

**THE PATENTS ACT 1970 (AS AMENDED)
AND THE PATENT RULES 2006**

In the matter of Section 25 (1) of the Patents Act, 1970 (as amended) and The Patent Rules 2006, Rule 55;

In the matter of the Patent Application No. 329/DELNP/2004 filed in the name of M/S Tibotec Pharmaceuticals Ltd., Ireland, on 12/02/2004, International Filing Date 06/09/2002 (PCT/EP/02/10062) Published in Patent Office Journal U/S 11(A) on 01/04/2005;

In the matter of a Representation by way of opposition U/S 25(1) filed M/S S.Majumdar and Co., Mumbai on behalf of M/S Cipla Ltd., Mumbai on 26/09/2008.

Present:

Attorneys for the opponents: Mr. S. Majumdar, Ms Amrita Majumdar, Dr. Sanchita Ganguly of M/S S.Majumdar and Co., Mumbai;

Representatives of the Opponents: Sh. M.Singh of M/S Cipla Ltd., Mumbai

Attorneys for the Applicants: Sh. Naveen Sharma, Ms Gowree Gokhale of M/S Nishit Desai Associates, Mumbai

Representative of the Applicants: no one attended from M/S Tibotec Pharmaceuticals Ltd. Their attorneys presented the arguments

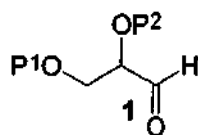
HEARING HELD ON 24/04/2009

D E C I S I O N

A representation by way of opposition u/s 25(1) was filed on 26/9/2008 by the opponents as mentioned above (herein after opponents) against the grant of patent in respect of the above mentioned patent application filed by M/s Tibotech pharmaceuticals Ltd. Israel and (herein after applicants).

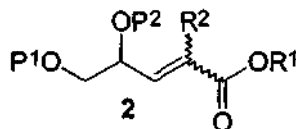
The application initially contained 33 claims. First Examination Report was issued on 13/08/2007 and in final response by the applicants on 07/07/2008 the claims were reduced to 15. The Claims are reproduced below:

1. A method for the synthesis of hexahydro-furo[2,3-b]furan-3-ol of formula (7) starting from an intermediate of formula (1) wherein P¹ and P² represent each independently a hydrogen, a hydroxy-protecting group or may together form a vicinal-diol protecting group,



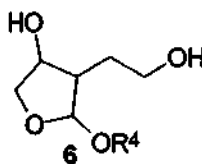
- (i) transforming said intermediate of formula (1) into a nitromethane derivative of formula (3) wherein R^1 represents alkyl, aryl or aralkyl, R^2 represents hydrogen or $C(=O)OR^3$, R^3 represents alkyl, aryl or aralkyl, or R^3 , if present, and R^1 taken together with the atoms to which they are attached may form a 6 to 8-membered cyclic group which may be optionally substituted with alkyl, aralkyl, or aryl, and, wherein said transformation of intermediate of formula (1) into derivative of formula (3) is done: - (Formula 3 depicted here pl. See from impugned Specification);

by a process comprising the steps of first condensing an intermediate of formula (1) with $CHR^2R^5-C(=O)-OR^1$ wherein R^5 represents a hydrogen, a carboxylic ester, a phosphonium salt or a phosphonate ester, resulting in an α,β -unsaturated ester of formula (2), and reacting said ester of formula (2) with nitromethane resulting in an intermediate of formula (3); or,



- by a process comprising the steps of first condensing an intermediate of formula (1) with nitromethane, resulting in an intermediate of formula (8) and secondly, reacting said intermediate of formula (8) with $CHR^2R^8-C(=O)-OR'$ wherein R^8 is hydrogen or a carboxylic ester; of formula 8; (Formula 8 depicted here pl. See from impugned Specification);

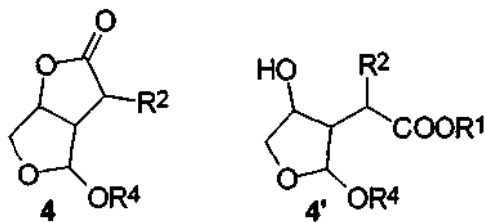
- (ii) subsequently transforming said nitromethane derivative into a tetrahydrofuran derivative of formula (6) wherein OR^4 represents an alcoholate,



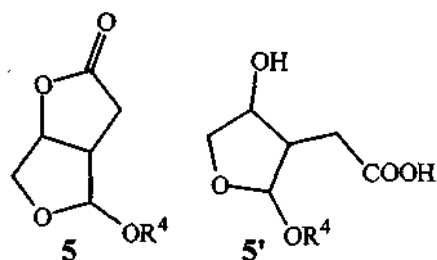
and, wherein said transformation of intermediate of formula (3) into derivative of formula (6) is done:

- by a process comprising the steps of first submitting said intermediate of formula (3) to a Nef

reaction by treating it with a base and subsequently with a strong acid resulting in a mixture of intermediates of formula (4) and (4'),

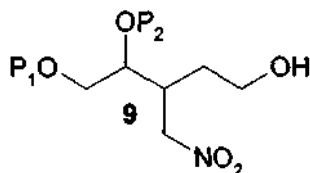


and, in case R² is different from hydrogen, decarboxylating the intermediates of formula (4) and (4') thus forming intermediates of formula (5) and (5') respectively, and then reducing intermediates of formula (4) and (4'), or intermediates of formula (5) and (5') with a suitable reducing agent resulting in intermediate of formula (6); or,



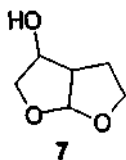
- by a process comprising the steps of first reducing intermediate of formula (3) wherein R² is

hydrogen with a suitable reducing agent, resulting in an intermediate of formula (9) and then submitting the obtained intermediate of formula (9) to a Nef reaction by treatment with a base and then with a strong acid resulting in intermediate of formula (6);

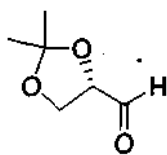


and,

(iii) then transforming the intermediate of formula (6) into hexahydro-furo[2,3-b]furan-3-ol of formula (7) by way of an intramolecular cyclisation reaction.



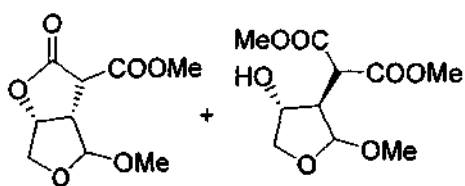
2. A method as claimed in claim 1 for the synthesis of hexahydro-furo[2,3-b]furan-3-ol of formula (7.1) starting from an intermediate of formula (1), wherein P¹ and P² taken together form an isopropylidene,



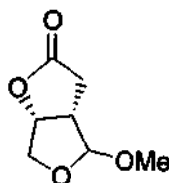
condensing said intermediate of formula (1) resulting in an intermediate of formula (2), wherein P¹ and P² taken together form an isopropylidene, R² represents -C(=O)OR³, wherein R³ is methyl and R¹ is methyl, (A structural Formula depicted here pl. See from impugned Specification);

reacting said ester of formula (2) into a nitromethane derivative of formula (3) wherein P¹ and P² taken together form an isopropylidene, R² represents -C(=O)OR³, wherein R³ is methyl, and R¹ is methyl,

transforming said intermediate of formula (3) using a base and subsequently an acid to yield intermediates of formula (4) and (4'), wherein R² represents -C(=O)OR³, wherein R³ is methyl, R¹ is methyl and R⁴ is methyl,



decarboxylating intermediates of formula (4) leading to an intermediate of formula (5), wherein R⁴ is methyl,



reducing said intermediate of formula (5) with a suitable reducing agent resulting in an intermediate of formula (6), wherein R⁴ is methyl, transforming the intermediate of formula (6) into compound 7.1 by way of intramolecular cyclization reaction. (A structural Formula 7.1 depicted here pl. See from impugned Specification);

3. A method as claimed in any one of claim 1 or 2 wherein intermediate of formula (3) is submitted to a Nef reaction using acidic quenching while keeping the temperature below -10 °C during said quenching.
4. A method as claimed in any one of claims 1 to 3 wherein the decarboxylation of intermediates of formula (4) and (4') is performed in a buffered aqueous solution.
5. A method as claimed in any one of claims 1 to 4 wherein intermediate (6) is prepared via reduction of intermediates of formula (4) and (4') or intermediates of formula (5) and (5') using lithium borohydride in tetrahydrofuran or NaBH₄ in the presence of LiCl.
6. A method as claimed in any one of claims 1 to 5 wherein the cyclisation of intermediate of formula (6) to the compound of formula (7) is performed by adding a strong acid to the reaction mixture containing intermediate of formula (6).
 7. A method as claimed in claim 6 wherein the cyclisation reaction is performed at a temperature lower than 5 °C.

8. A method as claimed in claim 7 wherein the temperature of the reaction mixture while adding the strong acid to the reaction mixture remains lower than -5°C .
9. A method as claimed in claim 1 wherein for R^8 is hydrogen or a carboxylic ester, the carboxylic ester is defined as $\text{C}(=\text{O})\text{-OR}^1$.
10. A method as claimed in any one of claims 1 to 9 wherein hexahydro-furo[2,3-b]furan-3-ol of formula (7) is isolated by adding a small excess of a tertiary amine, followed by the removal of water and removal of formed salts.
11. A method as claimed in any one of claims 1 to 10 wherein R^1 and R^3 each independently are C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl or together with the atoms to which R^1 and R^3 are attached form a 6 to 8-membered cyclic group optionally substituted with C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl, and wherein R^4 is C_{1-6} alkyl.
12. A method as claimed in any one of claims 1 to 11 wherein R^1 , R^3 and R^4 each independently are methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, *tert*-butyl or pentyl.
13. A method as claimed in any one of claims 1 to 12 wherein P^1 and P^2 together form an acid labile vicinal-diol protecting group.
14. A method as claimed in any one of claims 1 to 13 wherein P^1 and P^2 is a dialkyl methylene radical.
15. A method as claimed in any one of claims 1 and 3 to 14 wherein R^5 is hydrogen, $\text{R}^6\text{-C}^{\wedge}\text{O}$, $(\text{R}^6)_3\text{P}=\text{O}$ wherein R^6 is alkyl, aryl or aralkyl, or $(\text{R}^7\text{O})_2\text{P}(=\text{O})-$ wherein R^7 is alkyl, aryl, aralkyl.

The opposition herein below has been discussed only on the basis of the finally amended 15 claims.

The filing of representation and all opposition related activities was completed by both the parties within the prescribed time limits of the Patent Act 1970 (as amended and Patent rules 2006).

The grounds of opposition finally on the day of hearing relied upon by the opponents are as under:

- (i) The impugned invention is obvious and lack inventive step; Section 25[1(e)]
- (ii) the impugned invention is not an invention and is not patentable. Section 25[1(f)]

Discussion on the grounds of Opposition:

(1) The impugned invention is obvious and lack inventive step; Section

25[1(f)]:-

To establish the ground of 25[1(e)] the opponent relied on following prior art citations and decisions of various authorities.

Exhibit 1- The logic of chemical synthesis: multistep synthesis of complex carbogenic molecules

Lecture note of Dr. E.J. Corey published in 1990

Exhibit 2- Organic Name Reactions

Knoevenagel Condensation; Knoevenagel Ber. 31, 2596(1898); Doebner, Ber. 33, 2140 (1900)

Exhibit 3- Organic Name Reactions; Horner reaction; Horner-Wadsworth-Emmons Reaction

U. Schollk08f, Ber, 87, 1318(1954) G.witting, W. Hang, ibid 88, 1654(1956)

Exhibit 4- Organic Name Reactions; Nef Reaction; J.U. Nef. Ann. 280, 263(1894)

Exhibit 5- WO94/26749 dated 24/11/94

Decisions

- (i) EPO board of Appeals- Case No. T 1034/01-dt.-29/01/2004
- (ii) EPO board of Appeals- Case No. T1067/00-dt.-26/6/2003

- (iii) EPO board of Appeals- Case No. T0452/91-dt.-5/07/1995
- (iv) EPO board of Appeals- Case No. T1059/01-dt.-26/11/2003
- (v) EPO board of Appeals- Case No. T0630/03-dt.-11/05/2006
- (vi) EPO board of Appeals- Case No. T0565/00-dt.-14/03/2003
- (vii) EPO board of Appeals- Case No. T0369/94-dt.-3/12/1996
- (viii) EPO board of Appeals- Case No. T 1116/98-dt.-30/06/2004
- (ix) EPO board of Appeals- Case No. T 0558/00-dt.-18/02/2004
- (x) US Court of Appeals For the Federal circuit 2006 1261-Pfizer Inc. Vs. Apotex Inc.
- (xi) In re John A. Durden, Jr. And Arthur P. Kurtz, Jr. 763 F.2d 1406; 226 U.S.P.Q.359

The impugned invention relates to a process for synthesis of hexahydro Furo[2,3,b]Furan-3-ol. The aforesaid product is a pharmacological moiety present in antiretroviral protease inhibitors and is admittedly known in the art.

The impugned invention has solved the problem of scale up and racemisation of the final product as prepared by the known methods. Two processes on page 2 of impugned specification has been given. However at best of all prior known process a maximum yield of 50% of the desired enantiomer of the above mentioned compound could be obtained. I agree to the opponents that the main object of the impugned invention are as under:-

- (i) To provide improved method for production of hexahydro-furo (2,3-b) furan-3 ol when compared to the prior methods vis a vis the disadvantages of the art known methods;
- (ii) To provide a method amenable for Industrial Scale up;
- (iii) Controlling the stereochemistry of Intermediates and final product;
- (iv) Increasing Enantiomeric yield greater than to that obtained using art known methods;
- (v) Using readily and abundantly available starting material and reagents.

It may be observed from page 11, 12 and claims of the impugned specification that the claimed process comprises of the following steps:-

- (i) O-glyceraldehyde of formula I is converted to formula 3 (Intermediates of formula 2 or 8 are formed in between);
- (ii) Compound of formula 3 is converted to the compound of formula 6 and the intermediates of formula 4 and 4' and/or 5 and 5' or 9 is formed during reactions;
- (iii) Compound of formula 6 is cyclised to produce hexahydro-furo(2, 3-b) furan-3-ol.

It has been admitted on page 11 of impugned specification that enantio selective and recemic version of synthesis of glyceraldehydes are known in the art. The p1 and p2 of formula 1 forms together preferably a vicinal diol group which is known in the literature not to develop any additional stereogenic centre thereby controlling the stereochemistry of the product as claimed in claim 1.

The arguments of the opponent that in view of applicant description on page 12 and 14 of the impugned Complete Specification as indicated by opponent the conversion process of compound 1 to 3 via intermediates 2 or 8 is admittedly known as the applicant himself admit that a person skilled in the art may employ other art known reaction procedures to arrive at the intermediate of formula 3 starting from formula 1" Pl. See page 14 line 23-32 of impugned Complete specification.

The conversion of compound 3 to 6 via intermediate 4 and 4' or/and 5 or 5' or 9 has been achieved by nef reaction in the following manner :

- (i) transformation of formula 3 compound to corresponding formyl derivative using nef reaction, this is performed by treating formula 3 with a base and with strong acid resulting formula 4 and 4' and on acidification converts into intermediate or formula 5 and 5' respectively;
- (ii) The conversion of formula 3 to 6 may alternatively be performed by a process comprising the steps of first reducing the intermediate of formula 3 with suitable reducing agent, resulting in intermediate of formula 9 and secondly submitting the obtained intermediate of formula 9 to a nef reaction by treatment with a base and then with a strong acid resulting is an intermediate of formula 6.

The applicant has admitted in the description on pages 14, 15, 16, 17, 18 of Impugned Complete Specification that nef reaction is known.

Lastly the formula 6 is converted to compound of formula 7 by cyclisation reaction, which occurs via an intramolecular trans acetalisation reaction and is performed by in any acid compatible organic solvent or a combination of a water immiscible solvent and water and in the presence of a strong organic or inorganic acid. Said reaction is performed by treatment of intermediate of formula 6 with a catalytic amount of a strong acid. This reaction is carried out at temperature between about -78°C and about 55°C . The preferred temperature lying between about -18°C and about room temperature.

Rest all the claims that is 2 to 15 are dependent on claim 1.

Applicant claims that known processes in this regard were neither amenable to industrial scale up nor could yield optically pure product unless different steps of purification were carried out. They claims that even though individual steps of the impugned invention is known the process as a whole is inventive and novel and it provides and alternate an nonobvious process for synthesising hexahydrofuro(2,3-b)furan-3-ol.

Now let us see what the cited prior art documents relied upon by the opponents depicts:-

It is seen that all the exhibits are the prior arts i.e. published before the priority date of the impugned application.

The specific portion highlighted by the opponents in the exhibits with the arguments thereto are given hereunder:-

Docu ment no.	Excerpts from the exhibits
Exhibit-1	<p>Lecture note of Dr. E J Corey published in 1990. Page 688, 3rd line onwards</p> <p><i>....In this approach, the target structure is subjected to a deconstruction process, which corresponds to the reverse of a synthetic reaction, so as to convert that target structure to simpler precursor structures, without any assumptions with regard to starting materials. Each of the precursors so generated is then examined in the same way, and the process is repeated until simple or commercially available structure result. This "retro synthetic" or "antithetic" procedure constitutes the basis of a general logic of synthetic planning, which was developed and demonstrated in practice over the ensuing decade. In an early example, retro synthetic planning for the tricyclic sesquiterpene longifolene (1) (Chart I) produced several attractive pathways for synthesis, one of which was selected and validated by experimental execution. The basic ideas of retro synthetic analysis were used to design many other syntheses and to develop a computer program for generating possible synthetic routes to a complex target structure without any input of potential starting materials or intermediates for the synthesis....</i></p> <p>Page 689, 4th line onwards</p> <p><i>..... Their application, even when the appropriate retron is absent, may justify the use of a number of non-simplifying transforms to generate that retron. In general, simplifying transforms function to modify structural elements which contribute to molecular complexity; molecular size, cyclic connectivity (topology), stereo center content, element and functional group content, chemical reactivity, structural instability, and density of complicating elements.</i></p> <p>3rd paragraph onwards</p> <p><i>The major types of strategies, which are of value in retro synthetic analysis may be summarized briefly as follows :</i></p> <p><i>4. Stereo-chemical strategies - general strategies, which clear, i.e. remove, stereo centers and stereo relationships under stereo control. Such stereo control can arise from transform-mechanism control or substrate structure control. In the case of the former the retron for a particular transform contains critical stereo chemical information (absolute or relative), on one or more stereo centers. Stereo chemical strategies may also dictate the retention of certain stereo center during retrosynthetic processing or the joining of atoms in three-dimensional proximity. A major function of stereo chemical strategies is the achievement of an experimentally valid clearance of stereo centers, including clearance of molecular chirality.</i></p> <p>Page 694, line 10th onwards</p> <p><i>....Despite the apparent simplicity of structure 6, a stereo specific route for the synthesis was not obvious, because no general methods existed in 1967 for the stereo controlled generation of the trisubstituted olefinic units, which it contains. The first stereo specific synthesis of 6 was possible using new methodology, which was specifically devised for this application....</i></p> <p>Page 700:- <i>This general synthesis of prostaglandins provided access to all PCs from a single intermediate, commonly known as the Corey lactone aldehyde. In various forms this flexible synthesis has been used by laboratories all over the world to prepare not only naturally occurring PCs, but also countless structural analogs on any scale.. The original version of the 1969 general synthesis of PCs is summarized briefly in Chart VIII. The bicycloheptenone 23 was synthesized stereo specifically by a novel Cu (II) catalyzed Diels-Alder reaction followed by alkaline hydrolysis of the resulting adduct. Alkaline peroxide converted 23 to the hydroxy acid 24, which was readily resolved using (+) ephedrine. Lactonisation and functional group</i></p>

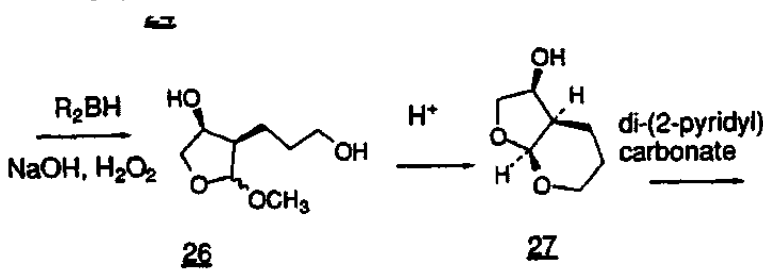
interchange operations transformed 24 into the Corey lactone aldehyde 25, a versatile precursor of all of the PCs and analogs thereof. Enone 26 (Am= Cs Hu), produced stereo specifically from 25 by **Horner-Emmons coupling**, upon reduction with zinc borohydride generated the required 15-(S)-alcohol along with the 15-®- diastereomer which was separated and recycled via 26 to the 15-(S)-alcohol.

Protection of the hydroxyl groups at C(11) and C(15) afforded the corresponding bistetrahydropyranyl (bis THP) ether, 27. Reduction of the lactone function of 27 to lactol (F.2, AIH) and **Wittig coupling** produced 28 stereo specifically. Acidic hydrolysis of 28 afforded PGF_{1a} (30), whereas oxidation of 28 followed by hydrolysis gave PGE₂ (29). Hydrogenation of the 5,6-double bond in 28 followed by these same final steps produced PGF_{1a} and PGE. A parallel series of transformations was used to convert 25 to PGE 3a and PGE₃. Although the 1969 bicycloheptenone route to PG's was highly effective for the synthesis on a large scale, it was not the ultimate. The Diels-Alder route to 23 produced racemic material which in turn necessitated the resolution of hydroxy acid 24. Another problem was the lack of stereo specificity in the reduction of the C(15) keto group of 26. **Both of these limitations these same final steps produced PGF_{1a} and PGE. A parallel series of transformations was used to convert 25 to PGE 3a and PGE₃. Although the 1969 bicycloheptenone route to PG's was highly effective for the synthesis on a large scale, it was overcome by the invention of novel methodology, which has simultaneously opened up some new areas of synthetic endeavor.**

Page 702....Second, using the chiral catalyst 33 (10 mole%) and **borane (0.6 mole equivalent) in tetrahydrofuran** as solvent at ambient temperature, the 15-ketone 34 was reduced to the 15-(S) alcohol 35 with 9:1 diastereo selectivity....

Page 704 The general synthesis of prostaglandins by the 1969 pathway can now be carried out efficiently and with total stereo chemical control, in a way that could not have been foreseen 20 years ago. Such progress augurs well for the future of chemical synthesis. It is not unlikely that today's chemical synthesis, magnificent as it may now appear, will prove to be rudimentary as compared to that of the next century.

This document as a whole is on retrosynthesis where preparation of prostaglandin has been exemplified. It would be very apparent on reading the third last excerpt that the limitations vis-a-vis large scale production and stereocontrol of prostaglandins could be circumvented using the retrosynthetic strategy. Even with the knowledge of the art known process which involves steps like **Horner-Emmons coupling, Wittig coupling large scale synthesis was possible and further scale up was done using retrosynthetic method.** In the present case, the problems associated with the prior art processes of preparation of hexahydro-furo (2,3-b) furan- 3-ol were that of scaling up and racemisation of the final product. A person skilled in the art, besides having common technical knowledge of using *Horner- Emmons coupling and Wittig coupling an other known steps which were used in processes for scaling up*, would have knowledge of retrosynthesis and its application to different known compounds, thereby making the impugned invention obvious. Therefore, the present invention is a mere optimization of the different process steps in accordance with this article on retrosynthesis, which the applicant has admitted in their reply statement to provide various alternate routes, and thus the best alternative route is to be verified through mere trial and error. Hence, the impugned invention is obvious and lacks inventive step with regard to Exhibit 1.

	<p>435. [1,2]-Wittig Rearrangement G. Wittig, <i>J. Lohmann, Ann.</i> 550, 260 (1942); G. Wittig, <i>Experientia</i> 14, 389 (1958) Rearrangement of ethers with alkyl lithiums to yield alcohols via a [1,2]-shift:</p> $R-CH_2-O-R' \xrightarrow{R''Li} R''H + \begin{matrix} R-CH-O-Li \\ \\ R' \end{matrix} \longrightarrow R-CH-OH$ <p>Reviews: H. E. Zimmerman in <i>Molecular Rearrangements</i> Part 1, P. de Mayo, Ed. (Wiley Interscience, New York, 1963) p. 372-377; L. Braudman, J. F. Arens in <i>Chemistry of the Ether Linkage</i> S. Patai, Ed. (Interscience, New York, 1967) pp. 570-580; U. Schöllkopf, <i>Angew. Chem.</i> 82, 795 (1970); A. R. Lepley, A. G. Chinnamin in <i>Molecular Rearrangements</i> vol. 3, B. S. Thyagarajan, Ed. (Interscience, New York, 1971); U. Schöllkopf, <i>Ind. Chim. (1979)</i>; G. Tennant, <i>Annu. Rep. Prog. Chem. Sec. B</i> 68, 241 (1972); R. W. Hoffmann, <i>Angew. Chem.</i> 91 (1979); <i>idem, Nachr. Chem. Tech. Lab.</i> 30, 483 (1982); C. Mersenheimer Rearrangements, Stevens Rearrangement</p>
<p>Exhibit 4</p>	<p>273. Nef Reaction T. Nef, <i>Ann.</i> 280, 263 (1894) Formation of aldehydes and ketones from primary and secondary nitroalkanes, respectively, by treatment with sulfuric acid</p> $\begin{matrix} H \\ \\ 2R-C-R' \\ \\ NO_2 \end{matrix} \xrightarrow{base} \begin{matrix} 2R-C-R' \\ \\ O-N^+O \end{matrix} \xrightarrow{H_2SO_4} \begin{matrix} O \\ \\ 2RCR' \end{matrix} + N_2O + H_2O$ <p>Modified conditions: W. Adam <i>et al.</i> <i>Synlett</i> 1998, 1335; P. Ceccherelli <i>et al.</i> <i>Synth. Commun.</i> 28, 3057 Application to spiroketals: T. Capocchi <i>et al.</i> <i>Tetrahedron Lett.</i> 39, 5129 (1998); Reviews: P. Salomè, <i>Chemistry of the Carbonyl Group</i>, S. Patai, Ed. (Interscience, N.Y., 1966) pp. 177-210; H. W. Pinnick, <i>Org. Rev.</i> 655 792 (1990); D. S. Gerson, H. P. Hesson, <i>Comp. Org. Syn.</i> 6, 937-943 (1991); R. Bailon, M. Pettini, <i>Tetrahedron</i> 60, 1017-1047 (2004)</p>
<p>Exhibit 5</p>	<p>Scheme 5 at page 18</p>  <p>Reaction scheme showing the conversion of compound 26 to compound 27. Compound 26 is a bicyclic furan derivative with a hydroxyl group, a methoxy group, and a hydroxymethyl group. It reacts with R_2BH, $NaOH$, and H_2O_2 to form a bicyclic intermediate with a hydroxyl group and a methoxy group. This intermediate then reacts with H^+ to form compound 27, which is a bicyclic furan derivative with a hydroxyl group and a methoxy group. The reaction is catalyzed by di-(2-pyridyl) carbonate.</p>

The opponents further submitted that the teaching of this document (Exhibit 1) either taken alone or in combination with Exhibits 2,3,4 and 5/ common technical knowledge clearly lead and motivate a person to design the process as claimed in the impugned application. Exhibit 1 pertains to retrosynthesis. Retrosynthesis is a technique whereby the structure of a target compound is transformed into a sequence of progressively simpler structures along various pathways which ultimately leads to simple or commercially available starting material for chemical synthesis. In simple terms, the structure of the target molecule is deconstructed to obtain simpler molecules thereby designing processes for the transforming the target into simpler deconstructed compounds or vice versa. These techniques, as already mentioned, is used for obtaining a simple and commercially available starting material as well as to design an optimum process for the preparation of the target compound. As mentioned in the article (Exhibit 1) even computer programmes are available for deconstructing the structures of various compounds. The opponent submitted that the impugned invention also uses such a retrosynthetic technique wherein the already known target molecule (hexahydro-furo (2,3-b) furan-3-ol) is deconstructed into the different intermediates to obtain the starting material, i.e. O-glyceraldehyde which again is a known compound and is abundantly available. Exhibit 1 also teaches the various strategies employed for retrosynthesis. Stereochemical strategies are of utmost importance in the present case since the applicant's objective is to obtain an optically pure product among others. It teaches that stereocontrol can be achieved on substrate-structure control. Therefore, the applicant choice of substituents at the P and PI position which is vicinal diol is an obvious selection given the nature (since it does not cause additional stereogenic centers) of such side groups when one of the objects is to obtain an optically pure product.

The other objective of the impugned application is to design a method which would be suitable for scale up. Exhibit 1 also teaches scaling up of other compounds, one such being prostaglandins. It is very clearly taught that the process designed by the help of retrosynthetic analysis can be manufactured on any scale. It is to be noted that prostaglandin was a

specific illustration of a compound formed by stereocontrol retrosynthetic analysis and the process in general involves the use of the same basic chemical reactions viz Wittig coupling, Horner-Emmons coupling among others. This was further scaled up by use retrosynthetic process. Therefore, by the process of retrosynthesis, target compounds can be deconstructed and then again reconstructed by way of common chemical reactions to give a simpler process of obtaining the target compound.

The opponent submitted that a person skilled in the art ought to be aware of such processes of retrosynthesis and has done nothing more than apply the same in the impugned invention. The process as claimed in the impugned invention adds no technical advance to the already known art and is an obvious application of prior known retrosynthetic process involving no inventive ingenuity. As mentioned above there are various methods of synthesis taught by retrosynthesis method and the applicants has admittedly chosen one. It is stated that such choice among various options cannot be regarded as inventive but only optimization of results. Therefore, Exhibit 1 with common technical knowledge of chemistry renders the present invention obvious.

It is stated that Exhibits 2,3 and 4 were relied upon to show the basic reactions of chemistry which have been used in the impugned invention. Exhibits 2 and 3 depict the Knoevenagel reaction and the Wittig reaction/ Horner Emmons reaction which have been used for converting compound 1, i.e. O-glyceraldehyde to compound 2. Exhibit 4 depicts the Nef reaction which is used for converting compound 3 to that of 6. The opponent submits that the applicant has merely used the general reactions used in chemistry for obtaining hexahydro-furo (2,3-b) furan- 3-ol and there is no inventive feature associated with using such well known processes of chemistry in order to obtain the desired product (as formulated using retrosynthesis).

It is stated that Exhibit 5 teaches HIV protease inhibitors along with a few schemes for the preparation of such inhibitors. Scheme 5 as depicted at page 18 of Exhibit 5 is of most relevance in the instant ground. Scheme 5 elucidates the formation of a compound 29. compound 27 of the scheme is hexahydro-furo (2,3-b) furan- 3-ol which is obtained by cyclisation of the compound 26 which corresponds to compound 6 in the impugned application. In the impugned application as stated above the cyclisation is performed in presence of an acid. Even in scheme 5 the conversion of compound 26 to compound 27 takes place in acidic conditions [H⁺]. It is well known fact in chemistry that H⁺ ions are generated in reaction with acids. Therefore the scheme V of Exhibit 5 clearly teaches the cyclization in presence of acid. It is also worth mentioning that the applicant in paragraph 7.7 of its reply has tried to distinguish the cyclisation step of the allegedly claimed method from that of Exhibit 5 by stating that it uses ozone which is hazardous and the impugned invention obviates the use of such hazardous reagents. It is submitted that the opponent has specifically relied on Scheme V at page 18 of Exhibit 5 where no ozone is mentioned. The applicant failed to understand scheme V properly as the same does not utilize ozone which is clear from the illustration itself and is unnecessarily trying to confuse and misdirect the Ld. Tribunal.

Therefore, a person skilled in the art, trying to solve the problems related to scale up and stereocontrol would definitely be motivated to apply the strategies of retrosynthesis to find an optimum method for the preparation of the known final product, hexahydro-furo (2,3-b) furan- 3-ol. The choice of the starting material is also obvious as it is admittedly widely available and is admittedly having vicinal diols which prevent further addition of stereocentre, thus providing the required stereoselection. Furthermore, the reactions used for the individual steps of the process are part of the general common knowledge in chemistry and was nothing but obvious to try with a probability of success. Therefore, the entire process of preparing the hexahydro-furo (2,3-b) furan- 3-ol from O-glyceraldehyde is an obvious process as the individual steps are completely bereft of inventive ingenuity.

The opponent submitted various foreign case laws to justify their stand in this regard. Their arguments relating to case laws cited is given hereunder:-

- (i) **EPO Board of Appeals; Case number: T_1034/01; Date of decision: 29 January 2004**
- (ii) **EPO Board of Appeals Case ;number: T 1067/00 Date of Decision: 26 June 2003**
- (iii) **EPO Board of Appeals Case number: T_0452/91 Date of Decision: 5 July 1995**
- (iv) **EPO Board of Appeals; Case number: T_1059/01; Date of decision: 26 November 2003;**
- (v) **EPO Board of Appeals; Case number: T_0630/03 Date of decision: 11 May 2006**

- (vi) **EPO Board of Appeals: Case number; T 0565/00; Date of decision: 14 March 2003**
- (vii) **EPO Board of Appeals: :Case number: T_0369/94; Date of decision: 3 December 1996**
- (viii) **EPO Board of Appeals: Case number: T 1116/98 Date of decision: 30 June 2004**
- (ix) **EPO Board of Appeals: Case number: T_0558/00; Date of decision: 18 February 2004**
- (x) **Pfizer Inc. v. Apotex Inc. (United States Court of Appeals for the Federal Circuit 2006 1261**
- (xi) **In re John A. DURDEN, Jr. and Arthur P. Kurtz, Jr 763 F.2d 1406; 226 U.S.P.Q. 359**

The applicant rebuttal is given below :

Obviousness and Lack of inventive step:

Section 2(1) (ja): 'inventive step' means a feature of an invention that involves **technical advance** as compared to the existing knowledge **or** having **economic significance** or both and that the invention is not obvious to a person skilled in the art.

Under these proceedings, the burden is on the Opponents to prove that the invention as claimed is obvious to the person skilled in the art. The Opponents neither in their representation, nor in their arguments have identified, who the person skilled in the art would be, and how the present invention, with the knowledge of the prior art existing as at the priority date, would be obvious to such person. The obviousness must be tested objectively with reference to individual claims and without the benefit of hindsight.

In the prior art there were methods available to manufacture formula 7. However, the present invention describes a completely new and non-obvious method employing the materials and steps, not at all disclosed, attempted or even hinted in the prior art, in particular not known or suggested for the synthesis of the compound of formula 7.

None of the references cited by the Opponent provide any information or indication/suggestion to the person skilled in the art, in order to arrive at the claimed invention for preparation of formula 7 as well as newly selected starting material and intermediates for use in the method, as described in the instant specification. The prior art cited by the Opponents whether read in isolation or together, does not show how that knowledge would have lead the person skilled in the art to

arrive at identifying formula 1 as the starting material in a synthetic route to obtain formula 7, and how to proceed to synthesize formula 7 starting with formula 1 (thus which steps to be taken), and furthermore within such route, how to reach from formula 1 to formula 3 with given alternatives, then from formula 3 to 6 and from 6 to 7, i.e. how and why to adopt this specific synthetic route. Further, nothing in the prior art suggests that following such route would lead to advantages as specified above-Patents are granted to even non-obvious variations or improvements in the known processes, and in the present matter the Applicant has come up with a completely new method in order to achieve desired objects of the present invention, which is non-obvious to the person skilled in the art in view of what was known before the priority date.

The Claimed Method is Not Anticipated: The Opponent has admitted that the claimed invention as a whole is not anticipated by any document published prior to priority date (Page 9, paragraph 5.1).

Favorable ISR and Indian Prosecution: The International application corresponding to the instant application has also been examined and as per International preliminary examination report, it has been considered that the claimed invention meets the criteria mentioned in article 33 (1) PCT i.e. satisfies the requirements of novelty,

inventive step and industrial applicability. Also, the instant application has been thoroughly examined by Indian patent office and the patentability of the claimed invention has been acknowledged. In the international search report only three prior art references have been considered by the examiner. All these prior arts are mentioned in the present specification on pages 2 and 3 viz. Ghosh et al *J. Med. Chem.* 1996, 39(17), 3278-3290, Pezeck et al. *Tetrahedron Lett.* 1986,27, 3715-3718 and Uchiyama et al., *Tetrahedron Lett.* 2001,42, 4653-4656. These documents cited in the international search report are categorized as 'A' meaning: "documents defining the general state of the art which is not considered to be of particular relevance".

Several methods of preparation of formula 7 were known since at least 1986. All the earlier methods had drawbacks and these methods were not amenable for industrial scaling up. Page 3 of the specification provides other drawbacks of the prior art. In spite of these drawbacks, no one from 1986 till the inventors of the present invention, has arrived at the synthetic route suggested by the present invention. Long felt need is one of the tests of non-obviousness. [Patent Manual 3.17.1 (c)]

Technical advance

The claimed method is amenable to industrial scaling up, unlike methods as known on the priority date. In view of known methods and their drawbacks (including as specified in page 2, lines 14 -35 and page 3, lines 1-21 of the Specification) the claimed invention is clearly a technical advance over the prior art and it is not obvious to the person skilled in the art. It is submitted that industrial scaling up is one of the necessary footstep in order to make theoretical and even laboratory-level processes to establish not only their economic significance but also their techno-economic feasibility as such. The claimed invention is a novel and inventive method for achieving the objects of the claimed invention and thus is a clear technical advance over prior art which was cited in the background of the specification.

Economic Significance: The present invention employs readily available starting material and reagents and leads to higher yield. Thus the present invention gives benefit of economic significance.

Prior art cited by the Opponents: The Opponents have cited 5 prior arts and they claim that the invention would be obvious to the person skilled in the art in the background of that prior art.

None of the prior art cited by the opponent is close to the claimed invention. The claimed invention is completely new, i.e. the method is not an improvement of known process but is a completely new process characterized by a sequence of steps to be taken as defined by the claims. In fact, none of the references cited by the opponents is close enough to provide even a slightest clue to arrive at the claimed invention.

Incorrect approach to test non-obviousness:

The Opponents have attempted to argue that to overcome the drawback of the prior art methods viz. lack of industrial scaling up, the Applicants have used the knowledge existing in the prior art i.e. Exhibit 1. The Opponents have further argued that by retrosynthesis, the Applicants arrived at a precursor being formula 1 and each process employed i.e. for conversion of formula 1 to formula 3 and from formula 3 to formula 6 and from formula 6 to formula 7 is known and therefore, the present invention is obvious. This is a totally misconceived manner to test obviousness, evanescent of the invention as claimed. The invention concerns a method for synthesizing formula 7 comprising a combination of steps starting from formula 1, said

combination of steps being defined by the claims. Thus the invention relates to a method that should be assessed on its patentability in its entirety, not by assessing each step individually.

The lecture note cited by the opponent, published by E.J. Corey provides general information about retrosynthetic analysis with its background information and various methods of retro-synthesis. It is submitted that the emphasis on lecture note published by E.J. Corey by the opponent is misleading and it is not relevant for the purpose of considering non-obviousness. In fact none of the cited prior art including Corey et al is close to the claimed invention wherein identified objects are achieved in a novel and inventive manner. Mere knowledge of retrosynthesis strategies or some vague information about industrial scaling up would not lead person skilled in the art to arrive the claimed synthetic route. The Opponents have wrongly claimed that the Applicants have selected this specific route out of the number of alternatives available and therefore, the present invention is obvious. The Opponents have not shown as to how Exhibit 1, would lead the person skilled in the art to start the synthesis from formula 1 and subsequently to the specific route i.e. formula 1 to formula 3 and from formula 3 to formula 6 and from formula 6 to formula 7. No suggestion is to be found in any of the cited documents that any of these reaction types as specified in Exhibits 2 to 5 could be useful at some stage in a synthetic route to obtain formula 7. The combination of steps as defined by current claim 1 to obtain stereoisomerically pure formula 7 is clearly non-obvious in view of the known prior art. The advantages of each of the steps to lead to industrial scaling up and at the same time maintaining control of stereochemistry is not obvious.

The Opponent have wrongly contended that no extraordinary skills are required to devise convenient and economic reaction strategy and it appears that it is Opponent's viewpoint that inventing all convenient and economic reaction strategies are well within the realms of knowledge of a synthetic chemist. The Applicant states that mere perception of the problem does not provide an appropriate solution to the same. Neither a mere perception of a problem nor background information about retrosynthesis provides any teaching or suggestion to arrive at the claimed invention. The Applicant states that the inventiveness in the present invention lies not in what the desired end product is, but rather in, *how it is obtained taking into account the* limitations imposed by the complex stereochemistry of the molecule and the large scale requirement. The claimed method has further advantage of using readily available starting material such as O-protected glyceraldehyde. The reagents further used in the method are safe and available in bulk. Each step provides the desired compound in good yield and each step may be performed stereo selective, which allows synthesis of pure stereoisomeric forms of the desirable compound when using, where appropriate, optically pure starting material and reagents. Thus the method according to the present invention is amenable to industrial scaling up.

The opponent's agent confusingly argued regarding equal or higher yield and ignored the clear object of achieving above mentioned benefits without compromising on yield. It is respectfully submitted that the reading of these sections of the document by the opponent's agent could not provide any basis to even considering the question of obviousness which was attacked earlier on the basis of Exhibits 1-5. It is also submitted that opponent continuously attempted to mislead the proceedings by using the term 'process' interchangeably for reactions utilized in the method and also for the method as a whole and those arguments went to the extent that the novel method is known process to produce known product.

Further, the invention has to be considered as a whole for consideration of inventive step. It is thus not sufficient to draw the conclusion that a claimed invention is obvious merely because individual parts of the claim taken separately are known or might be found to be obvious. [Patent Manual 2008-3.11 (i)].

The Opponents are testing the obviousness with hindsight: Patent Manual 2008 para 3.12 reads as follows:

"Ex-Post Facto Analysis in relation to Inventive Step

3.12.1 The examiner (or any other person) who is considering the question of whether or not an invention is obvious has to bear in mind that it is an ex-post facto analysis. He can be very easily misled by a line of reasoning involving taking the solution and working backwards to the problem by a succession of easy steps. In considering a prior publication, the examiner has to avoid looking at the document under the influence of the application he is examining, and should attempt to place himself in the shoes of the skilled person faced with the problem at hand.

3.12.2 In the *Windsurfing International Inc. v. Tabur Marine (Great Britain) Ltd*, [1985] RPC 59, the Court of Appeal held that the question of obviousness "has to be answered, not by looking with the benefit of hindsight at what is known now and what was known at the priority date and asking whether the former flows naturally and obviously from the latter, but by hypothesizing what would have been obvious at the priority date to a person skilled in the art to which the patent in suit relates".

It is only with hindsight upon learning about the present invention, that one skilled in the art can know which process would provide sufficient yield of the end product and at the same time would be free from limitations and drawbacks imposed by the complex stereochemistry of the molecule and the large scale production requirements. For instance none of the known methods is suitable for the production of optically pure stereoisomers of formula 7 on an industrial scale. It is clear from the arguments of the opponent's agent that teaching from the novel and inventive claimed method were utilized to work out arguments which lacked any substantial reasoning including the remark that it is an old process to obtain an old product. The opponent confusingly argued and used the term process for individual steps involved as well as overall novel and inventive method and in spite of the acknowledging novelty attempted to mislead the proceedings.

As established in various cases, person skilled in the art is an imaginary person who is assumed to be a technician skilled in the art but has absolutely no imagination or inventiveness. It is succinctly described in the English case of *Beloit v Valmet* [1995] RPC705 "the test of obviousness is not to ask what competent inventors did or would have done to solve the problem. Inventors are by definition inventive. The classical touchstone is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paraqon of deduction and dexterity, wholly devoid of intuition: a triumph of the left hemisphere over the right. The Question to be asked is whether this mythical creature would in the light of the state of the art and of common general knowledge as at the claimed date of the invention, have come directly and without difficulty to the solution taught by the patent. It is a very difficult test to satisfy." The opponent's agent argued the case without considering the viewpoint of any person skilled in the art and under the complete influence of instant application.

The "Windsurfer" approach [*Windsurfing International v Tabur Marine* (1985)] was adopted to assess inventive step. In this approach, the following four steps were taken:

The first is to identify the inventive concept embodied in the patent in suit.

- (1) Assume the mantle of the normally skilled but unimaginative addresses in the art at the priority date and impute to him what was, at the date, common general knowledge in the art in question.
- (3) Identify what, if any, differences exist between the matters cited as forming part of the state of the art and the alleged invention.
- (4) Finally the court has to ask itself whether, viewed without any knowledge of the alleged invention, those differences constitute steps to which would have been obvious to the skilled man or whether they required any degree of invention.

Upon application of this approach it is very clear that the present invention is non-obvious according to the applicant.

It may be observed from sec. 2[1(j)(a)] and the well established patent procedure in this regard that the invention claimed in the claims of the impugned application can be arrived at from the teaching of the cited prior arts or knowledge which provides the motivation to a person skilled in the art, than the impugned invention becomes obvious and devoid of inventive step.

The submissions of the opponents is agreeable that the impugned invention as claimed is obvious and does not have inventive step in the light of exhibits 1 to 5 and the decisions of the EPO board, US Courts for the reasons that :

- (i) the compound which is prepared by the impugned process as claimed has already been prepared by different known processes in the prior art as admitted by the applicant . Mainly the applicant has made an attempt to develop this process for the industrial level production and for obtaining high stereochemical purity.
- (ii) The steps of preparing compound 1 to compound 3 is already known in art as has been admitted by the applicant himself in the description .
- (iii) The compound of formula 1 is also known in the art with the property of having such groups which does not add stereocentres. Therefore, for a person skilled in the art with the aims keeping in mind to produce a compound of formula 7 with stereo selective synthesis obvious choice would be the compound 1 for preparation of compound 7.
- (iv) It is clear from the description above that the exhibit 1 teaches retro synthesis technique and explains what does it mean and how it may be applied to produce desired compound.
- (v) The exhibit 1 also teaches various strategies which may be considered in stereo selective synthetic methods.
- (vi) Exhibits 2, 3, 4 teaches the reactions which have been used by the impugned invention. Knoevenagel reaction and Wittig reaction, Horner Emmons reaction which have been

used in converting the compound 1 to compound 2. Exhibit 4 teaches nef reaction which have been used in converting compound 3 to 6.

Exhibit 5 teaches the cyclisation process. In scheme 5 of exhibit 5 compound 26 corresponds to compound 6 of impugned invention which is converted by cyclisation to compound 27 of scheme 5 which is hexahydro-furo(2,3-b) furan-3-ol. The cyclisation in both the invention is carried out in acidic conditions.

Therefore a person skilled in the art with the target to solve the problems of scale up and stereo control for a desired reaction (i.e. of impugned invention) would be motivated with reasonable expectation of success to apply the teachings of the available prior arts at his hands viz. Exhibit 1 to 5.

The choice of starting material i.e. o-glyceraldehyde in the impugned invention is known as admitted by the applicant in page 11 of Complete Specification for preparing the compound of formula 3 as admitted by applicant on p14 line 29-31.

Therefore, finally it appears that the applicant for preparing compound 7 from compound 1 has applied the known reactions on all the compounds, which were a prior knowledge (as discussed above) for this kind of synthesis. The applicants have only optimized the parameters of the synthesis in a routine way of experimentation as may easily be done by a skilled organic or pharma chemist using the prior arts and the knowledge available as discussed above and admitted by the applicant in impugned specification to synthesize the desired compound with desired stereo chemical property. Even the Windsurfer approach as argued by the applicant would have given the same result in the light of the cited prior art.

(2) NOT AN INVENTION NOT PATENTABLE, Section 25[1(f)]:

Opponent allegation is that the impugned claims are not patentable u/s 3(d) of the Patent act as the applicants used merely 'known processes without involving any new starting material or producing new end product' There is no comparative data which could even suggest the advantages of the claimed process of the product so formed over the known so far.

Applicant rebuttal is that opponents arguments that each step of the claimed process is known and the present invention employs known process for new use is totally ill conceived manner of interpretation of the present invention, definition of term invention and section 3(d). Applicant placed reliance on T 0829/00 27/5/03 annexed as annexure-1 to support to their argument.

It appears from all the above and description of the impugned specification that the applicants have not substantiated the technical advancement by the technical data which could establish the technical advance or economic significance of the impugned invention compared to the known one in the field. Further, clear from the aforesaid discussion about inventive step of the impugned

invention, that the invention under consideration appears to use known process with known substances to produce known final product with routine changes in the parameters which is obvious to a person skilled in the organic synthesis. Therefore the invention also fall u/s 3(d) and hence not patentable.

(3) FINAL CONCLUSION:

It is concluded from the aforesaid discussion that the claims of the impugned invention are obvious and devoid of the Inventive step in view of the admittedly known facts and prior art citations submitted as exhibit 1 to 5 by the opponents. The claims of the impugned application also fall U/S section 3 (d) of the Patent Act 1970 (as amended).

(4) Order:- In view of all the above mentioned discussion it is clear that the present invention is not patentable u/s 2(1)(j). And sec. 3(d) of the Patent Act, therefore the grant of patent is refused on this application.

Dated -24/07/2009

Sd/-
(DR. NILANJANA MUKHERJEE)
(ASSTT. CONTROLLER OF PATENTS & DESIGNS)