaction scheme at the top of the page). Document (16) also explicitly referred to valine as suitable starting material in the aforementioned reaction sequence.

Furthermore, the Appellant pointed out that document (1) referred in column 21, line 14 to the formation of a substituted imine as a useful intermediate to which, for the skilled person, the chemistry suggested in document (18) readily applied, leading in an obvious way to the oxazolidinone intermediate (II) of the patent in suit, with all the necessary C-N bonds formed and the carboxy group protected in the same way as in the ester of example 54.

According to the Appellant, it was easily recognisable for the skilled person that hydrogenolysis, more particularly hydrogenation as disclosed in example 54 of document (1), was a suitable method for the ring opening in view of the structural similarity between the oxazolidinone intermediate (II) of the patent in suit and the benzyl ester in example 54 of document (1). Both intermediates were esters having in common a benzylic ester bond (-C(O)-O-CRR'-aryl) which was cleaved upon hydrogenation, while the other bonds, in particular the bonds to the nitrogen atom of the valine unit, stayed intact. The Appellant also argued that such a ring opening reaction by hydrogenation for obtaining substituted amino acid derivatives was well

known and documented in the literature, as shown by document (20), in particular in scheme 2, second line on page 1631.

5.12 The Board considers it appropriate to point out that the technical disclosure in a prior-art document should be considered in its entirety. It is not justified to arbitrarily isolate parts of such a document from their context in order to derive therefrom technical information which the skilled person would not have objectively inferred without the benefit of hindsight.

Applying this principle to the present case, the Board cannot accept the Appellant's argument that document (1) teaches the skilled person that hydrogenolysis is in general a very suitable last step for producing valsartan.

As explained in point 5.2 above, document (1) refers to a broad range of compounds, methods for their preparation and various intermediates. Example 54 describes a multi-step synthesis of valsartan starting from (L)-valine with the carboxylic group being protected by a benzyl group. The last step in this synthesis is the removal of the benzyl group from **valsartan benzyl ester** to yield valsartan via hydrogenation in the presence of palladium on carbon, which is a commonly known way of removing this particular protective group. However, hydrolysis is an equally well-known method of cleaving an ester, including a benzyl ester. Incidentally, this way of removing a benzyl group is also used in document (1) (example 53). At the same time, the skilled person is well aware of the fact that the use of a different

amino acid ester as starting material, for example an alkyl ester as in example 16, does not require hydrogenation in the last step. Those esters are commonly cleaved via hydrolysis. Thus, in the Board's view, no particularly suitable last reaction step in the preparation of valsartan is taught in document (1). The only conclusion which the skilled person can draw from example 54 is that hydrogenation in the presence of palladium on carbon is a suitable last step, if the final intermediate is the benzyl ester of valsartan. Accordingly, the skilled person without the benefit of hindsight has no motive for keeping the hydrogenation conditions of example 54, which are linked to the particular intermediate used therein, and at the same time replacing that particular intermediate as advocated by the Appellant.

5.13 Even assuming in the Appellant's favour, that the skilled person would have considered such an approach, the oxazolidinone compound of formula (II) would not have been an obvious alternative for the benzyl ester of example 54.

The Board accepts the Appellant's argument that a skilled person trying to find an alternative protected intermediate for the benzyl ester of example 54 would have considered a standard textbook on protective groups in organic synthesis (document (18)). However, there he would have searched for alternative protective groups for carboxylic acids removable under the same reaction conditions as in example 54, rather than for just any alternative. In document (18) oxazolidinones are mentioned as protective groups for a carboxylic acid, in particular an amino acid, in which both

functional groups are protected by incorporating them into the oxazolidinone ring. However, document (18) is entirely silent as to any possible deprotection step via hydrogenolysis, let alone via hydrogenation as described in example 54 of document (1). Nor is such a reaction disclosed in document (16), to which document (18) refers as the original paper. On the contrary, according to documents (18) and (16) removal of the protective group takes place via hydrolysis. By that means the oxazolidinone is cleaved and the unprotected α-amino acid with its free amino and carboxyl group is regenerated. Such a hydrolytic cleavage would be of no use for the skilled person, even if he had considered applying the chemistry outlined in document (18) and (16) to the imine intermediate of document (1) as alleged by the Appellant, since it would remove the biphenyl unit, which is an essential part of valsartan.

The Board also does not share the Appellant's position concerning the alleged structural proximity of the claimed oxazolidinone and the benzyl ester. In the benzyl ester of example 54 the benzylic carbon atom is unsubstituted (C(=O)O-**CH_2**-phenyl). In the claimed oxazolidinone the corresponding C(=O)O-**CH**- group including the "benzylic" carbon is incorporated into a ring structure and, in addition, the "benzylic" carbon atom is attached to a ring nitrogen atom (-O-**CH**-N-), i.e. forms part of a cyclic N,O-acetal, leading to a sufficiently different steric and electronic environment compared to the simple benzyl ester. In the Board's opinion these differences are such that it cannot justifiably be assumed that the same conditions as employed in example 54 of document (1) for cleaving

the chain bond between the oxygen and the benzylic carbon are also suitable for cleaving the ring bond between the oxygen and the acetal carbon. The Appellant's arguments are mere speculation.

Document (20) cannot support the Appellant's arguments either. The Board notes that this document is a very specific paper with the title "Preparative Resolution of Heterocyclic Acetals Derived from Glycine, Mercapto acetic Acid, β-Alanine, and Formyl- or Acetylacetic Acid by recycling Chromatography on *Chiraspher* and Temperature Dependence of Separation Factors". It does not belong to the skilled person's general knowledge. It is not mentioned in document (18). Nor is it concerned with the synthesis of valsartan or structurally similar compounds, i.e. the same purpose. In fact, in the Board's opinion such a document could only have been found with knowledge of the invention.

5.14 The Appellant's second line of argument was based on the combination of document (1) with a different textbook, namely document (19). According to the Appellant, document (19) reflected the same common general knowledge as document (18), namely the use of oxazolidinones as a protective group for amino acids, including valine, which is the starting material in document (1). This was shown in reaction schemes 82-84 on page 77, 79 and 80, and its general applicability was confirmed on page 69 of document (19). In applying this general approach to the disclosure in document (1), the skilled person would arrive at the presently claimed oxazolidinone in an obvious manner.

With regard to the required ring opening via hydrogenation, the Appellant argued that document (19) explicitly suggested direct hydrogenolysis of the oxazolidinones as a very attractive possibility to yield substituted amino acid derivatives (page 79, lines 4-7 in the paragraph below scheme 83). According to the Appellant, direct hydrogenolysis in this context meant the hydrogenation of the oxazolidinones 396, 397 or 402 using the conditions according to step 2 shown in scheme 83 (i.e. hydrogen in the presence of palladium on carbon) without the previous hydrolysis step 1. Under these conditions the bond between the ring oxygen atom and the neighbouring ring carbon atom (**C**H-Ar) in the oxazolidinones 396, 397 and 402 was cleaved, as would be required for the formation of valsartan, and protective groups sensitive to hydrogenation (i.e. CBz) were removed, while all other bonds including the N-benzyl bond remained intact. Although it was acknowledged that details to support this suggestion were not published in document (19), the Appellant argued that the skilled person, if he actually needed further information, would have searched all papers published by Seebach and, as a consequence, would have come across document (20) providing him with the necessary information. The Appellant based its assertion on the fact that this author was mentioned on page 62 of document (19) as having made extensive contributions to the practical synthesis of amino acids.

During the oral proceedings the Appellant also referred to document (9), which was mentioned as reference "83" in the relevant passage on the hydrogenolysis of oxazolidinones on page 79 of document (19).

Document (9) described a process for the preparation of N-alkyl substituted amino acids via ring opening of oxazolidinones by ionic hydrogenolysis with triethylsilane. Table I illustrated the reaction sequence with valine as amino acid or $PhCH_2CH_2CHO$ as aldehyde starting materials (equation (e) and equation (d) of table I on page 77). According to the Appellant, the general applicability of this reaction was apparent from page 78, middle of the left column as well as page 78, right column, last paragraph before the "Experimental section". Its teaching could therefore be directly applied in the present case.

5.15 The Board is not convinced by the Appellant's arguments.

Document (19) is a textbook concerned with the synthesis of optically active α-amino acids. In a section with the title "**Asymmetric Derivatization of Glycine**" it describes an approach using oxazolidinones as a **temporary** protective group for the stereogenic centre of amino acids **during α-alkylation.** This approach was mainly developed by Seebach and co-workers and allows α-alkylation with a high degree of diastereoselectivity. Subsequently, the oxazolidinone is cleaved via hydrolysis to yield the desired optically active α-alkylated amino acids. This strategy is illustrated in reaction schemes 82-84 of document (19). The Board does not deny that a skilled person working in the field of amino acid synthesis is likely to be familiar with this concept. However, it fails to see any convincing reasons why the skilled person trying to find an alternative for the valsartan benzyl ester of example 54 would have taken document (19) into consideration. Although an amino

acid moiety forms part of its structure, valsartan is not an amino acid; nor is it, with respect to the starting material in example 54, i.e. valine, a valine derivative further alkylated in α-position. Moreover, while the Board can appreciate that the skilled person would consider documents in the field of protective groups in organic synthesis, where he could reasonably expect to find suggestions regarding an alternative protected intermediate, for example document (18), the same cannot be said for document (19), which is not concerned with this subject-matter.

The Board also notes that none of reaction schemes 82-84 discloses ring opening of oxazolidinones via hydrogenation to yield N-substituted amino acids. As in document (18) or (16), the oxazolidinone is cleaved by hydrolysis, which does not lead to N-substituted amino acids as would be required for valsartan. In reaction scheme 83 on page 79, a hydrogenation reaction with hydrogen in the presence of palladium on carbon, as in example 54 of document (1), is mentioned (page 79, preparation of amino acid 398 or 399 from oxazolidinone 396 or 397, step 2). However, this reaction has an entirely different purpose, namely the removal of the benzyloxycarbonyl (CBz) protective group on the nitrogen atom of the amino acid after hydrolytic ring opening with complete removal of the CH-Ar moiety has occurred.

Furthermore, although it is true that document (19) suggests "direct hydrogenolysis" of oxazolidinones 396, 397 or 402, the Board is not convinced that this suggestion refers to a hydrogenation reaction using hydrogen in the presence of palladium on carbon as

asserted by the Appellant. In the first place, in document (19) in reaction scheme 83 (transformation of oxazolidinones 396 or 397 to amino acids 398 or 399) step 2 refers to a **catalytic hydrogenation** reaction (page 78, last line to page 79, paragraph below reaction scheme 83, line 2). The suggestion in the last paragraph on page 79 mentions "direct **hydrogenolysis**", rather than "direct catalytic hydrogenation". Secondly, the explicit reference in document (19) to a document "83" implies that the suggested hydrogenolysis takes place under the conditions specified in that latter document, which is equivalent to document (9) of the present case. Thus, in the Board's opinion, the direct hydrogenolysis suggested in document (19) refers to the direct hydrogenolysis as disclosed in document (9).

Document (9) discloses **ionic hydrogenolysis** of certain oxazolidinones with **triethylsilane and trifluoracetic acid**. These reaction conditions are entirely different from those in example 54 of document (1). Accordingly, even assuming, in the Appellant's favour, that the skilled person would have considered document (19), he would not have been provided either by the document itself or by document (9) therein cited with an incentive to replace the benzyl ester in the last step of example 54 of document (1) with the claimed oxazolidinone. In this context, the Appellant's assertion that the skilled person would have searched all literature published by Seebach and, as a consequence, would have found document (20) cannot be accepted. In view of the reference to document "83" (i.e. document (9)) the skilled person had no incentive to search for further literature.

5.16 In support of its arguments with regard to inventive step, the Appellant also referred to document (24T), in particular pages 15, 20 and 21. The arguments provided in document (24T) with regard to the present documents (1), (19) and (14) (excerpts from an earlier edition of the textbook on protective groups (document (18)) are the same as those provided by the Appellant. Since the Board does not consider these arguments convincing, document (24T) cannot support the Appellant's case either.

5.17 In its statement of grounds of appeal the Appellant also argued that the preparation of valsartan as presently claimed differed from that according to document (1) merely in a reversal of reaction steps. Document (1) described imines as useful intermediates and recommended a reaction sequence for the preparation of valsartan where an imine was reduced and subsequently acylated (column 20, line 66 - column 21, line 17 and example 16, cf. column 35, lines 3-8). According to the patent in suit an imine (compound (VI)) was firstly acetylated, whereby an oxazolidinone was formed, and in a later step this oxazolidinone was subjected to a ring opening reaction, for example through reductive hydrogenation. The respective reaction sequences were summarised in document (22). According to the Appellant, the incentive to reverse the steps was to be found in the general knowledge of the skilled person, namely the well-known technique of using oxazolidinones as intermediates for the preparation of substituted amino acids, as illustrated in document (19).

5.18 The Board notes that during the oral proceedings before it the Appellant did not rely on this particular argument. It is also considered not convincing for the following reasons:

Document (1) refers in the passage in columns 20/21 to the preparation of an intermediate (IIIb) via the formation of an imine starting from a compound (IIa) (R_2-X_2-NH_2) with a compound (IIIc) (OHC-biphenyl) followed by reduction to an N-alkylated compound of the formula R_2-X_2-NH-CH_2-biphenyl. In this context no acylation reaction with valeryl chloride is mentioned. A reductive alkylation as outlined in columns 20/21 is used in example 16 for the preparation of valsartan. In this specific example the reduction of the imine is followed by an acylation reaction. However, in example 16, as in all other examples, the starting material is **protected**, not unprotected as indicated in document (22). Accordingly, the skilled person would not only have to reverse the reaction steps, but also to deprotect the carboxy group. The Appellant's reference to column 1, lines 26-27 defining R_2 as carboxyl group is not convincing, since there the definition of the substituents in the end product, i.e. compounds of formula (I), is given. During the preparation of such compounds protection of the carboxy group is necessary in order to avoid undesirable interference, as shown in all the examples.

Moreover, the reduction of the imine in document (1) is carried out with sodium cyanoborohydride as reducing agent (column 21, lines 16, column 34, lines 64 column 35, line 2, column, 43, lines 14-21). Nowhere in document (19), allegedly reflecting the skilled

person's general knowledge, is it taught that an oxazolidinone can be ring opened in the required position with sodium cyanoborohydride to yield an N-substituted amino acid. Thus, the skilled person had no incentive at all to consider reversal of the reaction sequence.

5.19 For the aforementioned reasons, the Board comes to the conclusion that none of the cited documents would have led the skilled person to modify the processes according to document (1) to arrive at the presently claimed process. Hence, the subject-matter of claim 1 of the main request and by the same token that of claims 11 and 12 involve an inventive step within the meaning of Article 56 EPC.

First and second auxiliary requests

6. The main request having been considered to satisfy the requirements of the EPC, there is no need to decide on these requests.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow P. Ranguis