FRENCH REPUBLIC
IN THE NAME OF THE FRENCH PEOPLE

***COUR D'APPEL* OF PARIS**
Division 5 – Chamber 2

DECISION DATED 13 JANUARY 2012

(No. 008, 19 pages)

Docket number: **10/17727.**

Decision referred to the *Cour d'Appel*: Judgment dated 02 July 2010 – *Tribunal de Grande Instance* of PARIS, 3rd Chamber 3rd Section – Docket No. 08/16206.

APPELLANT:

SANDOZ SAS
Represented by its legal representatives
Having its registered office at 49 avenue Georges Pompidou 92300 LEVALLOIS PERRET,

Represented by SCP MONIN – d'AURIAC, *Avoués* before the *Cour d'Appel*
Assisted by Mr Jacques ARMENGAUD and by Ms Elisabeth BERTHET-MAILLOLS, of SCP ARMENGAUD-GUERLAIN, attorneys-at-law, members of the PARIS Bar, courthouse box: W07.

RESPONDENT:

ELI LILLY AND COMPANY, a company governed by the laws of the United States of America
Represented by its legal representatives
Having its registered office at Lilly Corporate Center – Indianapolis – INDIANA 46285 (UNITED STATES),

Represented by SCP FISSELIER – CHILOUX – BOULAY, *Avoués* before the *Cour d'Appel*,
Assisted by Mr Dominique MENARD, pleading for the law firm HOGAN LOVELLS, attorneys-at-law, members of the PARIS Bar, courthouse box: J033.

COMPOSITION OF THE *COUR D'APPEL*:

The case was discussed on 18 November 2011, in public hearing, before the *Cour d'Appel* composed of:

Mr Eugène LACHACINSKI, Presiding Judge,
Ms Marie-Claude APELLE, Chamber Presiding Judge,
Ms Sylvie NEROT, Judge,

who deliberated.

Court clerk during the discussion: Mr Truc Lam NGUYEN.

DECISION:
After hearing all the parties,

- pronounced publicly by making it available at the court clerk's office, the parties having been previously notified under the conditions laid down in the second subparagraph of Article 450 of the French Code of Civil Procedure;
- signed by Mr Eugène LACHACINSKI, Presiding Judge, and by Mr Truc Lam NGUYEN, court clerk, present during the pronouncement.

ELI LILLY and Company, a company governed by the laws of the United States of America, is the owner of European patent EP 0 557 303 B1[TN], filed on 21 June 1993 and published on 1st October 1997 under the title "*stereoselective glycosylation process*". This patent claims priority from twelve U.S. patent applications, six of which are dated 22 June 1992 and the six other ones are dated 7 April 1993; the French translation of this patent was published on 7 November 1997.

The object of this patent is a new production process, with improved yield, of an active ingredient called "Gemcitabine", which is a medicine used for the treatment of cancer. This medicine is marketed in France by ELI LILLY under the trade name Gemzar®.

ELI LILLY is the holder of basic patent EP 122 707 protecting Gemcitabine; in France, this patent was the subject-matter of a Supplementary Protection Certificate that expired in March 2009.

Reproaching ELI LILLY for having retained its monopoly of use arising from the patent protecting the Gemcitabine product fallen in the public domain, SANDOZ FRANCE summoned it before the *Tribunal de Grande Instance* of Paris for the revocation of the French designation of European patent EP 0 577 303 B1.

By a judgment dated 2 July 2010, the *Tribunal* dismissed SANDOZ FRANCE's claim for invalidity of the claims of European patent EP 0 577 303 and ordered it to pay the sum of 300,000 euros to ELI LILLY pursuant to Article 700 of the French Code of Civil Procedure.

[TN] The number of the European patent is erroneous. The right number is EP 0 577 303 B1.

An appeal was lodged by SANDOZ FRANCE by a declaration to the court clerk of the *Cour d'Appel* dated 1st September 2010.

Having regard to the last pleading served on 10 November 2011, in which SANDOZ FRANCE requests that the *Cour d'Appel*:

- reverse the referred judgment in all its provisions;
- hold its appeal admissible;
- revoke the French designation of patent EP 0 577 303 in all its claims;
- order the transmission of the decision to be handed down to the *Institut National de la Propriété Industrielle* (French patent office) for registration in the *Registre National des Brevets* (French patent register);
- dismiss all of ELI LILLY and Company's claims;
- order ELI LILLY and Company to pay the sum of 290,000 euros to SANDOZ FRANCE pursuant to Article 700 of the French Code of Civil Procedure and all the legal costs;

Having regard to the last pleading served on 3 November 2011, in which ELI LILLY and Company requests that the *Cour d'Appel*:

mainly:

- affirm the referred judgment in all its provisions;
- hold that claim 1 of patent EP 0 577 303 protects an invention involving an inventive step;
- hold that the other claims of patent EP 0 577 303, depending on claim 1, protect an invention involving an inventive step;
- hold that the French designation of patent EP 0 577 303 is valid and dismiss all of SANDOZ FRANCE's claims;

in the alternative:

- hold that claim 1 of patent EP 0 577 303 will be limited by combining the latter with claim 11;
- order SANDOZ FRANCE to reimburse it for all the costs and fees that it had to incur to enforce and defend its rights pursuant to the provisions of Article 700 of the French Code of Civil Procedure;
- add an additional compensation of 204,000 euros to the sum of 300,000 euros granted on this head of claim with regard to the non-recoverable first-instance costs;
- order SANDOZ to pay the legal costs.

WHEREUPON:

1 – The subject-matter of the invention:

Patent EP 0 577 303 is a stereoselective glycosylation process for preparing 2'-deoxy-2,2-difluoro-beta-nucleosides, which include Gemcitabine.

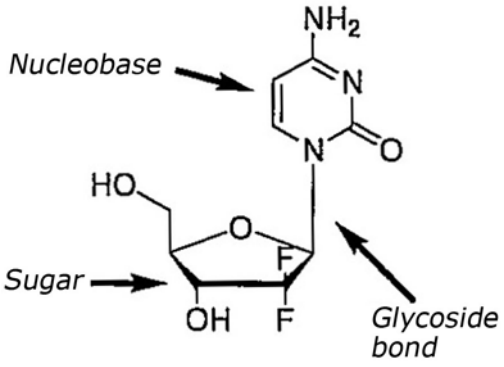
The sugar composing these nucleosides comprises one carbon atom at position 2, which carries no oxygen atom (sugar is 2-deoxy), but carries 2 fluorine atoms (2,2-difluoro).

The subject-matter of this patent is the production of Gemcitabine, which is an antiviral and antineoplastic medicine; Gemcitabine is part of the family of chemical compounds called **nucleosides**.

The parties to the dispute explain that nucleosides are basic constituting elements of RiboNucleic Acid (RNA) and DeoxyriboNucleic Acid (DNA), DNA and RNA being constituted of a succession of four nucleosides.

These nucleosides are themselves composed of two chemical parts: a sugar bound to a second part called nucleobase through a glycosidic bond.

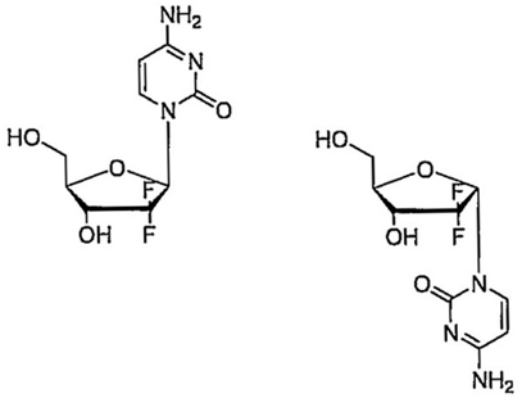
A nucleoside can have two isomers depending on the orientation in space of the glycosidic bond: one of these isomers is the one where the nucleobase part is situated above the sugar part, as the example herebelow reveals in the case of Gemcitabine, the other is the one in which the nucleic base is situated below the sugar.



Gemcitabine

These two isomers are:

- **the beta-anomer**, which presents a therapeutic effect and which constitutes Gemcitabine;
- **the alpha-anomer**, which has no therapeutic effect, anomers only differing from one another, as indicated hereabove, by the way in which the atoms are orientated in space.



beta-anomer alpha-anomer

During the glycosylation reaction, the resulting nucleoside will consequently comprise a mixture of the alpha-anomer and beta-anomer in variable proportions.

From an alpha-anomer enriched starting product, in the present case a sulfonate leaving group also called sulfonyloxy or mesilate, one achieves a beta-anomer enriched final product by the effect of an anomeric inversion.

This glycosylation reaction is performed by means of a nucleophilic substitution (SN) reaction, which can only be of two types: S_N1 (first-order nucleophilic substitution) or S_N2 (second-order nucleophilic substitution).

Accordingly, the subject-matter of the invention consists in a process intended to produce, with a high yield (page 1, line 11 of the French translation of the patent[TN]), a mixture containing more Gemcitabine with a beta-anomer proportion greater than the alpha-anomer proportion, with an alpha-to-beta ratio greater than 1:1.

2 – <u>The solution recommended by patent EP 0 577 303:</u>

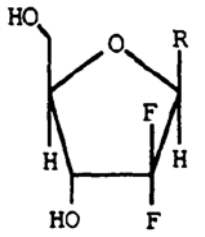
To solve the problem facing the person skilled in the art at the priority date, the invention proposes, according to ELI LILLY, a synthesis process that had never yet been applied to nucleosides.

The essential characteristics of this process are to use a starting product, which is hard to obtain considering the 2 fluorine atoms, which include a mesilate leaving group, which reacts with another compound, a nucleobase, and to implement an S_N2 mechanism.

ELI LILLY maintains that this process consequently leads to the production of Gemcitabine in an anomeric ratio that can be far greater than 1:1 as proved by the 25 examples of synthesis of Gemcitabine, which show a reaction yield higher than the best yield obtained in the prior art document.

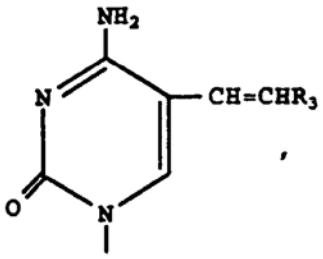
3 – <u>Claim 1 reads as follows:</u>

A process for preparing a beta-anomer enriched nucleoside of the formula



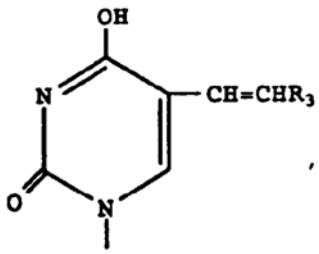
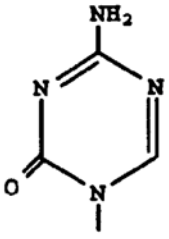
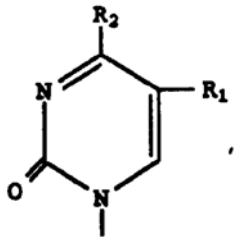
(I);

wherein R is a nucleobase selected from the group consisting of

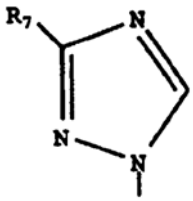


,

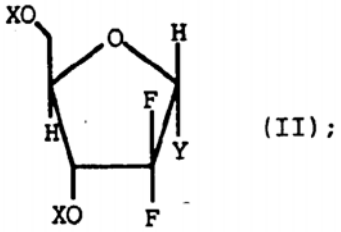
[TN] All the references to the patent refer to the French translation of the European patent.

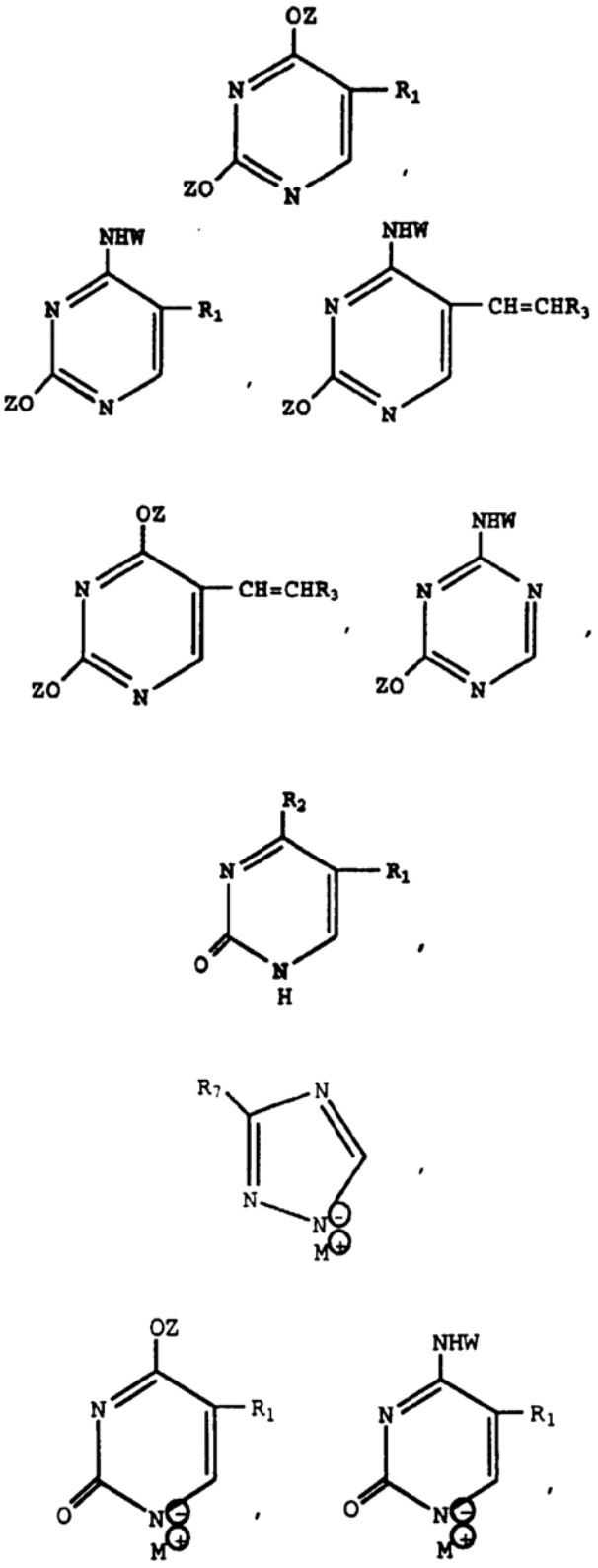
and



wherein R_1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl and halo; R_2 is selected from the group consisting of hydroxyl, halo, azido, primary amino and secondary amino; R_3 is selected from the group consisting of hydrogen, alkyl, and halo; R_7 is selected from the group consisting of hydrogen, halo, cyano, alkyl, alkoxy, alkoxycarbonyl, thioalkyl, thiocarboxamido and carboxamido comprising conducting the S_N2 displacement optionally in a suitable solvent of a sulfonyloxy group (Y) from an alpha-anomer enriched carbohydrate of the formula


(II);

wherein X is independently selected from hydroxyl protecting group, with at least a molar equivalent of a nucleobase (R'') selected from the group consisting of



wherein R_1 through R_7 and Q are as defined above and Z is a hydroxyl protecting group; W is an amino protecting group and M^+ is a cation; and deblocking to form the compound of the formula (I).

4 – <u>The state of the art at the priority date of the patent:</u>

The parties to the dispute agree that the publications disseminated by Dr Henry G. Hertel and Dr T.S. Chou in 1987 and 1991, respectively, i.e. earlier than the priority date of 22 June 1992, disclosed a process of Gemcitabine synthesis, which enabled an alpha-to-beta anomeric ratio of 1:4 for the first

researcher, and an alpha-to-beta anomeric ratio of 1:1 for the second researcher, both selecting a sulfonyloxy leaving group such as a mesilate group, and implementing a synthesis mechanism according to the S_N1 process.

SANDOZ also relies on the Howell document to dispute the inventive step of the patent.

Contrary to the arguments that it presented before the first-instance judges, SANDOZ considered before the *Cour d'Appel* that it should focus its explanations on only three documents analysed either separately or in combination.

4 – 1 The Chou and Hertel documents

The document by T.S. Chou (Stereospecific Synthesis of 2-deoxy-2,2-difluororibonolactone and its use in the preparation of 2'-deoxy-2',2'-difluoro-beta-D-ribofuranosyl Pyrimidine Nucleosides: the key role of selective crystallization, SYNTHESIS 1992, 565-570) constitutes, according to the opposing parties, one of the documents of the closest prior art, the other document being the one by L.W Hertel (Synthesis of 2-deoxy-2,2-difluoro-D-ribose and 2-deoxy-2',2'-difluoro-D-ribofuranosyl Nucleosides, Journal of Organic Chemistry 53 (1988) 2406-2409).

SANDOZ maintains that the Chou document describes the production of 2'-deoxy-2',2'-difluoronucleoside of a formula identical to that of final nucleoside I of the disputed patent by the reaction of a sulfonate (or sulfonyloxy) group of a carbohydrate, as separating group, this carbohydrate being of a formula identical to that of the formula-II carbohydrate of the disputed patent with a nucleobase identical to that of the patent and deblocking to form 2'-deoxy-2',2'-difluoronucleoside.

It adds that this prior art document uses the same non-polar solvents and the same temperature as the patented process.

It indicates that, with the help of two experiments, a final nucleoside was obtained, presenting a beta-to-alpha anomeric ratio qualified as approximately equal to 1:1 corresponding to the lowest ratios claimed by the patent.

It specifies that the Chou document merely expresses a hypothesis by casting doubts on the S_N1/S_N2 mechanism at issue, while specifying that the S_N1 mechanism is predominant, which enables the person skilled in the art to deduce that the accessory mechanism can only be the S_N2 mechanism since there are only two nucleophilic substitution mechanisms and that the Chou document describes the synthesis of the highly pure, stable alpha-anomer enriched starting carbohydrate II by a crystallisation process that enables the preparation of industrial-scale quantities.

SANDOZ concludes that the invention protected by the patent only differs from the Chou publication through two elements:

- the beta-to-alpha anomeric ratio is defined as "approximately equal" to 1:1 (beta-alpha ratio 1:1) in the publication while the patent provides for a beta-anomer in excess of the alpha-anomer (beta-alpha ratio 1:1);
- the prior art process follows a predominant S_N1 path while the patent includes an S_N2 path.

ELI LILLY indicates that the Chou process leads to obtaining a mixture containing as much alpha-

anomer as beta-anomer, that this synthesis process follows an S_N1 reaction mechanism since it achieves the same alpha-beta anomeric ratio regardless of the anomeric ratio of the starting material used to prepare Gemcitabine and that several experiments show that, except for a very low transformation of the starting products, no reaction mechanism occurs other than the S_N1 mechanism, which should be considered as predominant with respect to the other tested mechanisms and enables a beta-alpha ratio of 1:1, which constitutes significant improvement with respect to the prior art.

It maintains that the Chou prior art document does not disclose an S_N2 reaction insofar as only a purely S_N1 reaction is mentioned, which the experimental evidence furthermore demonstrated.

It maintains that, contrary to SANDOZ's allegations, there are frequently pure S_N1 and S_N2 reactions, that the prior art document describes a pure S_N1 reaction and certainly not an S_N2 reaction like in the patent, which Professor Vorbrüggen's explanations confirm; it adds that SANDOZ, which alleges that the prior art documents applied the S_N2 mechanism, had to experimentally demonstrate this assertion; it reproaches SANDOZ for not explaining itself on the modifications that should be made to the S_N2 reaction to improve the prior art anomeric ratio.

4 – 2 The Howell document

According to SANDOZ, the Howell document describes the reaction of an alpha-anomer enriched carbohydrate with corresponding nucleobases in an S_N2 reaction, which causes the formation of nucleoside presenting an excess of beta-anomer.

It explains that the aim sought in the Howell process is the preferential formation of beta-anomer from an alpha-anomer through an S_N2, that the final nucleoside is extremely close to that which is protected by the patent so that the person skilled in the art would be interested in this document to obtain Gemcitabine and that the (alpha-anomer) starting carbohydrate is identical to that of the process protected by the patent, except for the presence of a single fluorine atom in the Howell products whereas there are two fluorine atoms in the patent and that the leaving group of the starting products is bromine in the Howell document while it is sulfonyloxy or sulfonate or mesilate in the disputed patent.

SANDOZ concludes that the Howell document taught the person skilled in the art that he could obtain beta-anomers in excess from an alpha-anomer enriched product by using the S_N2 mechanism; the person skilled in the art knowing the formula of Gemcitabine and knowing that these compounds are bifluorated and that the additional fluorine atom, which brought higher stability to the product, would have compensated this stability by using a starting product carrying a leaving group such as sulfonate, stronger than bromine.

ELI LILLY maintains, contrary to the appellant's allegations, that the person skilled in the art knew from the aforementioned prior art that he could not obtain an S_N2 reaction with a mesilate leaving group, but only an S_N1 reaction and that if he had wanted to draw a teaching from the Howell document, he would have replaced the mesilate leaving group by a halogen.

It concludes that, at the priority date of the patent application, the person skilled in the art could not imagine a process leading to an anomeric ratio and yield as interesting as the one described in the patent.

It also reproaches SANDOZ for not having produced in court a single experiment in support of its assertions and, in particular, on the fact that the Chou and Hertel documents allegedly relate to an S_N2 reaction and for having followed an *ex post facto* analysis to achieve the subject-matter of claim 1.

5 – <u>On the technical problem to be solved:</u>

As ELI LILLY maintains, it is up to SANDOZ to demonstrate that, at the priority date of the patent, the person skilled in the art would have found elements in the aforementioned state of the art that would have encouraged him, with a reasonable hope of success, to achieve the invention without himself engaging in any inventive step.

As it results from the constant case law of the Boards of Appeal of the European Patent Office, the issue is not one of knowing whether the person skilled in the art would have been able to carry out the invention by modifying the state of the art, but rather **whether he would have acted** in the hopes of achieving the advantages that were actually obtained considering the technical problem that was posed because the state of the art contained suggestions along this line (see: Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, page 201 I.D.5, "could-would approach" and *ex post facto* analysis[TN]).

The person skilled in the art should be a specialist in organic chemistry, more particularly in the field of sugar chemistry, and still more particularly in that of the stereoselective synthesis of nucleosides.

He must possess strong basic general knowledge in the aforementioned specialities without however being a researcher who devotes his activities to cutting-edge research.

According to Professor Boons (paragraph 78 Factors which favour S_N1 or S_N2), a specialist in nucleoside chemistry and in glycosylation, the parameters known to the person skilled in the art at the filing date of the patent application, which make it possible to favour either one of the nucleophilic reactions, are:

- steric effects, a large volume of occupation in space favours an S_N1 reaction while a low occupation favours the S_N2 mechanism;
- the electronic effects of the electrophile, the stabilisation of the carbocation favouring the S_N1 mechanism;
- the effects of the solvent that influence the equilibrium between the S_N1 and S_N2 reactions;
- the ability of the leaving group, its increase will cause an increase in the S_N2 reaction rate, but to a lower extent than the S_N1 reaction rate;
- the nucleophile concentration, the reaction rate of an S_N2 can be increased by increasing the nucleophile concentration while the reaction rate of an S_N1 is independent of the nucleophile concentration;
- the increase in nucleophilicity by making it an anion will favour the S_N2 reaction.

However, he adds that, despite the knowledge of these parameters, the person skilled in the art knows that it is still not possible to provide for the conditions that will lead to an S_N2-type reaction and that the glycosylation reactions generally follow an S_N1 mechanism even if they can, more rarely, follow an S_N2 mechanism.

He specifies that the conditions favouring the production of one anomer as opposed to another should

[TN] Case Law of the Boards of Appeal of the European Patent Office, 6th edition 2010, page 201 I.D.5, "could-would approach" and *ex post facto* analysis: "*So the point is not whether the skilled person could have arrived at the invention by modifying the prior art, but rather whether, in expectation of the advantages actually achieved (i.e. in the light of the technical problem addressed), he would have done so because of promptings in the prior art (T 219/87, T 455/94, T 414/98).*"

be determined in an empirical way and cannot be predicted.

To synthesize nucleosides, he indicates that a glycosylation reaction is implemented by using leaving groups among halides such as iodine, bromine, chlorine and fluorine or the O-acetyl groups.

He also maintains that if sulfonates such as mesilate were used as leaving groups in organic synthesis chemistry, the person skilled in the art would not have used sulfonates and, in particular, mesilate as leaving group in the nucleoside synthesis chemistry.

According to Professor Vorbrüggen, also a specialist in nucleosides, the person skilled in the art would not have been encouraged to use the 1-sulfonyloxy leaving groups of the patent, which, according to him, present an unusual characteristic, namely the traditional halogen leaving groups such as bromine cannot be transposed to the leaving groups provided for in the patent.

On the contrary, Professor Beau considers that evidence is found in Hertel patent U.S. 4,526,988 of 1985, Chou patent EP 0 306 190 of 1989 and the articles by Hertel, Wheeler and Chou published in 1988, 1991 and 1992, respectively, that the use of sulfonylated derivatives at the anomeric position as starting products of activated sugars that can be used in the glycosylation reactions was a perfectly obvious solution considering the experience of the researchers of this centre.

ELI LILLY, which acknowledges that the researchers mentioned by Professor Beau were working on sugars including sulfonyloxy as leaving groups, maintains, however, that no one achieved the result of the patent by the prior work; it explains that Gemcitabine is obtained from specific sugars that do not include an oxygen atom at the C-2 position and that the person skilled in the art, in the field of nucleoside synthesis, had problems with almost all the syntheses of 2'-deoxynucleosides and almost always obtained mixtures of (beta-anomer) beta-nucleosides with (alpha-anomer) alpha-nucleoside.

It quotes Professor Vorbrüggen's findings, according to which the processes for preparing 2-deoxynucleosides of the patent are complex, unpredictable with the knowledge acquired from the synthesis of other types of nucleosides, could hardly be said to lead to high yield and do not enable a control of the beta-to-alpha ratio.

6 – <u>On the inventive step of claim 1:</u>

Article 84 of the European Patent Convention sets forth that the claims define the subject-matter for which protection is sought and that they should be clear and concise and be supported by the description.

To achieve **a beta-anomer enriched nucleoside**, claim 1 of the patent requires to produce **an alpha-anomer enriched starting carbohydrate**, then from the latter, to carry out **an S_N2-type nucleophilic substitution** of a **sulfonyloxy** group to perform **deblocking** to achieve a beta-anomer enriched nucleoside.

The invention as contemplated in claim 1 of the patent is constituted only by these operations, the notion of yield relied on by the company holding the patent not being directly claimed *per se*, but is only mentioned in the description, especially from the definition of the phrase "anomer-enriched",

Which, alone or in combination, designates an anomeric mixture, in which the ratio of a given anomer is greater than 1:1 and encompasses a substantially pure anomer (page 6, lines 7 to 10) or also in the conclusion on page 25, lines 22 to 24, where it is indicated that "*In accordance with the present process, beta-anomer enriched nucleosides are prepared in an alpha-to-beta anomer ratio greater than 1:1 to about 1:9*".

In summary, any product in which the beta-to-alpha anomeric ratio is greater than 1:1 falls within the scope of claim 1.

The lactol starting materials intended to be used in the preparation of the alpha-anomer enriched carbohydrate of formula II used in the glycosylation process are known in the art according to the patent and can be easily synthesised through classical processes usually used by the person skilled in the art (page 7, lines 4 to 8).

This characteristic does not in itself involve an inventive step.

ELI LILLY explains, by reiterating Professor Boons' statements (paragraphs 49 to 67 S_N1 reaction and 68 to 77 S_N2 reaction), that an S_N1 reaction is performed in two steps; a first step being slower than the second one, this is the rupture of the bond between the electrophile and the leaving group to form a positively charged carbon ion, this is carbocation; a second step, in which the nucleophile attacks carbocation; the rate of an S_N1 reaction is only dependent on the electrophile concentration and is independent of the nucleophile concentration.

The appellant adds that if the starting product of the reaction is an alpha-anomer, an S_N1 reaction will necessarily lead to a mixture of alpha-anomer and beta-anomer of the final product with 50% of alpha-anomer and 50% of beta-anomer, i.e. a 1:1 ratio and conversely, to conclude then that there is no interest in using an alpha-anomer enriched starting product since the S_N1 reaction will always lead to a mixture of alpha-anomer and beta-anomer with a 1:1 ratio.

Unlike the S_N1 reaction, the S_N2 reaction is performed in a single step and keeps the stereochemistry of the chiral centre, but with an inversion of the stereochemistry; thus, with a pure alpha-anomer as a starting product, the final product will be a pure beta-anomer.

ELI LILLY explains that if some reactions present characteristics that come within the S_N1 and S_N2 reactions, some others are pure S_N1 reactions or pure S_N2 reactions.

According to SANDOZ, as claim 1 only mentions a nucleophilic substitution of the S_N2 type with no further precision, one should consider that the claim not only considers a glycosylation reaction according to an S_N2 mechanism, but also a reaction that can also include some S_N1 characteristics.

According to it, this substitution is precisely mentioned in the description on page 6, lines 28 to 29 in a dubitative form (*It is believed that the glycosylation reaction proceeds via SN2 displacement*) and is mentioned again on page 8, lines 1 to 5, when it is written that one can have an alpha-anomer enriched carbohydrate of formula III or IV reacted under conditions of nucleophilic substitution that favour the inversion (i.e. of the S_N2 type) to obtain the beta-anomer enriched nucleosides of formula I.

In addition, it maintains that in no place does the description indicate why the inventor "believes"

that the glycosylation reaction is performed by this path and not by another, which would be the S_N1 path, while claim 1 essentially considers the S_N2 nucleophilic substitution, as ELI LILLY, in addition, specifies in its pleading when it indicates that, for the first time, Gemcitabine could be obtained through an S_N2 reaction and that it is a fundamental difference with the prior art, in particular with the Hertel and Chou prior art documents, which obtain Gemcitabine according to an S_N1 reaction.

It criticises the patent in that none of the examples mentioned in the description of the invention specify how and why the reaction of the nucleophilic substitution is performed in the S_N2 path.

But, ELI LILLY, quoting the books by Francis A. Carey (Advanced Organic Chemistry – Plenum Press New York and London – First Printing April 1990, pages 257 to 270 and 271) and by Jerry March (Advanced Organic Chemistry Reactions, mechanisms and structure – Fourth Edition – John Wiley and Sons 1992, pages 294 to 307 and 339 to 361), shows that the person skilled in the art knew of the existence of reactions that are only submitted to a pure S_N1 mechanism or to a pure S_N2 mechanism, even though there are mixed situations that cannot be qualified as S_N1 or S_N2.

6-1 Inventive step over the Hertel document?

The Hertel document differs from the claimed invention in that the starting product is a sugar mesilate in a beta-to-alpha anomeric ratio of 1:1, the protecting groups of the sugar are different, the implemented mechanism is of the S_N1 type and not of the S_N2 type and the alpha-to-beta anomeric ratio is of 1:4 rather than greater than 1:1.

SANDOZ maintains that if there is an inventive step, this should be between the Hertel process, which led to an alpha-to-beta anomeric ratio of 4:1 and the Chou document, but certainly not between the latter and claim 1 of the patent, which only leads to poor improvement of the result since this increases from approximately 1:1 to greater than 1:1, which could be 1.1:1.

According to it, the person skilled in the art would not find it hard to overcome this difficulty, which it deems minor.

But, ELI LILLY relevantly replies that the person skilled in the art, who was aware of the Hertel document and who wanted to improve the synthesis process of Gemcitabine, would have begun by modifying the protecting groups of the starting sugar, which, in addition, was done in the Chou document with only an anomeric ratio of 1:1, as a result.

Thus, it appears that the person skilled in the art would not have found, in the Hertel document, any incentive to achieve the subject-matter of claim 1 of the disputed patent without himself engaging in any inventive step.

6-2 Inventive step over the Chou document?

To demonstrate that claim 1 lacks inventive step, SANDOZ maintains that the person skilled in the art would have taken into consideration this document published a few years before the Hertel document, which describes the production of 2'-deoxy-2',2'-difluoronucleoside of a formula identical to that of the final nucleoside I of the disputed patent, by the reaction of a sulfonate or

sulfonyloxy group of a carbohydrate as a separating group, this carbohydrate being of a formula identical to that of the carbohydrate of formula II of the disputed patent, with a nucleobase which is also identical to that of the patent, and a deblocking to achieve the final product.

It adds that this document describes a beta-to-alpha anomeric ratio "approximately" equal to 1:1, which corresponds to what is claimed, that the hypothesis of a "predominant" S_N1 reaction makes an S_N2 path possible and that the synthesis of the alpha-anomer enriched starting carbohydrate is obtained by a satisfactory crystallisation process.

But, as ELI LILLY rightly maintains, claim 1 of the patent contains fundamental differences with the cited document, which considers a reaction mechanism of the S_N1 type and not of the S_N2 type, which does not relate to an alpha-anomer enriched starting material by a stereoselective process and which does not disclose a final product, which is not a beta-anomer enriched nucleoside, but an alpha/beta mixture in a 1:1 ratio.

From this document, to achieve the invention, the person skilled in the art should first enrich the starting sugar mesilate to distinguish it from the alpha/beta mixture in a 1:1 ratio, then perform glycosylation by the S_N2 path to obtain a beta-anomer enriched nucleoside of the Gemcitabine type.

Likewise and contrary to SANDOZ's contentions, the Chou document provides the person skilled in the art with no path other than the S_N1 one, as the word "predominant" on which it relies to maintain that there would allegedly be a mechanism accessory to the S_N1 path – in a minor way, according to it – should be understood as applying to reactions that can affect the starting products and the final products and not the S_N1 reaction mechanism in itself.

SANDOZ refutes the experiments performed in the Chou document that tend to prove the S_N1 mechanism, adding that "*these experiments are not likely to prove anything since rigorous mechanistic studies (and more particularly kinetic studies) would have enabled evidence thereof. But such studies would have not been performed*".

But, contrary to SANDOZ's argument, it was not up to the company holding the patent, but to SANDOZ, on which the burden of prove is placed, to demonstrate by an experimental study, which it did not performed or produced in court, that the selected path is not a pure S_N1 path and that an S_N2 mechanism occurs in parallel in a minority way.

SANDOZ also maintains that the ratio of "approximately" 1:1 described in the Chou document cannot be distinguished from a ratio slightly greater than 1:1 protected by the disputed patent.

But the Chou document provides the person skilled in the art with no indication for concluding that the beta-to-alpha anomeric ratio is allegedly greater than 1:1, the adverb "approximately" meaning that the beta-to-alpha ratio is close to 1:1 without going so far as to exceed it.

Thus, from the Chou document that implements a pure S_N1 reaction, the person skilled in the art would not be encouraged to apply reaction conditions proper to an S_N2 reaction, which is considered by specialists as a rare reaction, and if this idea came to him, he would not have known which conditions to implement to obtain an anomeric ratio greater than 1:1.

In fact, and this is not disputed by SANDOZ, the person skilled in the art did not have at his disposal, at the priority date, a stereoselective synthesis process to obtain an alpha-anomer enriched starting product – a sugar mesilate –, the processes used before to achieve it (separation by crystallisation for example) being long, complex and costly, according to the experts.

Consequently, the first-instance judges relevantly acknowledged that by using a stereoselective process leading directly to an enrichment in starting carbohydrates in the form of alpha-anomer, which it patented the same day under No. 0 577 302, ELI LILLY could produce a starting product in the form of alpha-anomer, which enabled it to exploit the S_N2 path. At the priority date of the patent, the person skilled in the art, who did not know this process, was not encouraged to follow the S_N2 path.

Claim 1 implements a sulfonyloxy leaving group like the Chou document, which achieves Gemcitabine by the S_N1 path.

From this information, the person skilled in the art would not have been encouraged to use a mesilate leaving group to obtain Gemcitabine by the S_N2 path or, if he had wanted to choose this path, he would have selected a leaving group other than mesilate, a halogenate group, bromine or chlorine for example.

Thus, it appears that the person skilled in the art would not have found in the Chou document a real incentive to achieve the subject-matter of claim 1 of the disputed patent without himself engaging in any inventive step.

6-3 Inventive step over the Howell document?

SANDOZ maintains that the object of the Howell process, like for the disputed patent, is the preferential formation of beta-anomer from an identical alpha-anomer starting carbohydrate through an S_N2, the final nucleoside being extremely close to the claimed one.

The parties acknowledge that there are, however, between the Howell document and the patent, at least two differences that relate to the alpha-anomer enriched starting carbohydrate; the carbohydrate in the Howell document has a single fluorine atom at the C-2 position while, in the patent, it has two fluorine atoms at that position; the bromine atom constitutes the leaving group in the prior art document while a sulfonyloxy or sulfonate or mesilate is part of the starting product in the claimed invention.

To conclude that there is great similarity between the groups, the appellant indicates that the examples of the description mention halogens such as bromine (example 51), but also sulfonyloxy.

It concludes that the person skilled in the art would have adapted the Howell reaction since, knowing the formula of Gemcitabine and knowing that these compounds were bifluorated, he knew that this additional fluorine atom involved better stability of Gemcitabine and that it was preferable, in order to compensate this stability, to use a starting product carrying a stronger starting group such as sulfonate rather than bromine.

To compare claim 1 of the patent to the Howell document, it also relies on the patent application which originally provided for the possibility of having a monofluorated sugar as the starting product.

But, as ELI LILLY maintains, the person skilled in the art would not find the incentive information to achieve claim 1 of the patent in the Howell document, it being observed in addition that this document relates to the nucleoside synthesis by the S_N2 path, but does however not apply to Gemcitabine.

First, it is immaterial that the patent application originally made reference to a monofluroated sugar since the invention relates to a beta-anomer enriched nucleoside comprising two fluorine atoms on the sugar according to claim 1 of the patent.

Secondly, from Professor Vorbrüggen's statements, which are corroborated by those of Professor Boons, the person skilled in the art knows that the presence of a second fluorine atom modifies the conformation of the sugar nucleus and influences thereby the anomeric result of the glycosylation.

Thirdly, SANDOZ cannot rely on example 51 of the description, in which bromine appears as a leaving group, as the patent and its contents do not form part of the prior art.

Fourthly, the person skilled in the art knew that the sulfonyloxy groups, including mesilate, were excellent leaving groups, better than halogens such as bromine or chlorine; he knew also that their use led to an S_N1 reaction, which did not encourage him to use them since he knew that they did not make it possible to obtain an S_N2 reaction.

Thus, the person skilled in the art would not have been encouraged to implement the characteristics of the Howell document and to overcome the difficulties resulting therefrom to achieve the subject-matter of claim 1 of the patent.

6-4 Inventive step over the Chou and Howell combination?

According to SANDOZ, the combination of these two documents would make it possible, even more easily than if each were considered individually, to conclude that claim 1 of the patent lacks inventive step.

To obtain an excess of beta-anomer, SANDOZ, which bases its argument on Professor Beau's report, alleges that the person skilled in the art would have been encouraged to apply the S_N2 reaction described in the Howell document to the Chou starting products to achieve the claimed invention (page 16, antepenultimate paragraph of Professor Beau's report: "*Thus, the person skilled in the art would have examined the Chou (Synthesis "S_N1") and Howell ("S_N2") documents in combination and thought that, to make his benzoylated substrate with two more reactive fluorine atoms and, to do what Howell describes, he would have replaced bromine in alpha by a better leaving group such as sulfonate in alpha. By taking this prior information as a guide, the person skilled in the art could have changed the reaction conditions with the aim to achieve an excess of the beta-isomer of the nucleoside*".

But, ELI LILLY, basing itself on Professor Boons' statements, relevantly replies that, as the mesilate leaving group of the Chou document is not suited to solving the technical problem of the patent, which is to obtain Gemcitabine in an anomeric ratio greater than 1:1, the person skilled in the art would have then contemplated taking the halogen leaving group taught by the Howell document, but would not have achieved the subject-matter of the claim since he would have missed the first step, which is the stereoselective production of the sugar mesilate as the starting product.

Finally, Professor Beau's assertions rest on the mere supposition that the person skilled in the art could have used the information acquired on the monofluorated derivatives to modify the conditions of the glycosylation reaction in the desired direction, but do not contain sufficient indications to explain why he would have been encouraged to implement them or if he would have done so in the hopes of finding a solution to the posed technical problem, which is to obtain a beta-anomer enriched nucleoside by using the S_N2 path from an alpha-anomer enriched carbohydrate of a defined formula.

It follows that SANDOZ does not demonstrate that the combination of the Chou and Howell documents would have enabled the person skilled in the art to achieve the subject-matter of claim 1 of the patent without himself engaging in any inventive step.

7 – <u>On claims 2 to 14:</u>

These claims are all directly or indirectly dependent of claim 1 which is inventive, therefore, they should also be considered as involving an inventive step.

8 – <u>On the insufficient disclosure:</u>

Article 83 of the European Patent Convention provides that the invention should be disclosed in the patent application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Article 138 (1) b) of the European Patent Convention sets forth that the patent is revoked by a court decision if it does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

SANDOZ maintains for the first time on appeal that the patent description does not provide all the indications necessary to the person skilled in the art to obtain Gemcitabine by an S_N2 reaction.

It adds that only precise experiments would have enabled ELI LILLY to conclude that its process actually implemented an S_N2 path and that the person skilled in the art would not be able to reproduce this characteristic since the patent does not give him the means to that end.

It reproaches the company holding the patent for having only claimed S_N2 to distinguish itself from the Chou document.

ELI LILLY did not directly express itself on this new argument in its last appeal pleading; however, it maintains that the description of the patent examples on pages 32 and 45 provides the person skilled in the art with all the means necessary to enable him to obtain Gemcitabine according to an S_N2 reaction process and that SANDOZ did not previously dispute the validity of the patent for insufficient disclosure.

If each party is responsible for proving, in accordance with the law, the facts necessary to the success of its claim, the party which maintains that the invention is not sufficiently disclosed should provide proof, on the balance of probabilities, that the person skilled in the art would be unable to carry out the invention based only on his scientific and technological knowledge, it being specified that proof should be provided beyond a reasonable doubt and that the benefit of the doubt should be given to the patent holder.

SANDOZ does not provide this proof since it only maintains that the person skilled in the art would not be able to reproduce the S_N2 characteristic as the patent does not give him the means to that end, that the experiments, which it mentions in its pleading and whose charge it places on the patent holder, were a means for it to demonstrate that the person skilled in the art, with his common general knowledge and the information leaned from the description, would have not achieved the subject-matter of the claim.

On the contrary, it should be noted that the description indicates in particular how the alpha-anomer enriched carbohydrate of formula II should be prepared according to a first low-temperature process (page 7, line 4 to page 10, line 18) or a second process called anomerization (page 10, line 25 to page 13 line 31), how the glycosylation reactions are performed (page 6, line 19 to page 7, line 3), which quantity and which type of nucleobase should be used with respect to the quantity of carbohydrate (page 14, lines 1 to 7), which solvents (page 17, lines 14 to 18) and conditions of temperature (page 8, line 3 to page 9, line 19) should be implemented, which catalysers (page 22, line 26 to page 23, line 5) and which protecting groups (page 12, line 33 to page 13, line 31) should be used.

However, mentioning the parameters known to the person skilled in the art at the filing date of the patent and quoting the statements of Professor Boons (paragraphs 78 and 79), who, even while specifying that it will not be always possible, for a given reaction, to provide the conditions that will lead to an S_N2-type reaction, also adds that to favour such an S_N2 mechanism, it is necessary to reduce the steric volume, i.e. the volume occupied in space, to act on the parameters leading to the carbocation stabilisation that favour the S_N1 path, to choose the nature of the solvent influencing the equilibrium between the S_N1 and S_N2 reactions, to increase the ability of the leaving group to increase the rate of the S_N2 reaction – the increase in the nucleophile concentration will increase the reaction rate of an S_N2.

It follows that the person skilled in the art, who knows the criteria favouring the S_N2 path will find the conditions to implement the invention in the numerous examples of the description of the patent.

In addition, it should be specified that it is reasonable to read the description and the claims with the intention of understanding them and of giving them meaning from a technical point of view rather than examining them without a constructive spirit and with the intention of finding reasons why it would not be possible to carry out the invention.

And even if some ambiguities remain in the presentation of the invention, which is not demonstrated, it would still be up to SANDOZ to demonstrate that they would prevent the person skilled in the art, despite his general technical knowledge, from carrying out the invention.

Likewise, the 58 examples mentioned in the description, which, according to SANDOZ, only show unequal and uncertain values with regard to the enrichment in beta-anomer are only used to illustrate the claims and cannot by themselves justify an insufficient disclosure.

Consequently, the description contains sufficient information to enable the person skilled in the art to carry out the invention.

9 – <u>Conclusion:</u>

The referred judgment, which dismissed SANDOZ's claim for invalidity of the claims of patent EP 0 577 303, will be affirmed in all its provisions, including those relating to Article 700 of the French Code of Civil Procedure.

10 – <u>On Article 700 of the French Code of Civil Procedure:</u>

It is unfair to let ELI LILLY bear the costs, which are not included in the recoverable legal costs and which should be set at the additional sum of 204,000 euros.

ON THESE GROUNDS

The *Cour d'Appel*

Affirms all the provisions of the judgment handed down by the *Tribunal de Grande Instance* of Paris on 2 July 2010, which dismissed SANDOZ's claim for invalidity of the claims of patent EP 0 577 303;

Dismisses all the claims lodged by SANDOZ;

Adding thereto,

Orders SANDOZ to pay the additional sum of 204,000 euros to ELI LILLY and Company on the basis of Article 700 of the French Code of Civil Procedure;

Orders SANDOZ to pay all the appeal legal costs, which will be collected under the conditions laid down in Article 699 of the French Code of Civil Procedure.

THE COURT CLERK THE PRESIDING JUDGE