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(54) **Title:** A PROCESS FOR SYNTHESIZING DIOL (VIII)-AN INTERMEDIATE OF MONTELUKAST SODIUM

(57) **Abstract:** A process comprises preparing benzaldehyde of formula I in a conventional manner, reacting the said benzaldehyde I with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula (II) by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods and then oxidizing directly under "Swern's conditions" to get a ketone of formula m, enolizing the said ketone in presence of a mild base such as alkali metal alkoxide and then reacting it with dialkyl carbonate under conditions effective to yield a β- ketoester of formula IV, benzylating the said β-ketoester so obtained in the preceding step to form the benzoate of formula V in presence of mild inorganic base followed by decarboxylating the said benzoate to a mixture of a ketoester of formula VI and its corresponding acid of formula VIA in the presence of acidic conditions, alkylating the acid VIA present in the mixture in the preceding step to obtain ketoester of formula VI and purifying it if so desired, asymmetrically reducing the ketoester of formula VI, to a chiral alcohol of formula VII using (-) diisopinocamphenylchloroborane (-DIPC1) in presence of less than 4 times v/w aprotic solvent and optionally in presence of Lewis base with respect to the said ketoester of formula VI, treating the said chiral alcohol VII with cerium halo salt, and alkylmagnesium halide followed by isolating the title compound using hyflow supercel and ammonium chloride to get the intermediate diol of formula VIII. Atemately, the said alcohol to Heck coupling with methyl-2-iodobenzoate in presence of Lewis base, acetonitrile, and palladium acetate to yield ketoester (VI), which is converted to diol (VIII) as described herein above.

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This invention relates to A Process for Synthesizing Intermediates of Montelukast Sodium

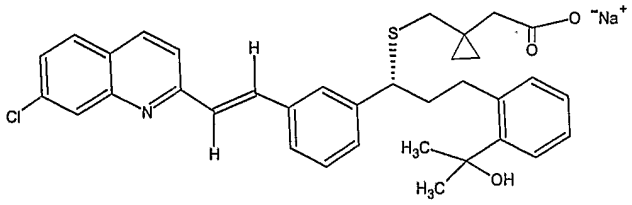
FIELD OF THE INVENTION:

This invention relates to a process for synthesizing intermediates of Montelukast Sodium, which is a potential leukotriene antagonist. The present invention particularly, relates to a process whereby the intermediates of Montelukast sodium are produced in high yields and high purity. The present invention more particularly relates to a process that is cost effective, environment and user friendly. Further, the process disclosed in this invention is more compatible to the economics of manufacturing of the title compounds and can be scaled up eventually leading to the commercialization of a process for the manufacture of Montelukast Sodium advantageously.

BACKGROUND OF THE INVENTION:

Montelukast Sodium, which can be described chemically as [R-(E)]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl] thio]methyl]cyclopropaneacetic acid, monosodium salt, and structurally by formula as given below, being a leukotriene antagonist is useful to treat, prevent or ameliorate in mammals especially in human beings: (i) pulmonary disorders including asthma, chronic bronchitis and related obstructive airway diseases, (ii) allergies and allergic reactions such as allergic rhinitis, contact dermatitis conjunctivitis and the like, (iii) arthritis inflammation or inflammatory bowel diseases, (iv) skin disorders, (v) cardiovascular

disorders, (vi) ocular conditions like uveitis, cerebral disorder, (vii) glomerular nephritis, (viii) hepatitis and allograft rejections.



Montelukast Sodium

The process for the preparation of [(E)]-2-[3(S)-[3-[2-(7-Chloro-2-quinolinyl)-ethenyl]phenyl]-3-hydroxypropyl]phenyl]-2-propanol (**VIII**) (refered as diol) is described in US 5, 565, 473 and US 5, 614, 632) and schematically represented in Figure 1 in the drawing accompanying the provisional specification, generally, comprises of following steps:

(a) condensing 7-Chloroquinaldine with isophthaldehyde to yield benzaldehyde **I**,

(b) converting the said benzaldehyde I into secondary alcohol **II**,

(c) oxidizing the alcohol thus obtained to aromatic ketone **III**,

(d) enolizing the ketone to β-ketoester **IV**

(e) benzylating the β-ketoester into benzoate **V**,

(f) decarboxylating the benzoate so obtained to a mixture of ketoester **VI** and its corresponding acid **VIA**,

(g) alkylating the acid in the above mixture into the corresponding ketoester **VI**

(h) reducing the ketoester **VI** asymmetrically to chiral alcohol **VII** and finally

(i) converting the chiral alcohol obtained in step (h) to title compound.

Methods for the preparation of benzaldehyde are described in US Patent No. 4,851,4 09 ('409) and US Patent No. 5,8 69,673 ('673).

In the process of synthesis of Montelukast Sodium, diol **VIII** is a key advanced intermediate for two of the several synthetic routes being pursued for assembling the basic skeleton of montelukast sodium. The purity of diol VIII is very critical in order to crystallize further intermediate such as mesylate in the process of synthesizing Montelukast sodium, other wise it does not precipitate out even after seeding or stirring for longer duration at low temperatures. Higher the purity of the diol **VIII**, faster is the crystallization of the mesylate. The quality of diol (VIII) in turn depends on the quality of the precursor's keto ester (VI) and hydroxyl ester (VII). The diol **VIII** is generally prepared from chiral alcohol ester **VII**, represented chemically as Methyl-[(E)-2-[3-[3-[2-[7-chloro-2-quinolinyl) ethenyl]phenyl]-3-hydroxypropyl]benzoate (**VII**), via Cerium chloride assisted double addition of methylmagnesium chloride, which in turn is generated through asymmetric reduction of the intermediate ketoester Methyl-[E]-2-[3-[3-[2-(7-chloro -2-quinolinyl) ethenyl]phenyl]-3-oxopropyl]benzoate (**VI**).

Therefore, in the whole process leading to superior grade Montelukast sodium in an economically feasible process, quality of the intermediates such as ketoester (**VI**), hydroxyl ester (VII) and diol (VIII) play a very important role.

In US-5, 565, 473 and EP-480, 717, several conventional and organo-metallic routes for synthesizing the ketoester **VI** have been described. In most of the routes involving organometallic reagents, Palladium catalyzed Heck coupling has been employed as the key element for assembling the backbone of the aromatic ring

system. Although the organometallic routes offer advantages of short step synthesis over the conventional route, the difficulties associated in synthesizing the desired halogen substituted aromatic intermediates, low yield and high cost of the organometallic complexes as well as the stringent and critical reaction parameters like anhydrous and inert, oxygen-free atmosphere employed therein make the process inconvenient and commercially unviable. Further, the presence of additional inorganic salts used in the reaction, poses problems in the isolation of ketoester. Tedious aqueous extractive workup procedures invoving special filtration techniques or repeated filtration through hyflow are needed to remove the organometallic complexes whose presence in the intermediate is likely to influence the reaction kinetics or the quality of product formation in the following stages Specifically, in this case, the intermediate vinyl alcohol (**III**) to the ketoester (IV) conversion, the palladium catalyzed Heck coupling is performed in the presence of a mixture of Lithium salts and phase transfer reagents. Moreover the presence of even small amount of palladium metal and its complexes in the synthesized ketoester **VI** considerably reduces the options for generating pure chiral alcohol/hydroxy ester **VII**, since reduction of the double bond also occurs while carrying out asymmetric reduction of the keto group in the presence of chloroborane methyl sulfide (CBS) complex (Please see J. Med. Chem.; **58**, 3733, 1993). This necessitates the use of (-) Diisopinocamphenylchloroborane, a not so stable and difficult to synthesize reagent that has to be used in more than molar equivalence for the completion of the reaction.

In the case of conversion of keto ester **(IV)** into hydroxy ester **(V)** problems were encountered as the reaction did not go to completion when performed as per the reported experimental conditions in THF (US-5, 565, 473, US-5, 545, 758 and US-5, 693, 816). Very often it was observed that once the reaction stops after 50-75% conversion had taken place in the presence of the desired quantity of (-) DIPCl, the reaction could not be made to go to completion by adding additional 2 or more equivalents of the reagent and even after extended periods of stirring.

The borane reagent (-) DIPCl is highly sensitive to both oxygen and water and the process requires stringent operational conditions such as inert or anaerobic atmosphere there by making the process complex and unconventional.

Another disadvantage of this route is that the vinyl alcohol **(III)** is difficult to crystallize from the reaction mixture and has to be purified via tedious column chromatography before being subjected to coupling with the aromatic halide under the Heck conditions

Also, the large amount of emulsion formation was observed during the solvent extractive workup of the reaction of cerium chloride assisted addition of methyl magnesium chloride to Methyl-[(E)-2-[3(S)-[3-[2-[7-chloro-2-quinolinyl) ethenyl] phenyl]-3-hydroxypropyl] benzoate (**VII**). It is also observed that in the formation the alcohol **II** involving the reaction between benzaldehyde **I** and alkyl magnesium halide in THF, difficulties are encountered in direct crystallization of resulting alcohol. Formation of large amounts of emulsion was encountered during the workup of the above-mentioned reaction. These operational problems lead to the wastage of lot of time in generating the desired alcohol derivative **I** and **VIII,**

thereby increasing the time cycle of the process and eventually reducing productivity.

The conventional process for synthesizing Methyl-[E]-2-[3-[3-[2-(7-chloro-2-quinolinyl] ethenyl]phenyl]-3-oxopropyl]benzoate (**VI**) is a multistep step (6) sequence and involves the selective condensation of 7-Chloroquanaldine with isophthaldehyde in the presence of acetic anhydride under controlled stochiometric conditions to form the intermediate [E]-3-2-(7-chloro-2-quinolinyl) ethenyl]benzaldehyde (**I**), which upon reaction with methyl magnesium chloride or bromide in tetrahydrofuran (THF) followed by activated manganese dioxide assisted oxidation of the resulting [E]-1-[3-]2-(7-Chloro-2-quinolinyl) ethenyl]phenyl]ethanol (**II**) affords the aromatic ketone intermediate **III** in low yield. The ketone **III** is then benzylated with Methyl-2-bromomethyl or iodomethyl benzoate in the presence of lithium diisopropylamide at low temperatures to directly form ketoester Methyl-[E]-2-[3-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropyl]benz-oate (**VI**) in low yields which has to be chromatographically purified in order to remove the dibenzylated compound and other impurities that are formed in appreciable amounts. Alternatively, the crude ketoester **VI** can be prepared in relatively higher yields via a three step route in which the ketone **III** sequentially undergoes facile sodium hydride induced one carbon homologation with dimethyl carbonate followed again by sodium hydride assisted benzylation of the resulting β-ketoester **IV** with methyl-2-bromoethyl benzoate which is then decarboxylated in hot acetic acid and hydrochloric acid to produce a crude mixture of **VI** and its corresponding acid **VIA**. The acid **VIA** is further selectively O-

methylated with methyl iodide in the presence of alkali metal carbonate to yield the crude ketoester **VI**. The crude **VI** thus obtained contains very little amount of the corresponding acid (<1%) and is purified via crystallization before being used in the next stage.

Use of highly moisture sensitive and explosive sodium hydride at two consecutive stages of such a short synthesis makes the scale up of synthesis of the ketoester **VI** very difficult and inconvenient for commercialization. Secondly, the oxidation of [E]-1-[3-]2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]ethanol (**II**) with stochiometric amounts of activated manganese dioxide is not very clean and does not go to completion. Purification of the reaction residue via tedious column chromatography produces the ketone **III** in low yields. Moreover the use of stochiometric amounts of manganese dioxide used in the transformation generates large quantities of manganese sludge on commercial scale which puts a huge load on the effluent treatment plant, thereby adding to the overall manufacturing cost.

In view of the above-mentioned several drawbacks of both the organometallic and conventional non-organometallic routes, there exists a need for an improved, operationally

convenient, environment friendly, time and cost effective process for synthesizing the key intermediates keto ester (**VI**), hydroxyl ester (**VII**) and diol (**VIII**) which can be scaled up and eventually result in the commercialization of a process for the production of Montelukast Sodium with increased yield and purity.

BRIEF DESCRIPTION OF THE DRAWING:

Figure 1 depicts the schematic representation of the process of the present invention.

SUMMARY OF THE INVENTION:

Accordingly, one of the main objects of the present invention is to provide a process, which obviates the drawbacks associated with the existing processes.

The other objective is to provide a process that is simple, easy to operate, environment friendly and high yielding.

Further, the process of this invention does not require any sophisticated equipment or stringent process parameters.

Yet other objective is to provide a process for the direct crystallization of the alcohol (**II**) from the reaction mixture avoiding the existing solvent extractive workup procedure in which extensive formation of emulsion occurs.

Another object of the present invention is to develop a high yielding process for the preparation of ketone **III** in which the tedious column chromatographic purification is avoided.

Yet another object of the present invention is to develop a high yielding process for the preparation of **III** wherein the problems associated with the generated manganese sludge due to the use of stochiometric quantities of manganese dioxide and the consequent load on the effluent treatment plant are eliminated.

Still other object of the present invention is to develop an alternate, safer and scaleable process for synthesizing the intermediates β- keto ester (**IV**) and the benzylated β- keto ester (**V**) by using milder reagents in place of the highly

moisture sensitive and explosive reagents like sodium hydride and LDA in the transformation.

Still another object of the present invention is to develop an alternate, milder and scaleable process for synthesizing β ketoester (**IV**) eliminating employing additional inorganic salts and phase transfer reagents.

Still another objective of the invention is to develop reproducible reaction conditions for the preparation of chiral alcohol **VII** via asymmetric reduction of benzylated ketoester (**VI**) using reduced amount of the expensive chiral reagent (-) diisopinocamphenylchloro borane. Further objective of the present reaction is to develop an alternative workup procedure for the isolation of diol (**VIII**), in which the problems associated with the delays encountered during de-emulsification of the reaction work up are eliminated.

We have discovered that by reversing the mode of reaction mixture workup and by adding calculated amount of ammonium chloride and water to the reaction mixture followed by stirring at 5 to 10°C helps in direct crystallization of the alcohol **II**, thereby solving the problem of emulsion formation.

We have also discovered that the oxidation of alcohol **II** under Swern's conditions using Lewis base instead of the one reported in presence of manganese dioxide enhances the yield of the ketone **III** up to 90% while maintaining purity of the product and eliminating tedious chromatographic purification.

Further, homologation of the said ketone **III** with dialkyl carbonate can be successfully achieved by substituting the moisture and temperature sensitive and explosive alkali metal hydride with milder agents such as alkali metal alkoxide.

Similarly the benzylation also can be affected in presence of mild bases avoiding use of sodium hydride. The reaction is preferably performed in 1, 4-dioxane in the presence of sodium methoxide at 75-80°C.

In the case of conversion of **VI** into **VII** problems were encountered as the reaction did not go as per expectations and a large excess of the expensive (-) DIPCl was needed for completing the reaction. After a considerable amount of experimentation it was observed in the present invention that the amount of solvent used in the reaction plays a key role in influencing the completion of the reaction. Higher the amount of solvent present in the mixture, the slower is the progress of the reaction. The reaction works reasonably well when conduced at –10°C to +20°C in the presence of 1.3 to 1.75 equivalents of (-) diisopinocamphenylchloroborane (65-75% solution in hexanes) in presence of lewis base, & in presence of 1.5 to 2.0 times v/w of aprotic solvent with respect to benzylated ketoester (**VI**).

The problems associated with the delays encountered during de-emulsification of the reaction work up involving the Cerium Chloride assisted addition of methylmagnesiun halides to the hydroxyl ester (**VII**) leading to the diol (**VIII**), are eliminated by addition of the celite to reaction mixture thereby resulting in the facile filtration of the organic extracts with little or no emulsion formation.

STATEMENT OF THE INVENTION:

Accordingly the present invention provides a process for synthesizing diol (**VIII**)- an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods and then oxidizing directly under "Swern's conditions" to get a ketone of formula **III**,

(c) enolizing the said ketone in presence of a mild base such as alkali metal alkoxide and then reacting it with dialkyl carbonate under conditions effective to yield a β- ketoester of formula **IV**,

(d) benzylating the said β-ketoester so obtained in the preceding step to form the benzoate of formula **V** in presence of mild inorganic base followed by decarboxylating the said benzoate to a mixture of a ketoester of formula **VI** and its corresponding acid of formula **VIA** in the presence of acidic conditions,

(e) alkylating the acid **VIA** present in the mixture in the preceding step to obtain ketoester of formula **VI** and purifying it if so desired,

(f) asymmetrically reducing the ketoester of formula **VI**, to a chiral alcohol of formula **VII** using (-) diisopinocamphenylchloroborane (-DIPCl) in presence of less than 4 times v/w aprotic solvent and optionally in presence of Lewis base with respect to the said ketoester of formula **VI**,

(g) treating the said chiral alcohol **VII** with cerium halo salt, and alkylmagnesium halide followed by isolating the title compound using hyflow supercel and ammonium chloride to get the intermediate diol of formula **VIII**.

In accordance with the other aspect of this invention there is provided a process for synthesizing diol **(VIII)**-an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible ethereal solvent to yield the alcohol of formula **(II)** by addition of ammonium salt and water ,

(c) subjecting the said alcohol to Heck coupling with methyl-2-iodobenzoate in presence of Lewis base, acetonitrile, and palladium acetate to yield ketoester **(VI)**,

(d) asymmetrically reducing the ketoester of formula **VI**, to a chiral alcohol of formula **VII** using (-) diisopinocamphenylchloroborane (-DIPCl) in presence of less than 4 times v/w aprotic solvent and optionally in presence of Lewis base with respect to the said ketoester of formula **VI**,

(e) treating the said chiral alcohol **VII** with cerium halo salt, and alkylmagnesium halide followed by isolating the title compound using hyflow supercel and ammonium chloride to get the intermediate diol of formula **VIII**.

In accordance with other aspect of the present invention there is provided a process for synthesizing alcohol **(II)**-an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods.

In accordance with yet other aspect of the present invention there is provided a process for synthesizing ketone **(III)**-an intermediates of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods and then oxidizing directly under "Swern's conditions" to get a ketone of formula **III**,

In accordance with yet other aspect of the present invention there is provided a process for synthesizing ketoester **(VI)**-an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods and then oxidizing directly under "Swern's conditions" in presence of Lewis base, to get a ketone of formula **III**,

(c) enolizing the said ketone in presence of a mild base such as alkali metal alkoxide and then reacting it with dialkyl carbonate under conditions effective to yield a β- ketoester of formula **IV**,

(d) benzylating the said β-ketoester so obtained in the preceding step to form the benzoate of formula **V** in presence of mild inorganic base followed by decarboxylating the said benzoate to a mixture of a ketoester of formula **VI** and its corresponding acid of formula **VIA** in the presence of acidic condition,

(e) alkylating the acid **VIA** present in the mixture in the preceding step to obtain ketoester of formula **VI** and purifying it if so desired,

(f) asymmetrically reducing the ketoester of formula **VI**, to a chiral alcohol of formula **VII** using (-) diisopinocamphenylchloroborane (-DIPCl) in presence of less than 4 times v/w aprotic solvent and optionally in presence of Lewis base with respect to the said ketoester of formula **VI**,

In one of the embodiments of the present invention, the reaction in step (a) may be carried out in presence of acetic anhydride at a temperature in the range of 90-150°C for a period of 10-30 hrs., preferably at 100-110 °C for 12-15 hrs.

In other embodiment of the present invention, Grignard reagent used may be of formula R_1MgX where R_1 is alkyl with C1 to C4 exemplified by methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or vinyl and X is halide preferably iodide, the reaction being carried out in presence of ethereal solvent including but not restricted to 2-methoxytetrahydrofuran, tetrahydropyran, 1, 2-dimethoxyethane, 1, 2-diethoxy -ethane, preferably tetrahydrofuran or mixture thereof, at a temperature ranging from -25 to +40°C, preferably at -5 to +10°C.

In another embodiment of the present invention, the direct isolation and crystallization of the alcohol of formula **II** after workup was effected by adding calculated amount of 1 to 25% preferably 2 to 10% more preferably 10% aqueous soution of ammonium salt such as ammonium acetate, ammonium chloride, preferably ammonium chloride solution in an amount of 2 to 10 preferably 3 to 5 times of benzaldehyde **(I)** and water in the range of 5 to 50 preferably 10 to 15 times of benzaldehyde **(I)** to the reaction mixture and then straightaway crystallizing the product by stirring the mixture at –10 °C to 35°C preferably 5°C -10°C for extended period of 2 to 10 preferably 4 to 8 hours, then isolating by centrifugation, filtration and drying.

Another embodiment of the invention is that the oxidation of alcohol **(II)** in step (b) being performed under Swern's conditions employing oxalyl chloride, dimethyl sulfoxide and Lewis base exemplified by alkyl amine such as triethyl

amine, tri n-propylamine, tri n-butylamine, tri n-pentylamine, and diisopropyl ethyl amine preferably triethyl amine of 5 to 15 molar preferably 8 to 12 molar equivalents w. r. t the alcohol **(II)** as the reagents and the reaction is performed at -60 °C to +30°C preferably -60°C to +10°C over a period of 4 to 6 hrs., employing molar equivalents of DMSO between 2 to 8, preferably 4 to 6 equivalents and that of oxalyl halide between 1.5 to 4, preferably 2 to 2.5 equivalents with respect to the alcohol **(II)**

Yet another embodiment of the invention is that the enolization of the ketone **III** in step (c) may be effected by milder bases of formula R_3OM wherein R_3 is alkyl with C1 to C3 and M is Na or K selected from alkali metal alkoxide including sodium methoxide, sodium ethoxide, sodium n-propoxides, sodium n-isopropoxide, sodium n-butoxides, sodium isobutoxide, sodium tertiary butoxide as well as their potassium salt derivatives in an amount of 1.5 to 7 molar equivalents w. r. t. to ketone with dialkyl carbonate wherein alkyl may be with C1 to C3 in an amount ranging from 2 to 8 preferably 3 to 4 molar equivalents of ketone, in polar solvents like THF, 1,2 dimethoxyethane, 1,2 diethoxyethane, dimethyl formamide, dimethyl acetamide preferably 1,4-dioxane in an amount of 2 to 10 v/w with regard to ketone at 10 to 100 °C, preferably at 40 to 90°C more preferably at 60 to 90°C , still more preferably at 70 to 80°C.

Still another embodiment of the invention, the benzylation of the β-ketoester of formula **IV** in step (d) may be performed by reacting the said ketoester with alkyl-2- halomethylbenzoate preferably methyl or ethyl and n-propyl ester derivative and halo may be chloro, bromo or iodo particularly alkyl-2-bromomethylbenzoate

using much milder and safer alkali metal bases like sodium or potassium carbonates in polar aprotic solvents like dimethylformamide, dimethylacetamide, dimethylsulfoxide, hexamethylphosphorous-triamide, 1, 4 - dioxane, tetrahydrofuran, 1, 2- dimethoxyethane and 1, 2 – diethoxy -ethane etc. using 1.1 to 1.5 molar equivalents of methyl 2-bromomethyl benzoate, 1 to 3 molar, preferably 1 to 1.5 molar equivalents of anhydrous potassium carbonate and 2 to 10, preferably 3 to 5 times v/w of dry dimethylformamide w. r. t. the amount of β - keto ester (**IV**) 10 to 150 °C, preferably at 55 to 65°C, over a period of 4 to 48 hrs, preferably over 8 to 12 hrs.

The decarboxylation in step (d) is carried out using a mixture of acetic acid and hydrochloric acid in a known manner. Further, the purification may be carried out by crystallizing with 8 to 12 times acetonitrile, or with a mixture of dichloromethane and

methanol 4 to 15 preferably 7 to 10 times v/w each w.r.t. ketoester.

Further, the asymmetrical reduction of the ketoester **VI** to chiral alcohol **VII** may be effected by employing 1.2 to 2.0 eq. of (-) diisopinocamphenylchloroborane (-DIPCl) (65-75% solution in hexanes) in 1.5 to 4.0 times v/w of aprotic solvent exemplified by ethers such as diethyl ether, diisopropyl ether, di n-butyl ether, diisopentyl ether, anisole, cyclic ethers such as tetrahydropyran, 2-methyltetrahydrofuran, and 2-ethoxyfuran, most preferably tetrahydrofuran and the Lewis bases that may be used include but are not limited to alkyl amine like triethylamine, tri n-propylamine, tri n-butylamine, trisopropylamine,

triisobutylamine, most preferably diisopropylethylamine in 0.25 to 2 molar equivalents, preferably 0.5 to 0.75 molar equivalents w. r. t. the keto ester **(VI)**

As another embodiment of the invention, the cerium halo salt and alkylmagnesium halide used for converting the chiral alcohol **VII** to the diol intermediate **VIII** may be such as methyl or ethyl and propylmagnesium chlorides, bromides or iodides and the isolation may be undertaken by simply dumping the reaction mass into as stirred suspension of hyflow supercel in 8 to10% ammonium salt preferably ammonium chloride followed by centrifuging or filtering through a bed of hyflow supercel. The procedure may also be carried out in the presence of water immiscible organic solvents like benzene, toluene, ortho or para xylene, and halogenated solvents like methylene dichloride, chloroform, and 1,2-dichloro ethane, which may be used in pure form or as mixtures in any suitable composition.

The Lewis base used in Heck coupling of alcohol **(II)** in step (c) include but are not limited to alkyl amines like triethylamine, tri n-propylamine, tri n-butylamine, diisopropyl ethyl amine, in an amount of 0.1 to 10 times preferably 0.5 to 1 times, palladium acetate used may vary from 0.1% w/w to 2.5 % w/w, preferably 0.5 to 1.5% w/w and the amount of acetonitrile may vary between 1 and 100 times, preferably 3 and 10 times v/w w. r. t the benzaldehyde **(I)** used. The reaction may be performed at 10 to 100°C, preferably at 65 to 75°C over a period of 1 to 100 hrs, preferably for 5 to 25 hrs.

The invention is further illustrated with the help of examples. However, this should not construe the scope of the invention. Any deviation from this, apparent and or obvious to an ordinary skilled person in the field forms a part of this invention though not explicitly substantiated.

General: All chemicals used, unless otherwise specified, were of commercial grade and were analyzed before use. IR spectrum was recorded on NICOLET-AVAATAR 320 FTIR spectrophotometer, ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.47 MHz) spectra were measured on Bruker DPX-300 spectrometer at ambient temperatures. EIMS spectrum were recorded onVG-70-250S mass spectrometer at NIPER, Mohalli, Punjab and RSIC, Punjab University, Chandigarh, India.

EXAMPLE 1:

Preparation of [E]-3-[2-(7-Chloro-2-quinolinyl)ethenyl]benzaldehyde (I).

To a 2.0 lt. round bottom flask fitted with a mechanical stirrer, thermometer pocket and condenser were charged 7-chloroquinaldine (100 g, 0.56 mol), isophthaldehyde (90.40 g, 0.67 mol), toluene (400 ml), acetic anhydride (109.30 g,101 ml, 1.0 mol) and the mixture was refluxed at 100-105°C for 12 to 15 hours. After the reaction was over, the mixture was cooled to 25 to 30°C; hexane (400 ml) was added to the reaction mixture and stirred for two hours. The condensed product was filtered, washed with hexane (100ml) and dried at 50 to 60°C for 4 to 6 hours. The crude product (158 g) and ethyl acetate (2.37 lt) were charged in a round bottomed flask and heated to reflux with stirring at 60 to 70°C for 30 minutes. The hot solution was filtered through cloth and the filtrate was

concentrated to almost half the volume (i.e. approximately 7 lt) under vacuum. The solution was the cooled to 15 to 20°C, stirred for two hours, filtered and washed with ethyl acetate (120 ml, 15 to 20°C) and dried at 50 to 60°C to obtain [E]-3-2-(7-chloro-2-quinolinyl)ethenyl]benzaldehyde (**I**) as a yellow crystalline solid. Melting Point 149-151°C., Yield=124.80 g (75.15 %); Purity (HPLC) = 98.96 %.

EXAMPLE 2:

[E]-1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]ethanol (II)

To a cooled (-10 to 0°C) and stirred suspension of [E]-3-2-(7-Chloro-2-quinolinyl) ethenyl]benzaldehyde (**I**) (80 g, 0.27 mol) in tetrahydrofuran (500 ml) in a 2.0 lt/4 neck round bottomed flask fitted with a mechanical stirrer, thermometer pocket and calcium chloride drying tube under nitrogen gas atmosphere, methylmagnesium chloride (150 g, approx. 2.75 molar solution in THF) was added drop wise over 45 minutes keeping the temperature to –10 to 0 °C. The reaction mixture was stirred at –05 to +05°C and progress of the reaction was monitored by TLC. After the reaction was over (approx 2 hours), ammonium chloride (300 ml, 10% aqueous solution) was added to reaction mixture and the reaction mixture was stirred for 30 minutes at 10 to 15°C followed by slow addition of water (1000 ml). The solid thus formed was filtered, successively washed with water (2 X 250 ml) and chilled isopropyl alcohol (2 X 100ml) and dried at 50 to 60°C for 6 to 8 hours to yield [E]-1-[3-[2-(7-chloro-2-quinolinyl) ethenyl]phenyl]ethanol (**II**) as a yellow solid. Melting point = 139-141°C, Yield = 75.26 g (89.43 %); Purity (HPLC) = 99.36 %., **^{1}H-NMR (300 MHz, $CDCl_3$) δ** = 01.52-01.54 (d, 3H, -CH(OH)C<u>H</u>$_3$); 02.34-02.28 (brs, 1H,-CH(O<u>H</u>)CH_3 exchangeable with D_2O); 04.97-04.90(q, 1H, -C<u>H</u>(OH)CH_3); 07.30-08.10-(m, 11H, olefinic and aromatic H)., **IR (KBr) Cm^{-1}** = 3276, 3058, 3020, 2972, 2928, 2873, 1637, 1608, 1501, 1446, 1408, 1353, 1312, 1219, 1224, 1167, 1153, 1086, 1069, 976, 032, 869, 848, 790, 697, 620, 474.

EXAMPLE 3:

[E]-1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]ethanone (III)

To a 2lt/4 neck round bottom flask fitted with a mechanical stirrer, thermometer pocket, calcium chloride drying tube and nitrogen inlet were successively charged with dichloromethane (600ml), dimethylsulphoxide (60.50 g, 54.9 ml, 0.77 mol). The solution was cooled to –55 to -60°C in a liquid N_2/methanol slush bath and oxalyl chloride (45.5 g, 32 ml, 0.36 mol) in a solution of dichloromethane (165 ml) was added drop-wise over a period of 30 minutes, keeping the temperature at –50 to -60°C and the reaction mixture was stirred for 5 minutes under nitrogen atmosphere. A suspension of [E]-1-[3-[2-(7-chloro-2-quinolinyl) ethenyl]phenyl]ethanol (**II**) (50 g, 0.16 mol) dichloromethane (1.5 lt.) was slowly added to the reaction mixture over 30 minutes at –50 to -60 °C and stirred for 15 minutes. Triethylamine (165 g, 225 ml, 1.63 mol) dissolved in dichloromethane (165 ml) was slowly added over 20 minutes. After stirring for 5 minutes at –55 to -60 °C, the temperature was slowly raised to +05 to +10 °C over 30 minutes and stirred for 15 minutes when the TLC of the mixture indicated it to be complete. Water (200 ml) was added to the reaction mixture, the organic layer was separated and aqueous layer was extracted with dichloromethane (200 ml) and the combined dichloromethane layers were neutralized (pH = 7-8) with sodium bicarbonate (approx 250-300 ml of 10% solution). Recovery of dichloromethane under vacuum provided crude residue, which was crystallized stirring in chilled isopropyl alcohol (200 ml, -5 to 0°C). After 1 hour of stirring, the resulting [E]-1-

[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]ethanone **(III)** was filtered, washed with chilled isopropyl alcohol (100ml) and dried at 50-55°C. The product thus formed was a yellow colored powder. Melting point =168-171°C ., Yield = 41.43 g (92 %); Purity (HPLC) = 99.97 %, **^{1}H-NMR (300 MHz, $CDCl_3$)** δ = 02.66 (s, 3H, $C\underline{H}_3$); 07.40 – 08.20 (M, 11H,olefinic and aromatic H):, **IR (KBr) Cm^{-1}**= 3066, 3049, 3003, 3030, 2927, 1679, 1606, 1595, 1497, 1427, 1406, 1355, 1277, 1191, 1144, 1069, 988, 968, 928, 869, 839, 790, 685, 616.

EXAMPLE 4:

Methyl-[E]-3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropanoate (IV). To a 2 lt/4 neck round bottom flask fitted with a mechanical stirrer, thermometer pocket, calcium chloride drying tube and nitrogen gas inlet, were successively charged , 1,4-dioxane (200ml), sodium methoxide (27.80 g, 0.51 mol) and [E]-1-[3-[2-(7-chloro-2-quinolinyl)ethenyl] phenyl]ethanone **(III)** (50 g, 0.16 mol) at 20 to 30°C. After stirring for 15 to 20 minutes, dimethylcarbonate (53.45 g, 50 ml) was charged and the contents were heated at 75-80 °C for 8 to 10 hours and progress of the reaction was monitored by TLC. After the reaction was over, the temperature was lowered to 20-30 °C, water (500ml) was added and the contents were stirred for 45-60 minutes. The resulting solid was filtered, slurry washed wt water (50ml) followed by washing with chilled isopropyl alcohol (50 ml) and dried in oven at 50 to 60 °C for 4 to 6 hours to afford Methyl-[E]-3-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropanoate **(IV)** as a pale yellow powder. Melting point =117 to 121°C, Yield = 51.17 g (86.72%); Purity (HPLC) = 98.51%:, **^{1}H-NMR (300 MHz, $CDCl_3$ + DMSO-d_6)** δ = 03.76(s, 3H, $OC\underline{H}_3$); 04.12 (s, 2H, $COC\underline{H}_2CO_2CH_3$); 07.38-08.20 (m, 11H, olefinic and aromatic H) :, **IR (KBr) Cm^{-1}** = 3426, 3108, 3066, 3030, 2999, 2954, 1759, 1656, 1609, 1593, 1498, 1446, 1407, 1385, 1336, 1276, 1253, 1215, 1176,1144, 1080, 1068, 1021, 972, 929, 911, 883, 835, 797, 729.

EXAMPLE 5:

Methyl-[E]-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-(2-carboxymethyl)-oxopropyl]benzoate (V):

A 3.0 lt/4 neck round bottom flask fitted with a mechanical stirrer, thermometer pocket, calcium chloride drying tube under nitrogen gas atmosphere was successively charge with dimethylformamide (1200ml), Methyl-[E]-3-[3-[2-(7-chloro-2-quinolinyl) ethenyl]phenyl]-3-oxopropanoate (**IV**) (300 g, 0.82 mol), methyl-2-bromoethyl benzoate (237 g, 1.03 mol) and crushed K_2CO_3 (146 g, 1.05 mol) at 25 to 30 °C and the mixture was heated at 57 to 63 °C with vigorous stirring for 6 to 8 hours. After the reaction over, the mixture was cooled to 20 to 25 °C ammonium acetate solution (15% aqueous solution, 900 ml) was added slowly to quench the reaction and stirred for 1 hour. Additional water (1800 ml) was slowly added to the mixture ad stirred for 2 hours. The precipitated solid was filtered, washed with water (2400ml) and then the wet product as stirred with methanol (1800 ml) at 20 to 30 °C for 1 hr. Finally, Methyl-[E]-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-(2- carboxymethyl)oxopropyl]benzoate (**V**) was filtered and washed with methanol (300 ml) and obtained as a pale yellow powder after being dried in the oven at 60-65 °C for 6-8 hours. Melting point = 119 to 122 °C Yield = 368.5 g (87.77 %); Purity (HPLC) = 98.33 %:, **^{1}H-NMR (300 MHz, $CDCl_3$) δ** = 03.60-03.79 (d, 2H, --CHC$\underline{H}_2$- merged with-OCH_3); 03.63 (s,3H, OC$\underline{H}_3$) 03.90 (s, 3H, OC$\underline{H}_3$); 05.05-05.09 (t, 1H, -CO-C$\underline{H}$-(CH_2)CO-); 07.24-08.22 (m, 15H, olefinic and aromatic H):, **^{13}C-NMR (75.47 MHz, $CDCl_3$) δ** = 34.14 ($\underline{C}H_2$-$C_6H_4CO_2CH_3$); 52.11 (OC-CH-CO_2-$\underline{C}H_3$); 52.53 (O$\underline{C}H_3$); 54.99 (O$\underline{C}H_3$); 119.67, 125.62, 126,96, 127.09, 127.39, 128.06, 128.65, 129.04, 129.32, 129.66, 131.03, 131.67, 132.16, 133.64, 135.44, 136.10, 136.83, 139.98, 146.48, 156.20 (olefinic and aromatic C); 167.55($\underline{C}$O), 169.77(aliphatic $\underline{C}O_2CH_3$); 194.88 (aromatic $\underline{C}O_2CH_3$):, **IR (KBr) Cm^{-1}** = 3066, 3021, 2952, 2843, 1751, 1711, 1677, 1607, 1576, 1498, 1436, 1337, 1303, 1285, 1266, 1157, 1134, 1084, 1067, 963,926, 871, 762,684,622.

EXAMPLE 6:

Methyl-[E]-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropyl]benzoate (VI)

Step 1: To a 2.lt/4 neck round bottom flask, fitted with mechanical stirrer, thermometer pocket and reflux condenser were successively charged glacial acetic acid (585 ml), concentrated hydrochloric acid (117 ml), Methyl-[E]-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-(2-carboxymethyl)oxopropyl]benzoate (**V**) (117 g, 0.22 mol) at 25 to 30 °C and the reaction mixture was heated with stirring at 60-65 °C for 10 to 12 hrs. After the reaction was over(monitored by TLC), the mixture was cooled to 25 to 30 °C, saturated ammonium chloride solution (540 ml) was slowly added to the reaction and stirred for 1 hour. The resulting crude product containing impure Methyl-[E]-2-[3-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropyl]benzoate (**VI**)and its corresponding acid **VIA** was filtered, successively washed with water (234 ml), methanol (117 ml) and dried at 50 to 60 °C and was used as such in the next step. Yield = 107 g.

Step 2: To a 3 lt/4 neck round bottom flask, fitted with a mechanical stirrer, thermometer pocket, and reflux condenser were successively charged acetone (1.28 lt), K_2CO_3 (40 g, 0.29 mol), **step 1** product (107 g, 0.24 mol)and methyl iodide (31.5 g, 13.8 ml, 0.22 mol) at 25 to 30 °C and the reaction mixture was slowly heated to 50 to 55 °C and stirred for 6 to 8 hours. After the reaction was over(as monitored by TLC), the mixture was filtered through hyflow bed to remove the precipitated inorganic salts and the bed was washed with acetone (255 ml). Complete recovery of acetone under vacuum at 40 to 45°C provided crude

residue to which were successively charged dichloromethane (1.1 ml) and water (430 ml) at 20 to 25 °C. After stirring for 5 minutes, the organic layer was separated, washed with water (430ml), and evaporated at 35 to 40 °C under vacuum. To the crude residue thus obtained was charged isopropyl alcohol (270 ml) and the mixture was cooled to 0 to +05 °C and stirred for 4 to 6 hours. Filtration followed by washing with cold IPA(100 ml) afforded Methyl-[E]-2-[3-[3-[2-(7-chloro-2-quinolinyl)ethenyl] phenyl]-3-oxopropyl]benzoate (**VI**) as a pale yellow to light brown solid. Yield = 96.5 g (69.2 % on 100 % assay basis); Purity = 99.03 %; Assay (HPLC) = 75.2 % .

Step 3:-<u>Purification of crude keto ester (VI) : Method I</u>: To a 1 lt/3 neck round bottom flask fitted with a mechanical stirrer and a thermometer pocket were charged the above crude Methyl-[E]-2-[3-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropyl]benzoate (**VI**) obtained in **step 2** (45 g,), dichloromethane (225 mL) and the mixture was stirred at 38 to 40 °C for 15 minutes, during which, complete dissolution of solid took place. Methanol (450 mL) was slowly added to the solution and the mixture was stirred for 20 minutes at 28 to 30 °C, the organic layer was decanted and tarry and oily material was separated. The above decanted solution was filtered through hyflow bed to remove small amount of suspended polymeric material and dichloromethane from the mixture was distilled off at 40 to 42 °C followed by stirring at 5 to 10 °C for 8 hrs. The solid thus formed was filtered, washed with chilled methanol (45 mL, 0 °C) and dried in oven at 50 to 55 °C for 6 hrs to obtain pure (**VI**) as a pale yellow

solid. Melting point = 121 to 124°C. Yield = 30.58 g (68 %); Purity (HPLC) = 99.22 %; Assay (HPLC) = 98.14 %.

Purification of crude (VI): Method II: : To a 500 mL/3 neck round bottom flask fitted with a mechanical stirrer and a thermometer pocket were charged the above crude **VI** obtained in step 2 (45 g) and acetonitrile (450 mL) and the mixture was heated to 75-80 °C for 20 minute, during which time complete dissolution of solid took place. The solution was filtered hot through hyflow bed to remove the suspended and tarry material and then slowly cooled to 23 to 25 °C and stirred for 8 hrs at that temperature. The precipitated material was filtered and successively washed with cold acetonitrile (2 x 25 mL) and hexanes (45 mL) and dried at 55 to 60°C to obtain pure Methyl-[E]-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropyl]benzoate (**VI**) as a light yellow to cream colored powder. Melting Point = 122 to 124°C; Yield =34.5 g (76.66 %). Purity (HPLC) = 99.52 %; Assay (HPLC) = 98.92 %. **^{1}H-NMR ($CDCl_3$) δ** = 03.40 (bs, 4H, -CO-C<u>H</u>$_2$-C<u>H</u>$_2$C$_6$H$_4$CO$_2$CH$_3$); 03.90 (s, 3H, OC<u>H</u>$_3$); 07.38-08.28-(complex multiplet, 15H, olefinic and aromatic H).

EXAMPLE 7:

Methyl-[(E)]-2-[3(S)-[3-[2-[7-chloro-2-quinolinyl)ethenyl]phenyl]-3-hydroxypropyl] benzoate (VII):

To a 1.0 lt/4 neck round bottom flask fitted with a mechanical stirrer, thermometer pocket and calcium chloride drying tube under nitrogen gas atmosphere were charged (-)-diisopinocamphenylchloroborane (190 mL, 65 to 75% solution in heptanes) and tetrahydrofuran at –5 to 0°C for 10 minutes.

Purified Methyl-[E]-2-[3-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-oxo-propyl]benzoate **(VI)** (100 g, 0.22 mol) dissolved in anhydrous THF (300 mL) was slowly added over 20 minutes and reaction mixture was allowed to stir for 6 hours at 0°C and then at 12 to 15°C till the reaction was complete (12 hours). After the reaction was over, the mixture was poured into aqueous solution of diethanolamine (3 lt. of 1% solution) at 28 to 30 °C and stirred for 20 minutes followed by addition of hexanes (1 lt). The mixture was stirred for 30 minutes at 30 °C, the solid was filtered, successively washed with water (2 x 200 mL), hexanes (200 mL) and dried at 40 to 45 °C for 8 hrs to yield crude hydroxyl ester **(VII)** as a yellow monohydrate powder. Moisture content (approx) =7.0 – 8.0% w/w, Yield = 98.31 g; Purity (HPLC) = 99.70 %; Assay (HPLC) = 95.78 %:

Purification of hydroxy ester (VII) To a 2 .0lt/3 neck round bottom flask fitted with a mechanical stirrer and a thermometer pocket were charged the above crude **VII** (95 g), methanol (950 mL) and triethylamine (9.5 mL) and the mixture was heated to 65 to 70 °C for 20 minutes, during which time complete dissolution of solid took place. The solution was filtered hot through hyflow bed to remove the suspended and tarry material and then 50% of methanol was distilled off slowly under normal conditions and the solution was cooled to -12 to -10 °C and stirred for 8 hrs at that temperature. The precipitated material was filtered under vacuum, washed with chilled methanol (50 mL) and dried at 55 to 60°C to obtain pure Methyl-[(E)-2-[3(S)-[3-[2-[7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-hydroxypropyl]benzoate **(VII)** as a light yellow colored powder. Melting point= 99 to 103 °C; Yield = 90 g (94.5 % from pure **VI**); Purity (HPLC) =99.85 %;

Assay (HPLC) = 99.05 %. **^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm)** = 02.06-02.17(t, 2H, HOCH-CH_2-$C\underline{H}_2$); 03.08-03.17 (t, 2H, -HOCH-$C\underline{H}_2CH_2$); 03.86 (s, 3H, $OC\underline{H}_3$); 04.74-04.77 (t, 1H, OH); 07.25-07.86(complex multiplet, 15H, olefinic and aromatic H).

EXAMPLE 8:

[(E)]-2-[3(S)-[3-[2-(7-Chloro-2-quinolinyl)-ethenyl]phenyl]-3-hydroxypropyl]phenyl] -2-propanol (VIII):

To a 3 lt/4 neck round bottom flask fitted with a mechanical stirrer, reflux condenser and calcium chloride drying tube under an atmosphere of nitrogen gas were charged tetrahydrofuran (1.25 lt) and anhydrous cerium chloride (55 g, 0.10 mol) and the grayish white suspension was heated to reflux for 2 hours. The suspension was then cooled to –15 to -10°C and methyl magnesium chloride (435 g, 2.75 molar solution in THF) was added drop wise over 30 minutes keeping the temperature at –5 to 0 °C and the contents were stirred for 1 hour at the same temperature. Methyl-[(E)-2-[3(S)-[3-[2-[7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-hydroxypropyl] benzoate **(VII)** (100 g, 0.22 mol, azeotropically dried in refluxing toluene) dissolved in toluene (1.0 lt) was added drop wise over 30 minutes at –10 to 0 °C. The solution was stirred at 0 to +05 °C and the progress of the reaction was monitored by TLC. After stirring for two hours, the reaction mixture was poured into a suspension of hyflow supercel (200 g) in 10 % ammonium chloride solution (1.0 lt) and stirred for 15 to 20 minutes. The above contents were filtered through hyflow bed and the bed was washed with toluene(200 ml). The organic layer was separated and the aqueous layer was

extracted with toluene (200 ml) and the combined toluene were washed with water (2 X 250 ml) and dried over sodium sulphate. Complete recovery of toluene under vacuum at 50 to 55 °C provided viscous oil which was dissolved in toluene (400 ml) at 30 to 40 °C. Hexane (1.0 to 1.2 lt) was slowly added over 30 minutes to the above solution and the mixture was stirred for 5 to 6 hours at 35 to 40 °C. The precipitated solid was filtered, washed with hexane (500 ml) and dried at 45 to 50 °C for 4 to 6 hours to provide [(E)-2-[3(S)-[3-[2-(7-Chloro-2-quinolinyl)-ethenyl]phenyl]-3-hydroxypropyl]phenyl]-2-propanol **(VIII)** as a off white to light yellow powder. Melting point = 118 to 121°C:, Yield = 84.75g (84.75%); Purity (HPCL)= 99.62%; Assay (HPLC) =98.05%:, **^{1}H-NMR ($CDCl_3$) δ =** 01.65 and 01.68 (2s, 6H, $C(OH)(C\underline{H}_3)_2$; 02.13-02.17(q, 2H, $-CH(OH)C\underline{H}_2CH_2-$); 03.13-03.30(dd, 2H, $CH(OH)CH_2-C\underline{H}_2$); 3.46 (bs, 1H, $C(O\underline{H})(CH_3)_2$; 4.42 (bs, 1H, $CH(O\underline{H})CH_2-$); 04.69-04.71 (t, 1H, $CH(OH)CH_2-C\underline{H}_2$); 07.13-07.55 (complex multiplet, 15H, olefinic and aromatic H); **^{13}C-NMR ($CDCl_3$) δ =** 29.67 ($\underline{C}H_3$), 31.64 ($C\underline{H}_3$), 31.96(HO-CH-$\underline{C}H_2$-CH_2); 41.85(HO-CH-$CH_2\underline{C}H_2$); 72.82(HO-$C\underline{H}CH_2CH_2$); 73.85 ($HO\underline{C}(CH_3)_2$); 119.26, 124.85, 125.43, 126.83, 127.06, 135.26, 135.93, 136.03, 140.16, 145.18, 145.47, 148.26, 156.76(aromatic C) **IR (KBr) Cm^{-1}** = 3392, 3056, 2967, 2925, 2869, 1719, 1636, 1607, 1497, 1441, 1408, 1372, 1310, 1261, 1143, 1131, 1068, 963, 929, 863,837, 787, 761, 697, 621.

EIMS m/z = 457(M^+)

EXAMPLE 9:

Preparation of [E]-1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-2-propen-1-ol (II): To a cooled (-10 to 0 °C) and stirred suspension of [E]-3-2-(7-Chloro-2-quinolinyl)ethenyl]benzaldehyde (**I**) (100g, 0.34 mol) in tetrahydrofuran (300 mL) and toluene (1000 mL) in a 3.0 lt/4 neck round bottomed flask fitted with a mechanical stirrer, thermometer pocket and calcium chloride drying tube under nitrogen gas atmosphere, vinylmagnesium bromide (500 g, , approx. 1.0 molar solution in THF) was added drop wise over 60 minutes keeping the temperature to –10 to 0 °C. The reaction mixture was stirred at –15 to + 20 °C and progress of the reaction was monitored by TLC. After the reaction was over (approx 2 hours), ammonium acetate (600 mL, 10% aqueous solution) was added to reaction mixture and the reaction mixture was stirred for 30 minutes. The toluene layer was separated and the aqueous layer was extracted with toluene (2 x 1000 mL), the toluene layers were combined, washed with water (2x1000 mL), dried over sodium sulfate and evaporated under vacuum at 55 to 60 °C to afford crude residue of [E]-1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-2-propen-1-ol **(II)** which is used as such in the next stage. Yield 126 g. Purity (HPLC) =92.5 %

EXAMPLE 10: Preparation of Methyl-[E]-2-[3-[3-[2-(7-Chloro-2-quinolinyl) ethenyl] phenyl]-3-oxopropyl]benzoate (VI) To a 1.0lt/4 neck round bottom flask fitted with a mechanical stirrer, thermometer pocket and calcium chloride drying tube under nitrogen gas atmosphere, were successively charged crude 1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-2-propen-1-ol (**II**) (125 g, 92.5 % pure), acetonitrile, methyl-2-iodobenzoate (100 g, 0.38 mol) and triethylamine (112 mL) and the mixture was stirred for 15 min. Palladium acetate (1.0 g) was

then added and the mixture was slowly heated to reflux at 80 to 85 °C and progress of the reaction was monitored by TLC. After the reaction was over (12-15 hr), fresh acetonitrile was added to the reaction mixture and the hot solution was filtered through hyflow bed to remove the palladium salts and then allowed to stir at 20 to 25 °C for 8 hr by which time most of the product had precipitated out. The solid was filtered and successively washed with cold (5 to 10 °C) acetonitrile (125 mL), mixture of water and acetonitrile (125 mL +125 mL each), slurry washed with cold acetonitrile (125 mL) and finally with hexanes (125 mL) and dried at 55 to 60 °C to afford crude keto ester (**VI**) as a brownish colored powder. Yield = 111.2 g (69.6% on 100 % basis); Purity (HPLC) =97.21%; Assay (HPLC) = 94.34 %).

Purification of crude keto ester (VI) : Crude ketoester (**VI**) (110 g) was charged into acetonitrile (1100 mL) in a 2 lt/3 neck round bottom flask and the mixture was heated to 75 to 85 °C till all the material had got dissolved and then filtered hot through hyflow bed to remove the suspended and tarry material. The solution was cooled to 20 °C and stirred for 12 hrs at that temperature and the precipitated material was filtered and successively washed with cold acetonitrile (2 x 55 mL) and hexanes (110 mL) and dried at 55 to 60 °C to obtain pure Methyl-[E]-2-[3-[3-[2-(7-Chloro-2-quinolinyl) ethenyl]phenyl]-3-oxopropyl]benzoate (**VI**) as a light yellow to cream colored powder. 122 to 124 °C Yield = 96.5 g (62.2 % from benzaldehyde **I**). Purity (HPLC) = 99.5 %. Assay (HPLC) = 98.5%; **^{1}H-NMR ($CDCl_3$)** δ = 03.40 (bs, 4H, -CO-C$\underline{H}_2$-

$C\underline{H}_2C_6H_4CO_2CH_3$); 03.90 (s, 3H, $OC\underline{H}_3$); 07.38-08.28-(complex multiplet, 15H, olefinic and aromatic H).

ADVANTAGES

- ❖ The process is high yielding .
- ❖ The process is cost effective user friendly, environmentally clean.
- ❖ The process is scalable and compatible for industrial application.
- ❖ The process does not require any stringent operational conditions.
- ❖ The process does not require any sophisticated infrastructure.
- ❖ The process leads to a title compound with high purity.

WE CLAIM:

1. A process for synthesizing diol **(VIII)**-an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods and then oxidizing directly under "Swern's conditions" to get a ketone of formula **III**,

(c) enolizing the said ketone in presence of a mild base such as alkali metal alkoxide and then reacting it with dialkyl carbonate under conditions effective to yield a β- ketoester of formula **IV**,

(d) benzylating the said β-ketoester so obtained in the preceding step to form the benzoate of formula **V** in presence of mild inorganic base followed by decarboxylating the said benzoate to a mixture of a ketoester of formula **VI** and its corresponding acid of formula **VIA** in the presence of acidic conditions,

(e) alkylating the acid **VIA** present in the mixture in the preceding step to obtain ketoester of formula **VI** and purifying it if so desired,

(f) asymmetrically reducing the ketoester of formula **VI**, to a chiral alcohol of formula **VII** using (-) diisopinocamphenylchloroborane (-DIPCl) in presence of less than 4 times v/w aprotic solvent and optionally in presence of Lewis base with respect to the said ketoester of formula **VI**,

(g) treating the said chiral alcohol **VII** with cerium halo salt, and alkylmagnesium halide followed by isolating the title compound using hyflow supercel and ammonium

chloride to get the intermediate diol of formula **VIII**.

2. A process for synthesizing diol **(VIII)**-an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible ethereal solvent to yield the alcohol of formula **(II)** by addition of ammonium salt and water

(c) subjecting the said alcohol to Heck coupling with methyl-2-iodobenzoate in presence of Lewis base, acetonitrile, and palladium acetate to yield ketoester **(VI),**

(d) asymmetrically reducing the ketoester of formula **VI**, to a chiral alcohol of formula **VII** using (-) diisopinocamphenylchloroborane (-DIPCl) in presence of less than 4 times v/w aprotic solvent and optionally in presence of Lewis base with respect to the said ketoester of formula **VI**,

(e) treating the said chiral alcohol **VII** with cerium halo salt, and alkylmagnesium halide followed by isolating the title compound using hyflow supercel and ammonium chloride to get the intermediate diol of formula **VIII**.

3. A process for synthesizing alcohol **(II)**-an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods.

4. A process for synthesizing ketone **(III)**-an intermediates of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium salt and water followed by isolating the alcohol thus precipitated by any known methods and then oxidizing directly under "Swern's conditions" to get a ketone of formula **III,**

5. A process for synthesizing ketoester **(VI)**-an intermediate of Montelukast Sodium which comprises:

(a) preparing benzaldehyde of formula **I** in a conventional manner,

(b) reacting the said benzaldehyde **I** with Grignard reagent in water miscible etheral solvent to precipitate the alcohol of formula **(II)** by addition of ammonium

salt and water followed by isolating the alcohol thus precipitated by any known methods and then oxidizing directly under "Swern's conditions" in presence of Lewis base, to get a ketone of formula **III**,

(c) enolizing the said ketone in presence of a mild base such as alkali metal alkoxide and then reacting it with dialkyl carbonate under conditions effective to yield a β-

ketoester of formula **IV**,

(d) benzylating the said β-ketoester so obtained in the preceding step to form the benzoate of formula **V** in presence of mild inorganic base followed by decarboxylating the said benzoate to a mixture of a ketoester of formula **VI** and its corresponding acid of formula **VIA** in the presence of acidic condition,

(d) alkylating the acid **VIA** present in the mixture in the preceding step to obtain ketoester of formula **VI** and purifying it if so desired,

(e) asymmetrically reducing the ketoester of formula **VI**, to a chiral alcohol of formula **VII** using (-) diisopinocamphenylchloroborane (-DIPCl) in presence of less than 4 times v/w aprotic solvent and optionally in presence of Lewis base with respect to the said ketoester of formula **VI**,

6. A process as claimed in the preceding claim wherein the reaction in step (a) is carried out in presence of acetic anhydride at a temperature in the range of 90-150°C for a period of 10-30 hrs., preferably at 100-110 °C for 12-15 hrs.

7. A process as claimed in the preceding claim wherein the Grignard reagent used is of formula R_1MgX where R_1 is alkyl with C1 to C4 exemplified by methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or vinyl and X is halide preferably chloride or bromide, the reaction being carried out in presence of ethereal solvent including but not restricted to 2-methoxytetrahydrofuran, tetrahydropyran, 1, 2-dimethoxyethane, 1, 2-diethoxy -ethane, preferably tetrahydrofuran or mixture thereof, at a temperature ranging from -25 to +40°C, preferably at -5 to +10°C.

8. A process as claimed in the preceding claim wherein the direct isolation and crystallization of the alcohol of formula **II,** in step (b), after workup is effected by adding calculated amount of 1 to 25% preferably 2 to 10% more preferably 10% aqueous solution of ammonium salt such as ammonium acetate, ammonium chloride, preferably ammonium chloride solution in an amount of 2 to 10 preferably 3 to 5 times of benzaldehyde **(I)** and water in the range of 5 to 50 preferably 10 to 15 times of benzaldehyde **(I)** to the reaction mixture and then straightaway crystallizing the product by stirring the mixture at –10°C to 35°C preferably 5°C -10°C for extended period of 2 to 10 preferably 4 to 8 hours, then isolating by centrifugation, filtration and drying.

9. A process as claimed in the preceding claim wherein the oxidation of alcohol **(II)** in step (b) is performed under Swern's conditions employing oxalyl chloride, dimethyl sulfoxide and Lewis base exemplified by alkyl amine such as triethyl amine, tri n-propylamine, tri n-butylamine, tri n-pentylamine, and diisopropyl ethyl amine preferably triethyl amine of 5 to 15 molar preferably 8 to 12 molar

equivalents w. r. t the alcohol **(II)** as the reagents and the reaction is performed at -60°C to +30°C preferably -60°C to +10°C over a period of 4 to 6 hrs., employing molar equivalents of DMSO between 2 to 8, preferably 4 to 6 equivalents and that of oxalyl halide between 1.5 to 4, preferably 2 to 2.5 equivalents with respect to the alcohol **(II).**

10. A process as claimed in the preceding claim wherein the enolization of the ketone **III** in step (c) is effected by milder bases of formula R_3OM wherein R_3 is alkyl with C1 to C3 and M is Na or K selected from alkali metal alkoxide including sodium methoxide, sodium ethoxide, sodium n-propoxides, sodium n-isopropoxide, sodium n-butoxides, sodium isobutoxide, sodium tertiary butoxide as well as their potassium salt derivatives in an amount of 1.5 to 7 molar equivalents w.r.t. ketone with dialkyl carbonate wherein alkyl may be with C1 to C3 in an amount ranging from 2 to 8 preferably 3 to 4 molar equivalents of ketone, in polar solvents like THF, 1,2 dimethoxyethane, 1,2 diethoxyethane, dimethyl formamide, dimethyl acetamide preferably 1,4-dioxane in an amount of 2 to 10 v/w with regard to ketone at 10 to 100°C, preferably at 40 to 90°C more preferably at 60 to 90°C , still more preferably at 70 to 80°C.

11. A process as claimed in the preceding claim wherein the benzylation of the β-ketoester of formula **IV** in step (d) is performed by reacting the said ketoester with alkyl-2- halomethylbenzoate preferably methyl or ethyl and n-propyl ester derivative and halo may be chloro, bromo or iodo particularly alkyl-2-bromomethylbenzoate using much milder and safer alkali metal bases like sodium or potassium carbonates in polar aprotic solvents like dimethylformamide,

dimethylacetamide, dimethylsulfoxide, hexamethylphosphorous-triamide, 1, 4 - dioxane, tetrahydrofuran, 1, 2- dimethoxyethane and 1, 2 – diethoxy -ethane etc. using 1.1 to 1.5 molar equivalents of methyl 2-bromomethyl benzoate, 1 to 3 molar, preferably 1 to 1.5 molar equivalents of anhydrous potassium carbonate and 2 to 10, preferably 3 to 5 times v/w of dry dimethylformamide w. r. t. the amount of β - keto ester (**IV**) 10 to 150 °C, preferably at 55 to 65°C, over a period of 4 to 48 hrs, preferably over 8 to 12 hrs.

12. A process as claimed in the preceding claim wherein the decarboxylation in step (d) is carried out using a mixture of acetic acid and hydrochloric acid in a known manner and the purification is conducted by crystallizing with 8 to 12 times acetonitrile, or with a mixture of dichloromethane and methanol 4 to 15 preferably 7 to 10 times v/w each w.r.t. ketoester.

13. A process as claimed in the preceding claim wherein the asymmetrical reduction of the ketoester **VI** to chiral alcohol **VII** is effected by employing 1.2 to 2.0 equivalents of (-) diisopinocamphenylchloroborane (-DIPCl) (65-75% solution in hexanes) in 1.5 to 4.0 times v/w of aprotic solvent exemplified by ethers such as diethyl ether, diisopropyl ether, di n-butyl ether, diisopentyl ether, anisole, cyclic ethers such as tetrahydropyran, 2-methyltetrahydrofuran, and 2-ethoxyfuran, most preferably tetrahydrofuran and the Lewis bases that may be used include but are not limited to triethylamine, tri n-propylamine, tri n-butylamine, trisopropylamine, triisobutylamine, most preferably diisopropylethylamine in 0.25 to 2 molar equivalents, preferably 0.5 to 0.75 molar equivalents w. r. t. the keto ester **(VI).**

14. A process as claimed in the preceding claim wherein the cerium halo salt and alkylmagnesium halide used for converting the chiral alcohol VII to the diol intermediate VIII is selected from methyl or ethyl or and propylmagnesium chlorides, bromides or iodides and the isolation is undertaken by simply dumping the reaction mass into as stirred suspension of hyflow supercel in 8 to10% ammonium salt preferably ammonium chloride followed by centrifuging or filtering through a bed of hyflow supercel.

15. A process as claimed in claim 2 wherein the Lewis base used in Heck coupling of alcohol (II) in step (c) include but are not limited to alkyl amines like triethylamine, tri n-propylamine, tri n-butylamine, diisopropyl ethyl amine, in an amount of 0.1 to 10 times preferably 0.5 to 1 times, palladium acetate used may vary from 0.1% w/w to 2.5 % w/w, preferably 0.5 to 1.5% w/w and the amount of acetonitrile may vary between 1 and 100 times, preferably 3 and 10 times v/w w. r. t the benzaldehyde (I) used and the reaction is performed at 10 to 100°C, preferably at 65 to 75°C over a period of 1 to 100 hrs, preferably for 5 to 25 hrs.

16. A process for synthesizing diol (VIII), alcohol (II), ketone(III), and ketoester (VI) an intermediates of Montelukast Sodium substantially as herein described with reference to the examples and drawings.

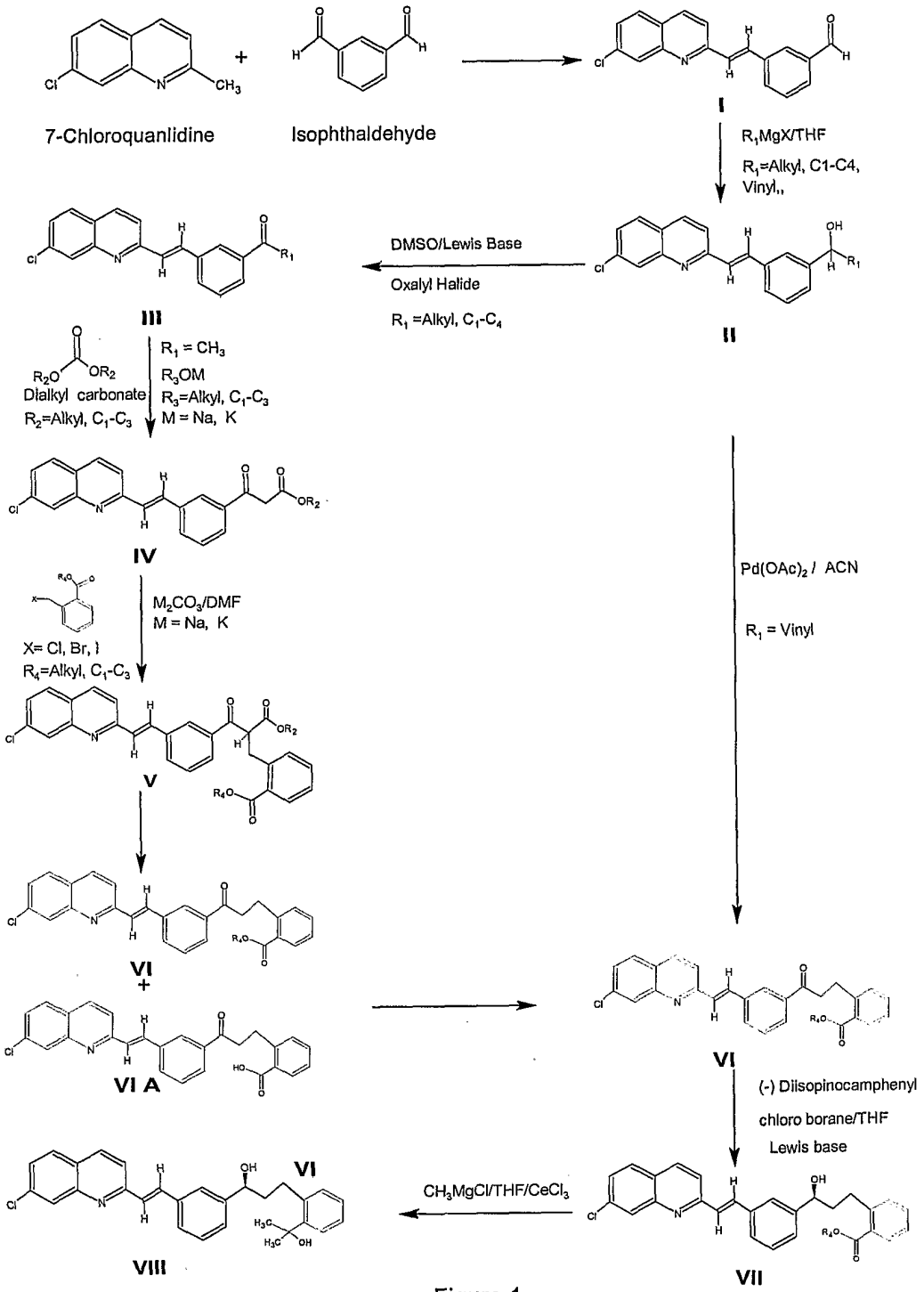

7-Chloroquanlidine
Isophthaldehyde
I
R1MgX/THF
R1=Alkyl, C1-C4, Vinyl,,
II
DMSO/Lewis Base
Oxalyl Halide
R1 =Alkyl, C1-C4
III
R1 = CH3
R3OM
R3=Alkyl, C1-C3
M = Na, K
Dialkyl carbonate
R2=Alkyl, C1-C3
IV
M2CO3/DMF
M = Na, K
X= Cl, Br, I
R4=Alkyl, C1-C3
V
VI
+
VI A
Pd(OAc)2 / ACN
R1 = Vinyl
VI
(-) Diisopinocamphenyl
chloro borane/THF
Lewis base
VII
CH3MgCl/THF/CeCl3
VIII

Figure 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN2005/000280

A. CLASSIFICATION OF SUBJECT MATTER
C07D215/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2005	30/12/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Zellner, A

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