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Datasheet for the decision of 19 March 2019

Case Number: T 1347/14 - 3.3.02

Application Number: 05760356.5

Publication Number: 1771431

IPC: C07D307/28

Language of the proceedings: EN

Title of invention:
INTERMEDIATES FOR THE PREPARATION OF HALICHONDRIN B

Applicant:
Eisai R&D Management Co., Ltd.

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - all requests (no)

Decisions cited:

Catchword:

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Case Number: T 1347/14 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 19 March 2019

Appellant: (Applicant)	Eisai R&D Management Co., Ltd. 6-10, Koishikawa 4-chome Bunkyo-ku Tokyo 112-8088 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 5 December 2013 refusing European patent application No. 05760356.5 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman	M. Maremonti
Members:	P. O'Sullivan
	M. Blasi

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application 05 760 356.5, taken at oral proceedings held on 21 November 2013.

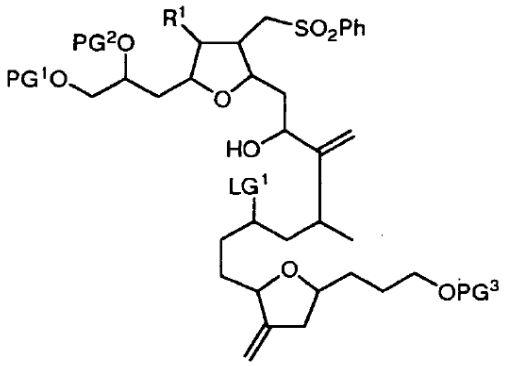
II. The decision was based on the set of claims 1-12 of the main request filed with the letter of 12 September 2013, and the set of claims 1-11 of auxiliary request 1 filed during oral proceedings (annexed to that decision).

The following evidence was on file during examination proceedings:

D1 : US 6,214,865
D2/D2a: Wan *et al.*, Org. Lett., 2002, Vol. 4, pp 4431-4434, including supporting information D2a, published therewith
D3 : Choi *et al.*, Pure Appl. Chem., 2003, Vol. 75, No. 1, pp 1-17

According to the decision under appeal:

For the purpose of assessing inventive step, documents D2/D2a, rather than document D1, represented the closest prior art. The compound **F-4** of claim 1 of the main request, having the structure



F-4

differed from compound **18** of D2a (page 6, top right hand structure) in the nature of the hydroxyl protecting groups PG^1 and PG^2 (silyl derivatives in the former, acetonide in the latter), and in that the compound **F-4** had an "open" structure in comparison to the central hydropyranyl ring structure of compound **18** of D2a. No technical effect arose from the distinguishing features, and the technical problem was the provision of intermediates with alternative protecting groups suitable in a process for the preparation of Halichondrin-B analogues. The claimed solution was obvious in view of D2/D2a in combination with the general knowledge of the skilled person. The same conclusions in respect of inventive step applied to the subject-matter of claim 1 of auxiliary request 1, defining a method for preparing the Halichondrin-B analogue **B-1939** from said compound **F-4**.

III. With the statement setting out the grounds of appeal the appellant, *inter alia*, filed the following evidence:

D4 : Austad *et al.*, Synlett 2013, 24, pp 327-332

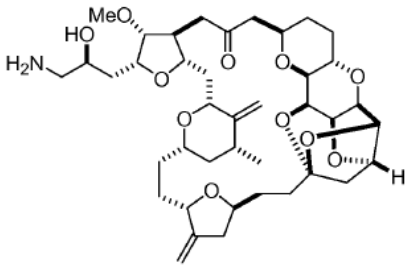
IV. A communication of the board was sent in preparation for oral proceedings pursuant to Article 15(1) RPBA. In particular the board provided the preliminary opinion that if D2/D2a were to be seen as the closest prior art, the alleged technical effect resulting from the replacement of the acetonide protecting group, namely the removal of chromatography from the process, was not derivable from the application as filed, nor did there appear to be sufficient evidence supporting it.

V. With its reply to the board's communication dated 11 March 2019, the appellant filed six sets of claims as a main request and auxiliary requests 1 to 5, and the following evidence:

D5 : Yang *et al.*, Organic Letters, Vol. 11(20), 2009, pp 4516-4519
D6 : WO 2016/038624

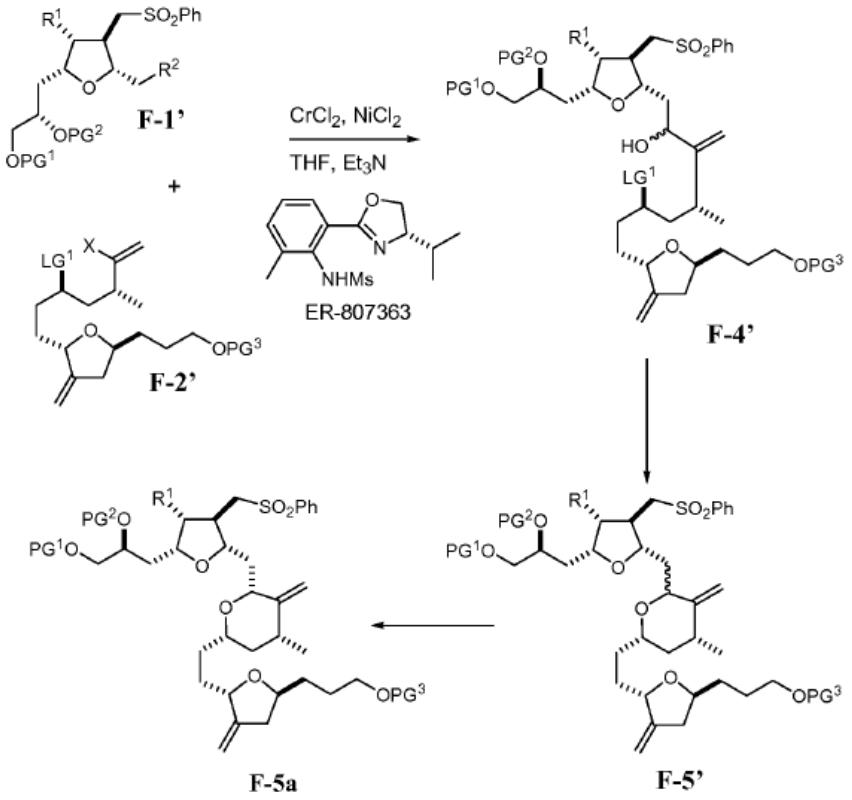
Claim 1 of the main request reads as follows:

"*1. A method for preparing a compound of formula B-1939*



B-1939

wherein the method comprises the following steps:



wherein

each of PG^1 and PG^2 is a suitable hydroxyl protecting group which, taken with the oxygen atom to which it is bound, is a trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, or another trialkylsilyl ether;
PG^3 is a suitable hydroxyl protecting group which, taken with the oxygen atom to which it is bound, is a silyl ether or an ester group;
R^1 is R or -OR, wherein each R is independently hydrogen, C_{1-4} haloaliphatic, benzyl, or C_{1-4} aliphatic;
R^2 is CHO or $-CH=CH_2$;
LG^1 is a suitable leaving group, wherein LG^1 is sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, or optionally substituted arylsulfonyloxy;
X is halogen or $-OSO_2(R^Y)$; and

R^Y is C_{1-6} aliphatic or a 5-7 membered saturated, partially unsaturated, or fully unsaturated ring, wherein R^Y is optionally substituted with up to 3 groups selected from halogen, R, NO_2, CN, OR, SR, or $N(R)_2$, wherein each R is independently hydrogen, C_{1-4} haloaliphatic, or C_{1-4} aliphatic."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request in the above scheme describing the method steps, whereby the transformation of compound **F-4'** to **F-5'** includes the reagent "*Potassium hexamethyldisilazide*", and the transformation of compound **F-5'** to **F-5a** includes "*Chromatography*".

Claim 1 of auxiliary request 2 differs from claim 1 of the main request in the above scheme describing the method steps, whereby the transformation of compound **F-4'** to **F-5'** includes the reagent "*Potassium hexamethyldisilazide*", and with the addition of the following text to the claim:

*" ... and wherein F-5' is purified via SiO_2 column chromatography to yield **F-5a**, wherein the column is first flushed with methyl tert-butyl ether to remove water, then flushed with heptane to remove the methyl tert-butyl ether, **F-5'** is loaded onto the column as a solution in heptane and then eluted from the column with heptane/methyl tert-butyl ether (5:1) then heptane/methyl tert-butyl ether (4:1) with the fractions monitored at 230 nm by UV detector."*

The respective claim 1 of auxiliary requests 3, 4 and 5 differ from claim 1 of the main request and auxiliary requests 1 and 2 respectively in the limitation of the groups PG^1 and PG^2 to t-butyldimethylsilyl.

VI. Oral proceedings before the board were held on 19 March 2019.

VII. Final requests

The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the claims of the main request, or alternatively, of one of auxiliary requests 1 to 5, all requests having been filed with the letter of 11 March 2019.

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

Main request - inventive step

In the assessment of inventive step, D1 was a more appropriate starting point for the skilled person than D2/D2a, which did not focus on the final preparation of analogues of Halichondrin B and was more mechanistic in nature. Even if D2/D2a were seen as the closest prior art, the claimed invention involved an inventive step.

The subject matter of claim 1 differed from the disclosure in D2/D2a in the use of silyl ether hydroxyl protecting groups PG^1 and PG^2. The effect of the difference was the provision of crystalline intermediate compounds **F-1'** and **F-6** which allowed for a reduced number of chromatographic steps in the synthesis of **B-1939**. In particular, D4 showed that compound **F-6** was obtained in crystalline form. The disclosures in D3 and D5 demonstrated that the acetonide protected compound **A** of D2a corresponding to compound **F-1'** was not crystalline, while the disclosure in D6 demonstrated that the acetonide protected analogue of **F-6** was not crystalline.

The technical problem was thus the provision of an improved method for preparing **B-1939**, or alternatively, the provision of an improved method wherein the improvement results in the possibility of obtaining at least compound **F-1'** in crystalline form.

D2/D2a provided the skilled person with no motivation to change the protecting group in compound **A** of D2a. It was conceded that t-butyldimethylsilyl (hereinafter: TBS) hydroxyl protecting groups were known from D1 to be employed in intermediates corresponding to the intermediates used according to D2/D2a. Nevertheless, D1 provided no motivation either for the skilled person to use TBS protecting groups in a method according to D2/D2a in order to solve the technical problem. Consequently, the subject-matter of claim 1 of the main request involved an inventive step over the disclosure in D2/D2a in combination with the disclosure in D1.

The same arguments applied to the subject-matter of claim 1 of all auxiliary requests, which also involved an inventive step.

Reasons for the Decision

Main request - inventive step

1. Claim 1 concerns a method for preparing compound **B-1939**, an analogue of Halichondrin B (a potent anti-cancer agent originally isolated from a marine sponge) having pharmaceutical activity (application, paragraph [0004]). The method of claim 1 at issue comprises a Ni/Cr mediated coupling reaction between fragment **F-1'** and **F-2'** (V, above).

2. Closest prior art

2.1 According to the contested decision, the disclosure of D2/D2a represented the closest prior art. The appellant submitted that document D1 was a more suitable starting point, since it was directed to *inter alia* the production of **B-1939** (as one of the two preferred options, col. 4, lines 39-40), it provided a synthetic route to the Halichondrins, and was therefore directed to a similar purpose as the present application. Furthermore, D1 was closer to the subject-matter of claim 1 from a structural viewpoint by virtue of the specific disclosure of compound **ER804027** (D1, column 45), a specific embodiment of the closed ring analogue **F-5'** of claim 1 at issue (disclosed in the application on page 85).

On the other hand D2/D2a was unsuitable since it was more mechanistic in nature, being mainly directed to improvements in the Ni/Cr-mediated coupling reaction. The reaction might be used in the preparation of certain intermediates that could be used in the synthesis of Halichondrin B and analogues thereof, but was not limited to that application.

Moreover, D2/D2a was structurally more remote from the claimed subject-matter, compound **18** (document D2a, page 6) differing from compound **F-5'** by its acetonide protecting group.

2.2 The board agrees that D2/D2a focuses on the coupling reaction. Indeed, this reaction was known before the publication date of D2/D2a, which was concerned with developing a stoichiometric process and providing a tridentate ligand allowing it to proceed

asymmetrically. Nevertheless, it also refers explicitly to the utility of the Ni/Cr-mediated coupling reaction when applied to polyfunctional molecules, and its uniqueness particularly at a late stage in a multiple-step synthesis where scalability and practicability are not necessarily a priority (D2, page 4431, left hand column). More specifically, it explicitly identifies the utility of the coupling reaction in producing Halichondrin analogues such as **ER-086526**, which is identical to compound **B-1939** recited in claim 1 at issue (D2, left column of page 4434, final paragraph and D2a, page 6, reaction of structures **A** and **15** to produce coupled product **18**; and in the application, structure **ER-086526**, paragraph [00210]). Accordingly, while D2/D2a does concern synthetic methodology, it also explicitly references the applicability and utility of the coupling reaction technology disclosed therein to the synthesis of **B-1939**, and thereby serves as a suitable springboard to a method directed to the synthesis of the same compound.

2.3 Consequently, the disclosure in D2/D2a represents a reasonable starting point for the skilled person in the assessment of inventive step.

3. Problem solved

3.1 It is undisputed (appellant's letter of 11 March 2019, 3.2.1.1) that the preparation method of claim 1 at issue differs from the disclosure in D2/D2a in the use of the silyl protecting groups PG^1 and PG^2, while in compounds **A** and **18** of D2a (page 6), an acetonide protecting group is provided.

3.2 According to the appellant, the effect of this difference was that the preparation of **B-1939** according

to claim 1 at issue proceeded via crystalline intermediates, specifically compound **F-1'** of claim 1 and downstream compound **F-6** (paragraph [0079] of the application). The advantages associated with the ability to crystallise over the need for chromatography was evident to the skilled person - it allowed the removal of unwanted impurities accumulated during a multi-step synthesis, was less cumbersome, and facilitated drug market approval in terms of reproducibility and quality. The use of silyl protecting groups was a preferred embodiment of the application (claims 6 and 7 as filed), and the skilled person would link the use of said protecting groups with purification via crystallisation as exemplified via the crystallisation of e.g. compound **F-1a**, a specific embodiment of compound **F-1'** of claim 1 at issue (application, paragraph [00104]). The objective technical problem had thus to be formulated in accordance with this technical effect (VIII, above).

3.3 The board notes that the application is generally directed to the provision of a method for preparing *inter alia* compound **B-1939**, and certain intermediates useful in the synthesis thereof (paragraphs [0002] and [0004]). The specific provision of crystalline compounds is explicitly discussed only in the context of compound **F-2b** (paragraphs [0023] and [0024]) and compound **ER-817664** (paragraph [0040]) However, neither compound is related to compounds **F-1'** and **F-6** invoked by the appellant, and neither comprise silyl protecting groups. Thus, the application as filed does not explicitly concern the mandatory provision of intermediates **F-1'** and **F-6** in crystalline form, let alone any advantage derivable therefrom. Nevertheless, to the benefit of the appellant, the board accepts that the provision of crystalline intermediates is generally

recognised as advantageous and is thus related to the general technical problem of providing an improved method, as set out in the application. This effect, if sufficiently demonstrated, may consequently be invoked in the formulation of the objective technical problem.

3.4 In order to assess the formulation of the technical problem as submitted by the appellant (VIII, above), it must be determined whether the distinguishing features of the claim provide the above-mentioned alleged technical effect. Alleged effects which are neither credible nor supported by sufficient evidence cannot be taken into consideration in determining the problem. The alleged technical effect underlying each of the above-mentioned compounds **F-1'** and **F-6** will thus be analysed in turn.

Compound **F-1'**:

3.5 According to the application (paragraph [00104]), TBS protected compound **F-1a** (**ER-806067**; the specific TBS-protected embodiment of **F-1'**) was isolated as a white crystalline solid. The appellant submitted that the disclosures in D3 and D5 served as evidence that the corresponding acetonide-protected compound **A** of D2a (page 6) was not crystalline.

3.6 In D3 (scheme 2 and page 5, final paragraph) the relevant compound **18**, corresponding to compound **A** of D2a, is said to be isolated in excellent overall yield. However, it is stated that "*For practical purposes, we routinely carried out the synthesis from **15** to **18** without purification of the intermediates, and the product was isolated by reprecipitation of the primary alcohol corresponding to **18** from methylene chloride/ hexanes at -78°C*".

3.7 According to the appellant, this text indicates, that rather than preparing aldehyde **18** directly, the authors of D3 prepared the crude aldehyde and then, for the purpose of purification, proceeded by reducing it to said primary alcohol, which was subsequently re-oxidised to the aldehyde **18**, the reason being that **18** was not crystalline and thus could not initially be isolated in sufficient purity. Had **18** been crystalline, the authors of D3 would have crystallised it and there would have been no need to proceed via the primary alcohol. Furthermore, although precipitated, the primary alcohol was also not crystalline, since if it had been, the authors of D3 would have stated this explicitly (e.g. as for compound **15** in scheme 2). D5 (page 4419, scheme 4 and page S10) served as evidence that the same primary alcohol (denoted compound **14** in D5) was not crystalline, since it was isolated as a "*pale brown oil*".

3.8 The board does not share the view of the appellant. The relevant section of D3 (page 5, final paragraph) states that " ... *the methylation smoothly proceeded to completion to furnish the methyl ether **18** in an excellent overall yield*", thereby giving the impression that **18** was the direct product of the methylation reaction, and that it could be isolated. However, according to scheme 2, (e), subsequent to the methylation step, further deprotection, re-protection and ozonolysis steps are required in order to yield compound **18**. Consequently, a contradiction arises in D3, rendering the nature and order of the actual steps taken unclear. No explanation is then provided in D3 as to why "[f]or practical purposes" in the synthesis of **15** to **18** "the product" was isolated as the primary alcohol corresponding to **18**, nor, in that case, how the

synthetic steps to produce the alcohol differed from those in scheme 2, (e). That the transformation would involve, as proposed by the appellant, preparation of the aldehyde **18**, reduction to the alcohol and later re-oxidation to the aldehyde - for the purpose of purification - finds no basis in D3 at all, since it may also have been possible to produce the alcohol without the need to pass via the aldehyde **18**. Furthermore, in D6 (pages 30-31, example 6, compound **II**) no difficulties are reported in preparing the same aldehyde as a pure compound. Consequently, the relevant passages in D3 are vague and unclear and lack any indication or explanation as to how, or why, the product was isolated as the primary alcohol corresponding to compound **18**. To conclude that the reason therefor is the lack of crystallinity of aldehyde **18** arising from the presence of the acetonide protecting group, amounts to nothing more than speculation.

3.9 Furthermore, the appellant's arguments based on D5 are not convincing. Whether the primary alcohol discussed in D3 is crystalline is not relevant for the more critical question of whether the acetonide bearing aldehyde **18** exhibits crystallinity. The latter is a different compound, and the effect of structural differences on crystallinity cannot be reliably predicted. To illustrate this, if the same inference logic were to be applied to the TBS protected compound **16** in D5 (pages S11 and S12), isolated as a colourless oil, one would be led to erroneously conclude that the corresponding aldehyde **F-1a** (application, paragraph [0104]) is also not crystalline.

3.10 It has therefore not been demonstrated that the acetonide-protected aldehyde **A** of D2a cannot be

obtained in crystalline form. The alleged effect (3.2, above) has consequently not been sufficiently demonstrated for the compound **F-1'** of claim 1.

Compound **F-6**:

3.11 According to the appellant, the provision of the TBS-protected downstream compound **F-6** (application, page 30, scheme IX) as a crystalline solid was the result of the incorporation of the TBS protecting groups in compound **F-1'** according to the claimed method. The crystallinity of **F-6** was demonstrated in D4 where the same compound (compound **2**, scheme 6) was provided as a white crystalline solid (D4, page 330, left hand column, final 5 lines). This was in contrast to the corresponding acetonide protected compound which could not be crystallised and was isolated as a white foam (D6, pages 34-35, example 12: preparation of compound **(VII)-A**).

3.12 The board disagrees. A specific preparation of TBS-protected compound **F-6** is described in the application (compound **ER-804028**, paragraph [00201]). Although isolated according to D4 as a white crystalline solid, in the application it was isolated as a (non-crystalline) white foam (last sentence of paragraph [00201]). Furthermore, the same compound **ER-804028** is characterised in D1 as an oil (column 46). Thus, not only was the crystallinity of this compound not part of the disclosure of the application as filed, but also the fact that it exists as a white foam (application), an oil (D1) and as a crystalline solid (D4) invalidates the arguments of the appellant with respect to the corresponding use of an acetonide instead of TBS protecting groups. Thus, that the acetonide-protected compound was isolated as a white foam according to D6

does not necessarily indicate that it does not exist in crystalline form. This conclusion is further supported by the reference in D4 to the crystallisation procedure to produce **2** in crystalline form (see page 332, right hand column, " ... *crystallization of 2*"). In order to obtain crystallisation of **2**, the authors of D4 first purified the crude product by flash chromatography. The fractions containing the product were pooled and evaporated to dryness, and azeotroped with *n*-heptane to provide a **residue**. The residue was subsequently dissolved in *n*-heptane, and a specific crystallisation process was performed to yield the crystallised product. Thus the authors of D4 in fact first obtained a **residue** of undefined physical properties, and only after a specific crystallisation procedure was performed were the desired crystals obtained. This process is informative in that it demonstrates the common general knowledge in the field of synthetic organic chemistry, that crystallisation, if at all achievable, does not necessarily occur spontaneously, but frequently requires the non-trivial investigation of specific crystallisation solvents and conditions which will suit the particular compound concerned. It follows from this that one cannot normally conclude with any level of confidence that a specific compound of the prior art does not exist in crystalline form merely due to it being isolated and characterised in a non-crystalline physical form, unless attempts to crystallise it had demonstrably failed. Otherwise, by that rationale, had the authors of D4 chosen not to pursue crystallisation of the **residue** of compound **2**, one would be led to erroneously conclude that compound **2** does not exist in crystalline form.

3.13 It has therefore not been demonstrated that the acetonide protected compound (D6, page 34, example 12,

compound **(VII)-A**), corresponding to downstream product **F-6** of the application, due to the presence of the acetonide protecting group, cannot be isolated in crystalline form. The alleged effect has consequently not been sufficiently demonstrated for the compound **F-6**, either.

3.14 Accordingly, it has not been convincingly demonstrated that compounds **A** of D2a and compound **(VII)-A** in D6 do **not** exist in crystalline form. Therefore, it has not been shown that the features distinguishing the subject-matter of claim 1 from D2/D2a, i.e. the use of TBS instead of acetonide protecting groups, leads to the alleged technical effect of allowing the provision of compounds **F-1'** and **F-6** in crystalline form.

3.15 As a consequence, the formulation of the technical problem as submitted by the appellant (VIII, above) cannot be accepted. The objective technical problem underlying the subject-matter of claim 1 is merely to be seen as the provision of an alternative method for preparing **B-1939**.

4. Obviousness

The skilled person, seeking to implement alternatives to the coupling procedure disclosed in D2/D2a in a method for preparing **B-1939** would consult D1, cited therein (page 4434, right hand column, reference 21) and relating to the total synthesis of **B-1939** (D1, column 76, identical to **ER-086526** mentioned in D2, see 2.2, above). D1 discloses the intermediate compound **ER-804027** (column 45), which differs from the coupled product **18** of D2a (page 6) only in nature of the hydroxyl protecting groups - TBS in the former and acetonide in the latter. Since the multi-step synthetic

route from **ER-804027** to **B-1939** was successfully implemented in D1 with TBS protecting groups as PG^1 and PG^2, the skilled person would realise that replacing the acetonide protecting group by TBS groups in compound **A** in D2a would provide a coupled product for which a proven successful route to the desired product **B-1939** was available. This replacement represents a synthetically trivial step and pertains to the routine practice of a person skilled in the art of synthetic organic chemistry. Thus replacing the acetonide protecting group in compound **A** with TBS protecting groups was an obvious measure leading the skilled person to the subject-matter of claim 1 at issue without exercising inventive step.

It follows that the subject-matter of claim 1 of the main request lacks inventive step under Article 56 EPC.

Auxiliary requests 1 and 2 - inventive step

5. The amendments to claim 1 of auxiliary requests 1 and 2 were made to specifically address the concerns of the board in respect of Article 123(2) EPC expressed in the communication sent in preparation of oral proceedings (point 2.2). As explained in the letter of the appellant dated 11 March 2019 (page 3, third paragraph), the reaction and purification conditions incorporated into the respective claims are standard measures and are not critical to the subject-matter of the underlying invention. Accordingly, during oral proceedings, the appellant did not defend these requests in the context of inventive step.

5.1 Consequently, the board concludes that the features added to the respective claim 1 of auxiliary requests 1 and 2 are standard measures and cannot form the basis

for acknowledging inventive step of the claimed subject-matter.

5.2 It follows that the conclusions provided for claim 1 of the main request apply *mutatis mutandis* to the subject-matter of the respective claim 1 of these requests, which consequently lack inventive step under Article 56 EPC.

Auxiliary requests 3, 4 and 5 - inventive step

6. The respective claim 1 of each of these requests differ from claim 1 of the main request and auxiliary requests 1 and 2 respectively in the limitation of the definition of PG^1 and PG^2 to t-butyldimethylsilyl (TBS).

Since the conclusions of the board with respect to the respective claim 1 of the main request and auxiliary requests 1 and 2 are directed to the specific embodiment wherein groups PG^1 and PG^2 are TBS, the same conclusions apply *mutatis mutandis* to the respective claim 1 of each of these requests, which consequently lack inventive step under Article 56 EPC.

7. Since the claimed subject-matter of all requests lack inventive step starting from D2/D2a as closest prior art, there is no need for the board to assess inventive step starting from the disclosure in D1 as closest prior art.

Conclusions

8. None of the appellant's requests meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. Maremonti

Decision electronically authenticated