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(54) Title: AN ENANTIOSELECTIVE PROCESS FOR THE SYNTHESIS OF (2S,4R)-4-HYDROXYPIPECOLIC ACID

(57) Abstract: The present invention relates to an improved process for synthesis of 4-hydroxy pipercolic acid. The present invention relates to an improved enantioselective process for the synthesis of (2S,4R)-4-hydroxypipercolic acid via Co(III) (salen)-catalyzed two stereocentered Hydrolytic Kinetic Resolution (HKR) of racemic 1,3-azido epoxide with good yields and high optical purity without any protecting groups. 10 31



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AN ENANTIOSELECTIVE PROCESS FOR THE SYNTHESIS OF (2*S*,4*R*)-4-HYDROXYPIPECOLIC ACID

FIELD OF THE INVENTION

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The present invention relates to an enantioselective process for the synthesis of (2*S*,4*r*)-4-hydroxypipelicolic acid. Particularly, the present invention relates to an improved process for the synthesis of (2*S*, 4*R*)-4-hydroxypipelicolic acid *via* Co (III) (salen)-catalyzed two stereocentered Hydrolytic Kinetic Resolution (HKR) of racemic 1,3-azido epoxide.

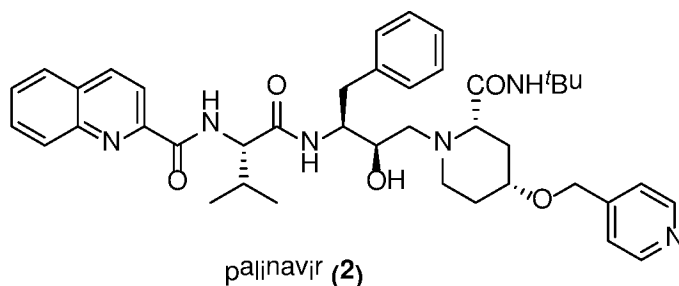
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BACKGROUND OF THE INVENTION

Pipelicolic acid and 4-hydroxypipelicolic acid are natural non-proteinogenic amino acids found in plants. In addition to the free amino acid, pipelicolic acid is also found in complex biologically active molecules. Derivatives of pipelicolic acid are known to display anaesthetic, NMDA agonist and antagonist, anticoagulant and glycosidase. Pipelicolic acids have also been used in peptide chemistry as analogues of proline. In the light of the diverse activities displayed by such pipelicolic acid derivatives, single enantiomer libraries using such compounds as the scaffold would be a highly desirable tool for screening.

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The synthesis of chiral functionalized pipelicolic acids is of considerable interest since this structural unit is widely found in biologically active natural products and synthetic pharmaceuticals. In particular, (2*S*,4*R*)-4-hydroxypipelicolic acid **1** (Fig. 1) is a naturally occurring non proteinogenic amino acid, isolated from the leaves of *Calliandra pittieri* and *Strophantus scandens*. It is a constituent of cyclodepsipeptide antibiotics such as virginiamycin S₂. It is also a key precursor in the syntheses of NMDA receptor antagonists 4 and HIV-protease inhibitor such as palinavir **2**.



In addition, 4-hydroxypipicolinic acid derivatives have been used in protein design to study its conformational effect in peptidomimetics. Due to its potential biomedical importance, considerable effort has been directed toward the enantioselective synthesis of (2S,4R)-4-hydroxypipicolinic acid **1**. However several of them suffer from certain limitations such as the use of chiral building blocks, inefficient separation of diastereoisomers, expensive reagents and a lengthy number of steps, etc.

A common synthetic route to racemic 4-hydroxypipicolinic acid derivatives has been to use an acyliminium ion cyclisation on a suitably protected homoallylic amine (Hays et al.; J. Org. Chem. 1990, 56, 4084–4086). This approach has been adapted to furnish enantiomerically pure cis 4-hydroxypipicolinic acid derivatives provided a chiral protecting group is used in the synthesis (Beaulieu et al.; J. Org. Chem. 1997, 62, 3440–3448). However, the protecting group does not offer any asymmetric induction, and the enantiomers have to be separated by a laborious co-crystallisation with (–)-camphorsulphonic acid.

Another common theme in the synthesis of enantiomerically pure cis 4-hydroxypipicolinic acid derivatives has been to fix the stereochemistry of the carboxylate group using a (L)-aspartic acid and use this stereocentre to direct reduction of a ketone at the 4-position (Golubev et al.; Tetrahedron Lett. 1995, 36, 2037–2440; Bousquet et al.; Tetrahedron 1997, 46, 15671–15680). Two routes derived from carbohydrate starting materials have been reported, an atom inefficient synthesis starting from D-glucoheptono-1,4-lactone (Di Nardo and Varela; J. Org. Chem. 1999, 64, 6119–6125) and from D-glucosamine (Nin et al.; Tetrahedron 1993, 42, 9459–9464). All of these approaches yield only the cis-diastereoisomer.

The most common approach has been to synthesise the cis-diastereoisomer followed by a tedious inversion of the 4-hydroxy group. An alternative approach has utilised a ring expansion of 4-hydroxy-L-proline (Pellicciari et al.; Med. Chem. Res. 1992, 2, 491–496) and provides access to both diastereoisomers of 4-hydroxy-L-pipecolates.

Article titled “Concise enantioselective synthesis of (+)-L-733,060 and (2S,3S)-3-hydroxypipicolinic acid by cobalt(III)(salen)-catalyzed two-stereocenter hydrolytic kinetic resolution of racemic azido epoxides” by DA Devalankar *et al.* published in *Synlett*, 2014; 25(1) pp 102-104 reports an efficient synthesis of the 2,3-disubstituted piperidines (+)-L-

733,060 and (2S,3S)-3-hydroxypipicolinic acid ($\geq 99\%$ ee) in high optical purity from commercially available starting materials and on a two-stereocenter HKR of racemic azido epoxide.

5 Article titled "Synthesis of (2R,4R)- and (2S,4S)-4-hydroxypipicolinic acid derivatives and (2S,4S)-(-)-SS20846A" by Mark Sabat et al. published in *Tetrahedron Letters*, 2001, 42(7) pp 1209–1212 reports syntheses of protected derivatives of both enantiomers of trans-4-hydroxypipicolinic acid (2) and the natural product (-)-SS20846A (3) were accomplished from vinylglycinols. Key transformations involved construction of the piperidine ring via
10 ring-closing metathesis (Grubbs' catalyst) and installation of the 4-hydroxy substituent by Prevost reaction. X-Ray diffraction analyses conclusively established the regio- and stereochemistry of key intermediates.

Article titled "Stereoselective synthesis of (2S,4R)-4-hydroxypipicolinic acid" by
15 Ernesto G. Occhiato et al. published in *European Journal of Organic Chemistry*, 2008, 3, pp 524–531 reports a new synthetic route to enantiopure (2S,4R)-4-hydroxypipicolinic acid from commercial ethyl (3S)-4-chloro-3-hydroxybutanoate. The synthesis is based on the Pd-catalyzed methoxycarbonylation of a 4-alkoxy-substituted δ -valerolactam-derived vinyl triflate followed by the stereocontrolled hydrogenation of the enamine double bond. The final
20 product was obtained after exhaustive hydrolysis in 20 % yield over 10 steps.

Article titled "Asymmetric synthesis of cis-4- and trans-3-hydroxypipicolinic acids" by Carlos Alegret et al. published in *European Journal of Organic Chemistry*, 2008, 1789–1796 reports enantioselective syntheses of cis-4- and trans-3-hydroxypipicolinic acids from 2,3-
25 epoxy-5-hexen-1-ol (7) are described. Regioselective C-3 or C-2 ring opening of the epoxide by the appropriate nitrogen nucleophile is the key step in each route.

Article titled "Concise and straightforward asymmetric synthesis of a cyclic natural hydroxy-amino acid" by Mario J. Simirgiotis et al. published in *Molecules* 2014, 19, 19516-
30 19531 reports an enantioselective total synthesis of the natural amino acid (2S,4R,5R)-4,5-dihydroxy-pipicolinic acid starting from D-glucose-1, 4-lactone is presented. The best sequence employed as a key step the intramolecular nucleophilic displacement by an amino function of a 6-O-p-toluene-sulphonyl derivative of a methyl D-arabino-hexonate and involved only 12 steps with an overall yield of 19%.

Article titled "Synthesis and conformational analysis of 3-hydroxypipicolinic acid analogs via CSI-mediated stereoselective amination" by In Su Kim et al. published in *Tetrahedron*, 2007, 63 pp 2622–2633 reports a short and efficient stereoselective synthetic approach toward substituted piperidines, involving (2S,3S)-3-hydroxypipicolinic acid (2R,3S)-3-hydroxypipicolinic acid and their acid-reduced analogs has been developed.

Article titled "Asymmetric synthesis of bioactive molecules and methodologies involving oxidative functionalization of alkanes, alkenes and hydrosilylation of ketones" by Pandurang Vilasrao Chouthaiwale published in a thesis submitted for the degree of doctor of philosophy in Chemistry reports Cobalt-catalyzed Hydrolytic Kinetic Resolution of Azido Epoxides: A Short Enantioselective Synthesis of (+)-Epi-cytoxazone, (-)-Cytoxazone and (+)-2-Oxazolidone.

Article titled "Formal synthesis of (2S,3S)-3-Hydroxypipicolinic acid" by Shubhankar Gadre reports synthesis of (2S,3S)-3-Hydroxypipicolinic Acid.

Article titled "Application of hydrolytic kinetic resolution (HKR) in the synthesis of bioactive compounds" by Pradeep Kumar et al. published in *Tetrahedron*, 2007, 63 (13), pp 2745–2785 reports Hydrolytic kinetic resolution (HKR) developed by Jacobsen has emerged in recent times as a powerful tool to synthesize both terminal epoxides and their corresponding diols in highly enantiomerically pure form.

Article titled "The synthesis of 4-Hydroxypipicolinic acids by stereoselective cycloaddition of configurationally stable nitrones" by Franca M. Cordero et al. published in *European Journal of Organic Chemistry*, 2006, 14, pp 3235–3241 reports the diastereoselective synthesis of trans- and cis-4-hydroxypipicolinic acids has been achieved with geometry-controlled nitrone cycloaddition chemistry. The cycloaddition of 3-butenol to enantiopure C-aminocarbonyl and C-alkoxycarbonyl nitrones having a definite (Z) and (E) configuration, respectively, occurs with complete regio- and exo selectivity. The acyclic (Z)-nitrone affords two cycloadducts in a 1:1 ratio, which can be separated and converted into (2R,4R)- and (2S,4S)-4-hydroxypipicolinic acids, respectively, in four steps. The cyclic (E)-nitrone reacts with complete diastereofacial selectivity and the elaboration of its sole adduct gives the methyl ester of (2R,4S)-4-hydroxypipicolinic acid, albeit in low yield.

Article titled "Synthesis of novel enantiopure 4-hydroxypipicolinic acid derivatives with a bicyclic beta-lactam structure from a common 3-azido-4-oxoazetidine-2-carbaldehyde precursor" by *Journal of Organic Chemistry*, 2008, 73(4), pp 1635-8 reports two different stereocontrolled accesses to new 4-hydroxypipicolinic acid analogues with a bicyclic beta-lactam structure have been developed by using intramolecular reductive amination or allenic hydroamination reactions in 2-azetidinone-tethered azides. The access to the cyclization precursors was achieved from 3-azido-4-oxoazetidine-2-carbaldehyde via metal-mediated carbonyl-allenylation in aqueous environment or by organocatalytic direct aldol reaction. The tin hydride-promoted cyclization of the 2-azetidinone-tethered azidoallene is totally regioselective for the central allenic carbon providing a fused piperidine.

Article titled "Chemoenzymatic synthesis of the four diastereoisomers of 4-hydroxypipicolinic acid from N-acetyl-(R,S)-allylglycine: chiral scaffolds for drug discovery" by Richard C. Lloyd et al. published in *Organic Process Research and Development* 2002, 6 (6), pp 762–766 reports all four diastereoisomers of 4-hydroxypipicolinic acid were prepared in a form conveniently protected for drug discovery applications with the use of industrially scaleable methodology. Resolution of the racemic starting material using proprietary acylases followed by an acyliminium ion cyclisation gave diastereomeric mixtures of 4-formyloxypipicolinic acid, which were differentiated using an enzyme-catalysed hydrolysis. The products were separated by partition, and by following a sequence of straightforward chemical steps, the individual stereoisomers of the protected 4-hydroxypipicolates were crystallized to optical purity in 100 g quantities.

Article titled "Enantioselective Synthesis of (2R,4S)- and (2S,4R)-4-Hydroxypipicolinic acid from d-Glucoheptono-1,4-lactone" by Cristián Di Nardo et al. published in *Journal of Organic Chemistry*, 1999, 64 (17), pp 6119–6125 reports enantiomerically pure (2R,4S)-4-hydroxypipicolinic acid [(+)-1] was synthesized from d-glucoheptono-1,4-lactone (2) via the 3,5-dideoxy-d-xylo-heptono-1,4-lactone (7). The latter was readily prepared by benzylation of 2, followed by β -elimination and diastereoselective hydrogenation of the resulting furanones (4). Compound 7 was converted into the 6,7-O-cyclohexylidene derivative 11, which on treatment with tosyl chloride for long periods afforded the 2-chloro derivative 14, the precursor of the azide 15. Hydrogenolysis of 15 and protection of the amine gave the N-benzyloxycarbonyl derivative 19, having the required

configuration for the stereocenters at C-2 and C-4. Removal of the cyclohexylidene group by hydrolysis and subsequent oxidative degradation of the resulting glycol system afforded the hexurono-6,3-lactone 21 as a key intermediate. Chemoselective reduction of the aldehyde function of 21 led to the alcohol 23, which was derivatized as the mesylate 24. Releasing of the amino group by hydrogenation, and dissolution of resulting 25 in aqueous alkali, promoted the intramolecular nucleophilic displacement of the mesylate to give (+)-1. Its enantiomer [(-)-1] was prepared by a similar sequence starting from 2.

Article titled "Enantiodivergent chemoenzymatic synthesis of 4-hydroxypiperidine alkaloids" by Laura Bartali et al. published in *European Journal of Organic Chemistry*, 2010, 30, pages 5831–5840 reports an efficient chemoenzymatic synthesis of both enantiomers of fagomine, as well as of cis and trans-4-hydroxypipicolinic acid is reported. The synthesis starts from commercial δ -valerolactam which, after a Pd-catalyzed methoxycarbonylation of the corresponding vinyl phosphate, is subjected to allylic oxidation to give a racemic 4-hydroxytetrahydropyridine derivative in 57% overall yield. This product is resolved by an enzyme-catalyzed esterification using immobilized lipases from *Candida antarctica* (Novozym 435) and *Burkholderia cepacia* (lipase PS Amano IM). The latter provides the corresponding R esters and the S alcohol in 95 and 94% ee, respectively. The S alcohol is then converted into l-fagomine by a stereoselective hydroboration/oxidation as key steps and the cis-(2R,4S)-4-hydroxypipicolinic acid by stereoselective hydrogenation. The corresponding d-fagomine and cis-(2S,4R)-4-hydroxypipicolinic acid, as well as trans-(2R,4R)-4-hydroxypipicolinic acid can be prepared by the same strategy after hydrolysis of the R ester obtained by kinetic resolution.

Article titled "An asymmetric dihydroxylation route to (2S,3S)-3-hydroxypipicolinic acid" by Mandar S. Bodas et al. published in *Tetrahedron Letters*, 2004, 45(46), pp 8461–8463 reports a concise enantioselective synthesis of (2S,3S)-3-hydroxypipicolinic acid starting from 1,4-butanediol using Sharpless asymmetric dihydroxylation and the regioselective nucleophilic opening of a cyclic sulfate as the key steps is described.

Article titled "Asymmetric synthesis of both the enantiomers of trans-3-Hydroxypipicolinic Acid" by Pradeep Kumar et al. published in *Journal of Organic Chemistry*, 2005, 70 (1), pp 360–363 reports both the enantiomers of trans-3-hydroxypipicolinic acid have

been synthesized employing the sharpless asymmetric dihydroxylation and epoxidation as the key steps starting from a commercially available starting material 1,4-butanediol.

Article titled "A short enantioselective synthesis of N-Boc-(2R,3R)-3-methyl-3-hydroxypipicolinic acid from geraniol" by Mark C. Noe et al. published in *Journal of Organic Chemistry*, 2008, 73, (8), pp 3295-3298 reports the asymmetric synthesis of (2R,3R)-3-methyl-3-hydroxypipicolinic acid, a key intermediate in the synthesis of dual MMP-13/aggrease inhibitors, is described. The title compound is prepared in seven steps with an overall yield of 41% starting from geraniol. Key steps in the synthesis include sharpless asymmetric epoxidation, which establishes the chiral centers, and a one-pot oxidative olefin cleavage/reductive amination sequence that closes the piperidine ring.

Article titled "Synthesis of (-)-Deoxoprosophriline, (+)-2-epi-Deoxoprosopinine, and (2R,3R)- and (2R,3S)-3-Hydroxypipicolinic Acids from D-Glycals" by Hari Prasad Kokatla et al. published in *Journal of Organic Chemistry*, 2010, 75(13) pp 4608-11 reports New syntheses of (-)-deoxoprosophriline, (+)-2-epi-deoxoprosopinine, and (2R,3R)- and (2R,3S)-3-hydroxypipicolinic acids are reported. Utilization of the chiral functionalities of Perlin aldehydes, derived from 3,4,6-tri-O-benzyl glycals, has been done along with chemoselective saturation of olefins and reductive aminations as key steps.

The methods which are available in the literature for the synthesis of (2S,4R)-4-hydroxypipicolinic acid aromatic have many limitations that includes the use of chiral building blocks, inefficient separation of diastereoisomers, expensive reagents, drastic reactions conditions, longer reaction sequences and poor yields.

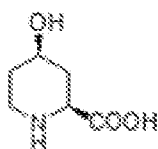
Therefore, there is need in the art to develop a process which overcome the prior art drawbacks. Accordingly, invention provide improved route for a short enantioselective synthesis of (2S,4R)-4-hydroxy pipicolinic acid **1**, by employing two stereocentered Hydrolytic Kinetic Resolution (HKR) of racemic-1,3-azido epoxide as a key step with good yields and high optical purity without any protecting groups.

OBJECTIVES OF THE INVENTION

The main objective of the present invention is to provide an improved process for the synthesis of (2*S*,4*R*)-4-hydroxypipelicolic acid **1** with high optical purity using two stereocentered Hydrolytic Kinetic Resolution (HKR) of racemic 1,3-azido epoxide.

5 SUMMARY OF THE INVENTION

Accordingly the present invention provides an enantioselective process for the synthesis of (2*S*,4*R*)-4-hydroxypipelicolic acid of formula 1



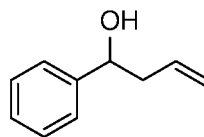
Formula 1

using (*R,R*)-salen Co^{III}(OAc) complex catalyst comprising the steps of :

- a) treating benzaldehyde of formula 3 with zinc allylbromide to obtain phenyl butenol of formula 4;

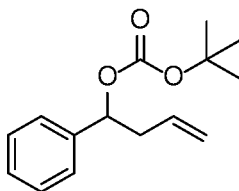


Formula 3



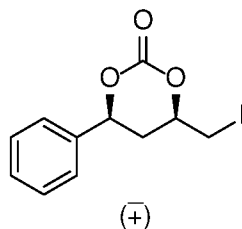
Formula 4

- b) protecting phenyl butenol of formula 4 of step (a) by using reagents to obtain protected alcohol of formula 5;



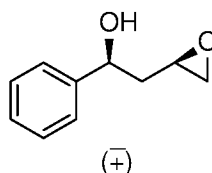
Formula 5

- c) treating protected alcohol of formula 5 of step (b) with reagents to obtain iodocarbonate derivative of formula 6 ;



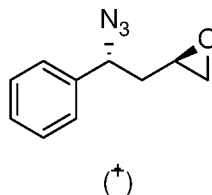
Formula 6

- 5 d) treating iodocarbon derivative of formula 6 of step (c) with reagents to obtain racemic *syn*-epoxy alcohol of formula 7 ;



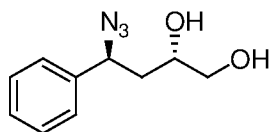
Formula 7

- 10 e) subjecting *syn*-epoxy alcohol of formula 7 of step (d) to mesylation reaction followed by treatment with NaN₃ in DMF at 40-60°C to obtain *anti*-1,3-azido epoxide of formula 8 ;

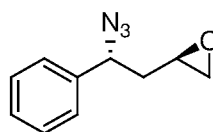


Formula 8

- 15 f) subjecting *anti*-1,3-azido epoxide of formula 8 of step (e) to Hydrolytic Kinetic Resolution with (*R,R*)-salen Co^{III}(OAc) complex and H₂O to obtain chiral *anti*-1,3-azido diol of formula 9 and chiral *anti*-1,3-azido epoxide of formula 10 in a ratio of 1.02:1;

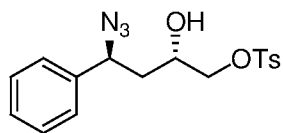


Formula 9



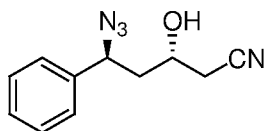
Formula 10

- 20 g) protecting primary hydroxyl group of azido diol of formula 9 of step (f) by using reagents to obtain hydroxyl protected azido diol of formula 11;



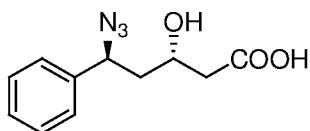
Formula 11

- h) treating compound of formula 11 with hydroxly of step (g) with sodium cyanide to
5 obtain nitrile of formula 12 ;



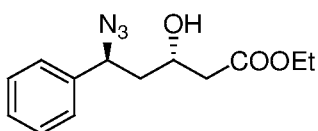
Formula 12

- i) hydrolysing nitrile of formula 12 of step (h) by hydrogen peroxide catalyzed
10 hydrolysis in aqueous NaOH to obtain acid of formula 13;



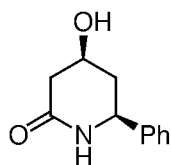
Formula 13

- j) esterifying acid of formula 13 of step (i) to obtain esters of formula 14;



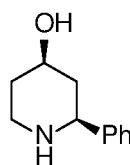
Formula 14

- k) subjecting ester of formula 14 of step (j) to intramolecular reductive cyclization over
Pd(OH)₂/H₂ to obtain cis-2,4-disubstituted piperidinone of formula 15;



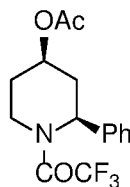
Formula 15

- l) reducing cis-2,4-disubstituted piperidinone of step (k) in presence of reagents to
obtain alkyl piperidine-4-ol of formula 16;



Formula 16

- 5 m) protecting hydroxyl group of alkyl piperidine-4-ol of formula 16 of step (l) product with reagents to obtain protected product of formula 17;



Formula 17

- 10 n) oxidizing of alkyl group protected product of formula 17 of step (m) using reagents to obtain (2S,4R)-4-hydroxypipericolic acid of formula 1.

In an embodiment of present invention the reagents of step (b) are di-*tert*-butyl dicarbonate, 4-dimethylaminopyridine and acetonitrile.

- 15 In another embodiment of present invention the reagents of step (c) are N-Iodosuccinimide and acetonitrile.

In still another embodiment of present invention the reagents of step (d) are Potassium Carbonate and methanol.

- 20 In yet another embodiment of present invention the reagents of step (g) are selected from the group consisting of 4-Toluenesulfonyl chloride, trimethylamine, dibutyltin oxide and 4-dimethylaminopyridine.

- 25 In still another embodiment of present invention the reagents of step (l) is selected from $\text{LiAlH}_4/\text{THF}$.

In still another embodiment of present invention the alkyl piperidine-4-ol of step (l) is 2-Phenylpiperidine-4-ol.

5 In yet another embodiment of present invention the reagents of step (m) are selected from the group consisting of TFAA/Et₃N and K₂CO₃/THF, K₂CO₃/THF, Ac₂O/Et₃N/DMAP either alone or in combination.

In yet another embodiment of present invention the reagents of step (n) are selected from the group consisting of NaIO₄/RuCl₃/CCl₄/MeCN/H₂O, K₂CO₃, Dowex 50 X8 resin (79%).

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts HPLC Data for showing higher optical purity.

15 Scheme 1 and 2 depicts schematic representation of instant process for synthesis of (2*S*,4*R*)-4-hydroxy pipecolic acid.

Scheme 1 depicts reaction conditions for formation of compounds 4 to 10 (i) 3-bromoprop-1-ene, Zn, NH₄Cl, THF/H₂O, 25°C, 2 h, 82%; (ii) (Boc)₂O, DMAP, CH₃CN, 25°C, 5 h, 92%;
 20 (iii) NIS, CH₃CN, -40°C to 0°C, 12 h, 80%; (iv) K₂CO₃, MeOH, 0°C to 25°C, 4 h, 95%; (v) (a) MsCl, NEt₃, CH₂Cl₂, 0°C, 45 min.; (b) NaN₃, DMF, 50°C, 4 h, 83% over two step; (vi) (*R,R*)-Co^{III}(salen) (0.5 mol %), H₂O (0.49 equiv), 0 to 25°C, 12 h.

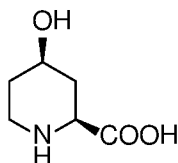
Scheme 2 depicts reaction conditions for formation of compounds 11 to 17 and subsequently
 25 compound 1 from 17 (i) TsCl, NEt₃, Bu₂SnO, DMAP, 0°C, 2 h, 98%; (ii) NaCN, EtOH/H₂O (4:1), 25°C, 24 h, 80%; (iii) NaOH, H₂O, H₂O₂, 12 h, 50°C, 93%; (iv) H₂SO₄, EtOH, reflux, 4 h, 84%; (v) 10% Pd/C, 25 °C, 12 h, 87%; (vi) LiAlH₄, 36 h (64%); (vii) i) TFAA/Et₃N, ii) K₂CO₃/THF, iii) Ac₂O/Et₃N/DMAP (80%); (viii) i) NaIO₄/RuCl₃/CCl₄/MeCN/H₂O, ii) K₂CO₃, iii) Dowex 50 X8 resin (79%)

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an improved enantioselective process for the synthesis of (2*S*,4*R*)-4-hydroxy pipecolic acid **1**.

In another embodiment, the present invention provides an improved enantioselective process for the synthesis of (2*S*,4*R*)-4-hydroxy pipercolic acid **1** by employing two stereocentered Hydrolytic Kinetic Resolution (HKR) of racemic-1,3-azido epoxide with good yields and high optical purity without any protecting groups.



(2*S*,4*R*)-4-hydroxypipercolic acid (**1**)

The present invention provides an improved process for the synthesis of (2*S*,4*R*)-4-hydroxy pipercolic acid **1** comprising the steps of :

- a) treating bezaldehyde **3** with zinc allylbromide to obtain phenyl butenol **4**;
- b) protecting homoallylic alcohol **4** as its *tert*-butyl carbonate **5** using di-*tert*-butyldicarbonate, DMAP and CH₃CN;
- c) diastereoselective iodine-induced carbonate cyclization of **5** furnished iodocarbonate derivative **6**;
- d) methanolysis of **6** under basic conditions gives racemic *syn*-epoxy alcohol **7**;
- e) subjecting *syn*-epoxy alcohol **7** to mesylation reaction followed by treatment with NaN₃ in DMF at 50°C to afford *anti*-1,3-azido epoxide **8**;
- f) subjecting compound **8** to HKR with (*R,R*)-salen Co^{III}(OAc) complex and H₂O, to obtain chiral *anti*-1,3-azido diol **9** and chiral *anti*-1,3-azido epoxide **10**;
- g) selective monotosylation of primary hydroxyl group of azido diol **9** afforded compound **11**;
- h) nucleophilic displacement of compound **11** with NaCN to give nitrile **12**;
- i) hydrogen peroxide catalyzed hydrolysis of the nitrile **12** in aqueous NaOH to give acid **13**;
- j) acid catalyzed esterification of **13** gives ethyl ester **14**;
- k) subjecting Ethyl ester **14** to intramolecular reductive cyclization over Pd(OH)₂/H₂ to provide *cis*-2,4-disubstituted piperidinone **15**;
- l) reduction of *cis*-2,4-disubstituted piperidinone **15** in presence of LiAlH₄/THF gives 2-Phenylpiperidine-4-ol **16**;

- m) protection of Hydroxyl group of compound **16** as acylate and amine as trifluoroacetamide to give **17**; and
- n) oxidation of phenyl group of compound **17** to give target molecule 4-hydroxy pipercolic acid.

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The synthesis of (2S,4R)-4-hydroxy pipercolic acid **1** commenced with commercially available benzaldehyde **3**, which on treatment with zinc allylbromide gave phenylbutenol **4** in 82% yield. The phenylbutenol **4** was then readily transformed into racemic syn-1,3-epoxy alcohol **7** in three-step steps:

10

- (i) homoallylic alcohol **4**, was protected as its tert-butyl carbonate **5** in 92% yield (di-tert-butyldicarbonate, DMAP and CH₃CN);

15

- (ii) diastereoselective iodine-induced carbonate cyclization of **5** furnished iodocarbonate derivative **6** in 80% yield (NIS, CH₃CN, 0°C, 24 h) and

20

- (iii) methanolysis of **6** under basic conditions gave racemic syn-epoxy alcohol **7**. The syn-epoxy alcohol **7** was further subjected to mesylation reaction followed by treatment with NaN₃ in DMF at 50°C gives required racemic anti-1,3-azido epoxide **8** in 83% yield with complete inversion at benzylic position, which was confirmed by ¹H and ¹³C-NMR. Compound **8** was then subjected to HKR with (R,R)-salen CoIII(OAc) complex (0.5 mol %) and H₂O (0.49 equiv), which produced the corresponding chiral anti-1,3-azido diol **9** (48%, 99% ee) and chiral anti-1,3-azido epoxide **10** (49%, 98% ee) in high optical purity. Compounds **9** and **10** were readily separated by a simple flash column chromatographic purification. Azido diol **9** is further used for the synthesis of (2S,4R)-4-hydroxy pipercolic acid. Selective monotosylation of primary hydroxyl group of azido diol **9** afforded compound **11** (TsCl, NEt₃, Bu₂SnO, DMAP, 0°C). It is then subjected to nucleophilic displacement with NaCN to give nitrile **12** in 80% yield. The structure of **12** is confirmed by its characteristic IR frequencies (2100 and 2253 cm⁻¹) due to azide and nitrile functions, respectively. Hydrogen peroxide catalyzed hydrolysis of the nitrile **12** in aqueous NaOH produced acid **13**, which is converted to the ethyl ester **14** in 84% yield via acid catalyzed esterification (cat. H₂SO₄, EtOH, reflux). Finally, the ethyl ester **14** is subjected to intramolecular

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reductive cyclization over Pd/C, H₂ (1 atm) to provide the known key intermediate cis-2,4-disubstituted piperidinone **15** (overall yield 12%). The spectral data and optical rotation of the synthesized key intermediate cis-2,4-disubstituted piperidinone **15** are in good agreement with reported values.

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The schematic representation of instant process is given in scheme 1 and scheme 2.

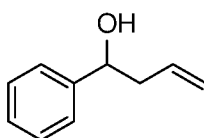
EXAMPLES

10 Following examples are given by way of illustration and therefore should not be construed to limit the scope of the invention.

EXAMPLE 1: Synthesis of 1-phenylbut-3-en-1-ol (4):

15 Solvents were purified and dried by standard procedures before use. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. IR spectra were recorded on a Perkin-Elmer model 683 B and absorption is expressed in cm⁻¹. ¹H NMR and ¹³C NMR spectra were recorded on Bruker AC-200 spectrometer unless mentioned otherwise. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer.

20 Purification was done using column chromatography (60-120 mesh). Enantiomeric excesses was determined on Agilent HPLC instrument equipped with a chiral column. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.



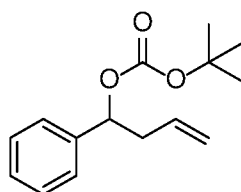
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Benzaldehyde (24 mmol) and 3-bromoprop-1-ene (29 mmol) in THF (30 mL) were added to zinc powder (48 mmol) in saturated NH₄Cl solution (60 mL) at 25°C. The resulting mixture was stirred for one hour, diluted with water, extracted with dichloromethane (3 x 50 mL), washed with brine, dried over Na₂SO₄. Concentration of the organic phases in vacuo

30 gave the crude reaction mixture which was purified via silica gel chromatography to afford the homoallylic alcohol as colorless oil (80% yield)

^1H NMR (200 MHz, CDCl_3): 2.12 (bs, 1H), 2.44-2.52 (tq, 2H), 4.65-4.71 (t, 1H), 5.08-5.18 (m, 2H), 5.67-5.88 (m, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): 4.38, 73.3, 118.3, 125.8, 127.5, 128.3, 134.4, 143.9.

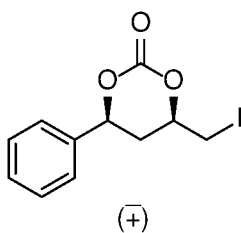
5 **EXAMPLE 2: Synthesis of tert-butyl (1-phenylbut-3-en-1-yl) carbonate (5):**



To a solution of alcohol 3 (36.7 mmol) in CH_3CN (160 mL) were added Boc_2O (55.03 mmol) and DMAP (14.7 mmol). After 5 h of stirring, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (110 mL), and imidazole (0.18 mol) was added. The resulting mixture was stirred at 26°C for 15 min, and then CH_2Cl_2 was added. The organic phase was washed with 5% HCl solution (3 $\times$), dried over anhydrous NaSO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography (2% ethyl acetate/hexane) gave (90%) as a yellow oil.

^1H NMR (200 MHz, CDCl_3): 1.44 (s, 9H), 2.40-2.76 (m, 2H), 5.01-5.13 (m, 2H), 5.50-5.77 (m, 2H), 7.25-7.35 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): 27.8, 41.0, 78.3, 81.9, 118.2, 126.5, 128.0, 128.4, 133.2, 140.0, 152.9.

20 **EXAMPLE 3: Synthesis of 4-(iodomethyl)-6-phenyl-1,3-dioxan-2-one (6):**

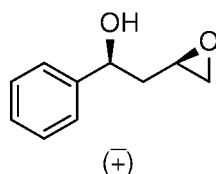


25 A solution of tert-butyl (1-phenylbut-3-en-1-yl) carbonate (1 mol), in acetonitrile was added NIS (2 mol) at 0°C slowly under nitrogen atmosphere. The reaction mixture was stirred for 12 hr. Then reaction was quenched with aq. Saturated solution of NaHCO_3 . The

reaction mixture was diluted with diethyl ether and organic layer was washed with aq. $\text{Na}_2\text{S}_2\text{O}_8$ until it becomes colorless. Dried over Na_2SO_4 . Removal of solvent under reduced pressure.

^1H NMR (200 MHz, CDCl_3): 1.82-2.03(m, 2H), 2.51-2.61 (dt, 1H, $J = 2\text{Hz}$), 3.19-3.41 (m, 3H), 4.49-4.62 (m, 1H), 5.37-5.44 (dd, 1H), 7.29-7.38 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): 5.3, 35.6, 77.1, 79.3, 125.85, 128.9, 129.1, 137.1, 148.0

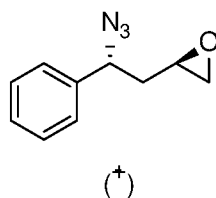
EXAMPLE 4: Synthesis of 2-(oxiran-2-yl)-1-phenylethan-1-ol (7):



To a solution of cyclic carbonate 10 (13.02 mmol) in anhydrous MeOH (52 mL) at 27°C was added K_2CO_3 (40.36 mmol), and the reaction was stirred for 2 h. The mixture was diluted with ether (200 mL) and quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ /saturated aqueous NaHCO_3 solution (1/1). The aqueous phase was extracted with ether (3 $\times$). The organic extracts were washed with brine (1 $\times$), dried over anhydrous MgSO_4 , and filtered. Removal of solvent left an oil which was purified by flash chromatography (30% ethyl acetate/hexane), affording 11 (96%) as a colorless oil:

Yield: 92 %, colorless gummy; IR: (CHCl_3 , cm^{-1}) 3256; ^1H NMR (200 MHz, CDCl_3): δ 1.81-2.12 (m, 2H), 2.41 (bs, 1H), 2.49-2.52 (q, 1H, $J = 2.65\text{ Hz}$), 4.92-4.99 (q, 1H, $J = 5.31\text{ Hz}$), 7.28-7.41 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): δ 41.6, 46.6, 50.0, 72.2, 125.7, 127.5, 128.3, 143.8.

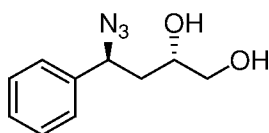
EXAMPLE 5: Synthesis of (2-azido-2-phenylethyl) oxirane (8):



To a solution of epoxy alcohol **7** (6.09 mmol) in CH₂Cl₂ (15 mL), triethyl amine (1.27 mL, 9.14 mmol) and Mesyl chloride (0.56 mL, 7.31 mmol) was added at 0°C under nitrogen atmosphere. The resulting solution was stirred at same temperature for 45 min. After the completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude product mesyl protected alcohol, which was used for next azidation reaction without purification. To a stirred mixture of crude mesylate (6.09 mmol) in DMF (10 mL), sodium azide (0.435 g, 6.70 mmol) was added. Reaction mixture was stirred for 4 h at 50°C. After the completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 mL), washed with water, brine and dried over anhydrous Na₂SO₄. The combined organic layer was concentrated under reduced pressure to give the crude azido epoxide **8**, which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (9:1) as eluent gave pure **8**.

Yield: 83%, colorless liquid; IR: (CHCl₃ cm⁻¹): 2096, 1244, 837, 748, 699; ¹H NMR (200 MHz, CDCl₃): δ 1.69-1.80 (m, 1H), 2.01-2.17 (m, 1H), 2.51 (dd, *J* = 2.6, 5.0 Hz, 1H), 2.82 (dd, *J* = 4.2, 4.8 Hz, 1H), 3.05-3.14 (m, 1H), 4.68-4.75 (dd, *J* = 4.3, 9.9 Hz, 1H), 7.28 - 7.41 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 39.8, 47.4, 49.2, 63.7, 126.6, 128.4, 128.9, 139.2; HRMS (*m/z*): calculated [M+Na]⁺ for C₁₀H₁₁ON₃Na⁺ : 212.0794 found: 212.0791.

EXAMPLE 6: Synthesis of (2*S*,4*S*)-4-azido-4-phenylbutane-1,2-diol (**9**):

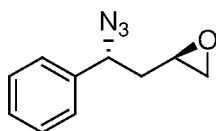


To a solution of (*R,R*)-Co-salen (0.027g, 0.5 mol%) in toluene (2 mL), acetic acid (0.02 g, 0.36 mmol) was added. It was allowed to stir at 25°C in open air for 30 min. During this time the color changed from orange-red to a dark brown, it was then dried under vacuum. To this racemic azido epoxide **8** (1.72 g, 9.13 mmol) and H₂O (0.08 mL, 4.47 mmol) was added at 0 °C. Then the reaction was allowed to stirred for 12 h at 25°C. After completion of reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral azido epoxides **10**, [solvent system; petroleum ether: ethyl

acetate (9:1)] and chiral azido diols **9** [solvent system; petroleum ether: ethyl acetate (1:1)] in pure form.

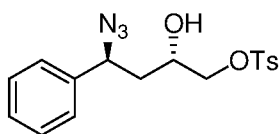
Yield: 48%, yellow colored liquid, $[\alpha]_D^{25} = -98.29$ (*c* 1, CHCl₃); IR: (CHCl₃ cm⁻¹) 3455, 2094; ¹H NMR (200 MHz, CDCl₃): δ 1.75-1.90 (m, 2H), 2.44 (br s, 1H), 2.88 (br s, 1H), 3.45-3.54 (m, 1H), 3.72-3.77 (m, 1H), 3.97-4.10 (m, 1H), 4.76-4.83 (dd, *J* = 5.2, 9.5 Hz, 1H), 7.26-7.40 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 40.0, 62.7, 66.7, 68.9, 126.7, 128.4, 128.9, 139.8; ; HRMS (*m/z*): calculated $[M+Na]^+$ for C₁₀H₁₃O₂N₃Na⁺ : 230.0900 found: 230.0897; Optical purity: 99% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (85:15), 0.5 mL/min, 254 nm). Retention time: *t*_{minor} = 21.50 and *t*_{major} = 25.69 min.

EXAMPLE 7: Synthesis of (*R*)-2-((*R*)-2-azido-2-phenylethyl) oxirane (**10**):



Yield: 49%, $[\alpha]_D^{25} = +149.12$ (*c* 1, CHCl₃); Optical purity: 98% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (97.5:2.5), 0.5 mL/min, 254 nm) Retention time: *t*_{major} = 15.35 min and *t*_{minor} = 18.84 min.

EXAMPLE 8: Synthesis of (2*S*, 4*S*)-4-azido-2-hydroxy-4-phenylbutyl 4-methylbenzenesulfonate (**11**):

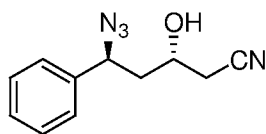


A solution of diol **9** (1.2 g, 5.79 mmol) in CH₂Cl₂ (50 mL) was treated with TsCl (1.1 g, 5.79 mmol), Bu₂SnO (0.54 g, 30 mol%), Et₃N (0.96 mL, 6.9 mmol) and DMAP (30 mg, cat.) at 0 °C and stirred for 2 h. After the reaction was complete (monitored by TLC), it was quenched with water (20 mL) and product was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated to give the

crude product **11**, which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (7:3) as eluent gave pure **11**.

Yield: 98%; gumi liquid; $[\alpha]_D^{25} = -63.08$ (*c* 1, CHCl₃); IR: (CHCl₃ cm⁻¹) 2097, 3455; ¹H NMR (200 MHz, CDCl₃): δ 1.67-1.78 (m, 2H), 2.45 (s, 3H), 2.88 (br s, 1H), 3.89-3.92 (m, 1H), 4.02-4.05 (m, 1H), 4.08-4.11 (m, 1H), 4.75 (dd, *J* = 4.12, 10.1 Hz, 1H), 7.26-7.28 (d, *J* = 7.8 Hz, 2H), 7.30-7.38 (m, 5H), 7.77-7.79 (d, *J* = 7.3 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 21.7, 39.5, 62.2, 66.4, 73.6, 126.7, 128.1, 128.4, 128.9, 129.9, 132.7, 139.4, 145.0; HRMS (*m/z*): calculated [M+Na]⁺ for C₁₇H₁₉O₄N₃SSNa⁺: 384.0988 found: 384.0984.

EXAMPLE 9: Synthesis of (3*S*, 5*S*)-5-azido-3-hydroxy-5-phenylpentanenitrile (**12**):



To a stirring mixture of monotosyl compound **11** (0.5 g, 1.38 mmol) in EtOH/H₂O (4 mL:1 mL) at 0°C was added NaCN (0.81 g, 1.66 mmol) in one portion. The reaction mixture was stirred at 25°C for 24 h, and then concentrated on rotatory evaporator and extracted with EtOAc (3 x 5 mL), washed with water, brine and dried over anhydrous Na₂SO₄. The combined organic layer was concentrated under reduced pressure to give the crude nitrile **12**, which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure **12** colorless liquid.

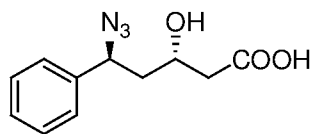
Yield: 80%, colorless liquid; $[\alpha]_D^{25} = -136.11$ (*c* 1, CHCl₃); IR: (CHCl₃ cm⁻¹) 3443, 2253, 2100; ¹H NMR (200 MHz, CDCl₃): δ 1.88-1.93 (m, 2H), 2.48-2.59 (m, 2H), 2.73 (br s, 1H), 4.23 (m, 1H), 4.79-4.82 (dd, *J* = 4.4, 9.5 Hz, 1H), 7.31-7.39 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 26.6, 42.9, 62.5, 64.7, 117.1, 126.7, 128.7, 129.1, 138.9; HRMS (*m/z*): calculated [M+Na]⁺ for C₁₁H₁₂ON₄Na⁺: 239.0903 found: 239.0900.

Optical purity: 99% ee determined by HPLC analysis (Chiral OD-H column, n-hexane/ 2-propanol (70:30), 0.5 mL/min, 254 nm). Retention time: *t*_{major} = 11.13 (99.53%) and *t*_{minor} = 13.63 min (0.47%).

The HPLC results indicate that, the enantiomeric excess (ee) is 99 %. The process is giving high enantiopure compound than any other method.

EXAMPLE 10: Synthesis of (3S, 5S)-5-azido-3-hydroxy-5-phenylpentanoic acid (13):

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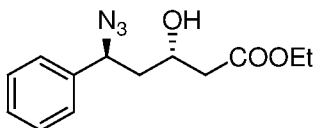


A solution of nitrile **12** (0.3 gm, 1.38 mmol) in 3M NaOH (6 mL) was added H₂O₂ (2 mL). The reaction mixture was stirred at 100°C for 12 h. After the reaction was complete (monitored by TLC), the reaction mixture was cooled to 0°C. To remove organic impurities, reaction mixture washed with Et₂O (15 mL). Then the aqueous phase was neutralized with dil HCl and was extracted EtOAc (3 x 10 mL), washed with water, brine and dried over anhydrous Na₂SO₄. The combined organic layer was concentrated under reduced pressure to give the crude acid **13**, which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (4:6) as eluent gave pure **13**.

Yield: 93%, colorless liquid; $[\alpha]_D^{25} = -108.00$ (*c* 1, CHCl₃); IR: (CHCl₃ cm⁻¹) 2922, 2101, 1711, 1673; ¹H NMR (200 MHz, CDCl₃): δ 1.51-1.65 (m, 1H), 1.75-1.89 (m, 1H), 2.31-2.33 (m, 2H), 4.07-4.20 (m, 1H), 4.63-4.70 (dd, *J* = 3.3, 10.9 Hz, 1H), 7.24 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 41.5, 42.9, 62.1, 64.2, 126.1, 127.6, 128.2, 139.5, 173.7; HRMS (*m/z*): calculated [M+Na]⁺ for C₁₁H₁₃O₃N₃Na⁺ : 258.0849 found: 258.0844

EXAMPLE 11: Synthesis of (3S, 5S)-ethyl 5-azido-3-hydroxy-5-phenylpentanoate (14):

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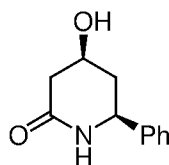


To a stirring solutions of **13** (0.15 g, 0.63 mmol) in ethanol (5 mL), H₂SO₄ (0.05 mL) was added. The reaction mixture was heated at 70°C for 12 h. After the reaction was completed, the reaction mixture was cooled to 25°C and concentrated in vacuo. The residue was diluted with 5 mL of H₂O and extracted with 10 mL of EtOAc. The organic phase was

dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude ester **14**, which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure **14**.

5 Yield: 84%, colorless liquid; $[\alpha]_{\text{D}}^{25} = -82.00$ (c 1, CHCl_3); IR: (CHCl_3 cm^{-1}) 3456, 2982, 2097, 1725; ^1H NMR (200 MHz, CDCl_3): δ 1.28 (t, $J = 7.0$ Hz, 3H), 1.75-1.82 (m, 2H), 2.41-2.57 (m, 2H), 3.23 (br s, 1H), 4.20 (q, $J = 7.0$ Hz, 2H), 4.26-4.35 (m, 1H), 4.83 (m, 1H), 7.26-7.41 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): δ 14.2, 41.3, 43.3, 60.8, 62.5, 64.7, 126.7, 128.2, 128.9, 139.9, 172.6; Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3$ requires C, 59.30; H, 6.51; N, 15.96; found C, 59.33; H, 6.45; N, 15.88%.

EXAMPLE 12: Synthesis of (4S, 6S)-4-hydroxy-6-phenylpiperidin-2-one (15):



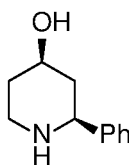
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To a solution of azido ester **14** (0.05 g, 0.19 mmol) in methanol (2 mL), 10% Pd/C (0.01 mg) was added and stirred under hydrogen atmosphere (1 atm) at 25°C for 12 h. The progress was monitored by TLC. After the completion of reaction (monitored by TLC), it was filtered through a celite pad and washed with EtOAc (3 x 10 mL). The combined organic phase was concentrated under *vacuum* to afford the crude product **15**, which was purified by column chromatography on silica gel using petroleum ether: ethyl acetate (3:7) as eluent to give lactam **15** in pure form.

25 Yield: 87%; colorless solid, mp 215 {lit.² mp 211-213}; $[\alpha]_{\text{D}}^{25} = -51.80$ (c 1, MeOH) {lit.² $[\alpha]_{\text{D}}^{20} = -52.3$ (c 0.88, MeOH- d^4)}; IR: (CHCl_3 cm^{-1}): 3355, 3030, 1651; ^1H NMR (200 MHz, MeOH- d^4): δ 1.52-1.70 (q, $J = 12.6$ Hz, 1H), 2.21-2.37 (m, 2H), 2.64-2.74 (m, 1H), 4.03-4.17 (m, 1H), 4.47-4.54 (dd, $J = 4.3, 11.3$ Hz, 1H), 4.75 (br s, 1H), 7.29-7.37 (m, 5H); ^{13}C NMR (50 MHz, MeOH- d^4): δ 41.5, 42.8, 56.3, 65.7, 127.5, 129.1, 130.0, 143.6, 174.2; HRMS (m/z): calculated $[\text{M} + \text{Na}]^+$ for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{NNa}^+$: 214.0838 found: 214.0834.

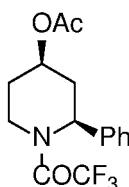
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EXAMPLE 13: Synthesis of 2-Phenylpiperidine-4-ol (16):



In a 25 mL single neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum and argon-filled balloon was placed **15** (0.433 g, 2.26 mmol) in THF (4 mL). The solution was cooled to -78 °C, and a 1 M solution of LiAlH₄ in THF (11.3 mL, 11.3 mmol) was added slowly via syringe, and the mixture was stirred at r.t. for 36 h. At this time the solution was cooled to 0 °C, quenched with aq sat Na₂SO₄ solution (2 mL), stirred for 0.5 h and filtered through Celite. The filtrate was washed with EtOAc (50 mL), and the organic phase was washed with 2 N NaOH (10 mL), brine (10 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (90:10:2, CH₂Cl₂/ MeOH/28% NH₄OH) to afford 0.25 g (62%) of a white solid; mp 101-102 °C (Lit. 13 mp 101-102 °C [α]₂₀^D +20.2 (*c* = 0.54, MeOH); ¹H NMR (200 MHz, CDCl₃) δ 1.40–1.60 (m, 2H), 1.93–2.16 (m, 2H), 2.46 (sb, 2H), 2.76 (dt, *J*=2.6 Hz and *J*=12.3 Hz, 1H), 3.10–3.26 (m, 1H), 3.60 (dd, *J*=2.38 and *J*=11.48 Hz, 1H), 3.65–3.84 (m, 1H), 7.20–7.40 (m, 5H); ¹³C NMR (50 MHz, CDCl₃) 29.6, 35.2, 43.7, 44.9, 60.1, 69.4, 126.5, 127.2, 128.4, 143.6;

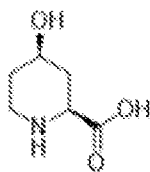
EXAMPLE 14: Synthesis of N-Trifluoroacetyl-(2S,4R)-4-acetoxy-2-phenylpiperidine (17) :



To an ice cold solution of aminoalcohol **16** (0.3 g, 1.69 mmol) in CH₂Cl₂ (25 mL) containing Et₃N (1.4 mL, 10 mmol) and dimethylaminopyridine (10 mg, 0.08 mmol) was added via a syringe through a septum trifluoroacetic anhydride (0.95 mL, 6.77 mmol). After stirring at 23 °C for 12 h, water was added and the solution was extracted, dried over MgSO₄, filtered, and evaporated. The crude product obtained was diluted in THF (25 mL) and K₂CO₃ (0.46 g, 3.38 mmol) was added. The mixture was stirred for 12 h. Water was added and the

reaction mixture was extracted with CH₂Cl₂. After drying over MgSO₄, the solution was filtered and placed into a one-neck 100 mL round bottomed flask. Triethylamine (0.94 mL, 6.8 mmol) and dimethylaminopyridine (10 mg, 0.08 mmol) were added before cooling to 0°C. Acetic anhydride (0.32 mL, 3.39 mmol) was added via a syringe through a septum and the solution was stirred at 26°C for 12 h. Water was added and the solution was extracted. The solution was dried over magnesium sulfate, filtered, and evaporated to give an oil which was purified by flash chromatography (cyclohexane:AcOEt, 80:20) to give the protected aminoalcohol **17** as a colorless oil (0.44 g, 82%): [α]_D²² = -45.5 (c 1.05, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆, 60°C): 1.26 (s, 3H), 1.28–1.37 (m, 2H), 1.56 (ddd, J=3.1, 6.6, 15.2 Hz, 1H), 2.39–2.46 (m, 1H), 3.2 (dtbroad, J not measurable, 1H), 3.79 (m, 1H), 4.72 (quint, J=3.5 Hz, 1H), 5.48 (m, 1H), 6.90–6.98 (m, 3H), 7.03–7.08 (m, 2H); ¹³C NMR (50 MHz, C₆D₆) 19.8, 29.4, 31.2, 36.7, 52.4, 66.1, 117.2 (q, J=287 Hz, CF₃), 125.2, 126.4, 128.4, 139.0, 156.2, 168.8; IR (nujol) 1747, 1702, 1607 cm⁻¹.

EXAMPLE 15: Synthesis of (2S, 4R)-4-Hydroxypipericolic acid (1):



Compound **17** (0.4 g, 1.27mmol) was placed into a flask equipped with a magnetic stirrer and containing 2 mL of carbon tetrachloride, 2 mL of acetonitrile, and 3 mL of water. Sodium periodate (4.07 g, 19 mmol) and ruthenium chloride hydrate (13 mg, 0.06 mmol) were added and the solution was vigorously agitated overnight. On the next day, the solution was filtered through a Celite pad and rinsed several times with dichloromethane. The dark solution was dried over magnesium sulfate, filtered, and concentrated. The crude acid thus obtained was diluted in methanol (15 mL); potassium carbonate (1.05 g, 7.6 mmol) was added, and the mixture was stirred at 27°C for 12 h. The solution was concentrated and acidified with 1 M HCl. Purification was performed over a column of Dowex 50W-X8 resin (100–200 mesh, 20 g) eluted with 5% NH₄OH under a light pressure. The ninhydrin positive fractions were combined and evaporated in vacuo to give a solid which was recrystallized from hot 25% water in EtOH. Evaporation and drying under vacuum over P₂O₅ gave pure **1** as a solid (0.11 g, 60%): D = -17.18 (c 1.02, H₂O), mp 267°C; ¹H NMR (400 MHz, D₂O):

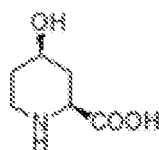
1.47–1.59 (m, 2H), 2.04–2.09 (m, 1H), 2.38–2.44 (m, 1H), 2.95 (dt, J=3.1, 13.2 Hz, 1H), 3.42 (ddd, J=2.7, 4.4, 13.2 Hz, 1H), 3.60 (dd, J=3.2, 12.9 Hz, 1H), 3.88 (tt, J=4.4, 11 Hz, 1H); ^{13}C NMR (50 MHz, D_2O) 31.0, 35.8, 42.5, 58.9, 66.6, 174.4.

5 ADVANTAGES OF THE INVENTION

- 1) Simple reaction sequence
- 2) Improved over all yield
- 3) High optical purity
- 10 4) Easily available cheap starting material

CLAIMS

1. An enantioselective process for the synthesis of (2*S*,4*R*)-4-hydroxypipelicolic acid of formula 1



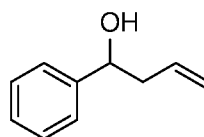
Formula 1

using (*R,R*)-salen Co^{III}(OAc) complex catalyst comprising the steps of :

- a) treating benzaldehyde of formula 3 with zinc allylbromide to obtain phenyl butenol of formula 4;

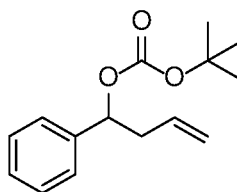


Formula 3



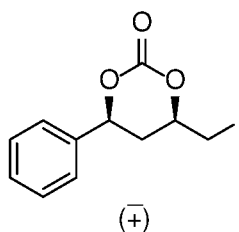
Formula 4

- b) protecting phenyl butenol of formula 4 of step (a) by using reagents to obtain protected alcohol of formula 5;



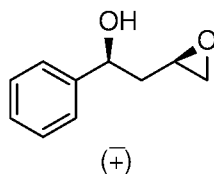
Formula 5

- c) treating protected alcohol of formula 5 of step (b) with reagents to obtain iodocarbonate derivative of formula 6 ;



Formula 6

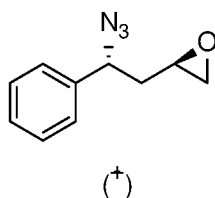
- d) treating iodocarbon derivative of formula 6 of step (c) with reagents to obtain racemic *syn*-epoxy alcohol of formula 7 ;



Formula 7

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- e) subjecting *syn*-epoxy alcohol of formula 7 of step (d) to mesylation reaction followed by treatment with NaN_3 in DMF at 40-60°C to obtain *anti*-1,3-azido epoxide of formula 8 ;

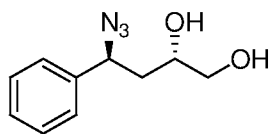


Formula 8

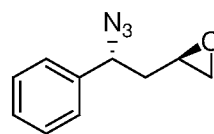
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- f) subjecting *anti*-1,3-azido epoxide of formula 8 of step (e) to Hydrolytic Kinetic Resolution with (*R,R*)-salen $\text{Co}^{\text{III}}(\text{OAc})$ complex and H_2O to obtain chiral *anti*-1,3-azido diol of formula 9 and chiral *anti*-1,3-azido epoxide of formula 10 in a ratio of 1.02:1;

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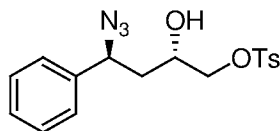
Formula 9



Formula 10

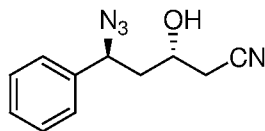
- g) protecting primary hydroxyl group of azido diol of formula 9 of step (f) by using reagents to obtain hydroxyl protected azido diol of formula 11;

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Formula 11

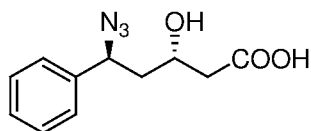
- h) treating compound of formula 11 with hydroxly of step (g) with sodium cyanide to obtain nitrile of formula 12 ;



Formula 12

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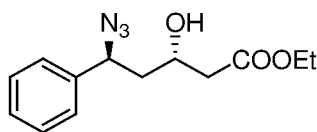
- i) hydrolysing nitrile of formula 12 of step (h) by hydrogen peroxide catalyzed hydrolysis in aqueous NaOH to obtain acid of formula 13;



Formula 13

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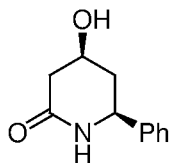
- j) esterifying acid of formula 13 of step (i) to obtain esters of formula 14;



Formula 14

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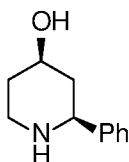
- k) subjecting ester of formula 14 of step (j) to intramolecular reductive cyclization over $\text{Pd}(\text{OH})_2/\text{H}_2$ to obtain cis-2,4-disubstituted piperidinone of formula 15;



Formula 15

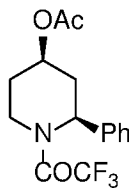
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- l) reducing cis-2,4-disubstituted piperidinone of step (k) in presence of reagents to obtain alkyl piperidine-4-ol of formula 16;



Formula 16

- m) protecting hydroxyl group of alkyl piperidine-4-ol of formula 16 of step (l) product with reagents to obtain protected product of formula 17;



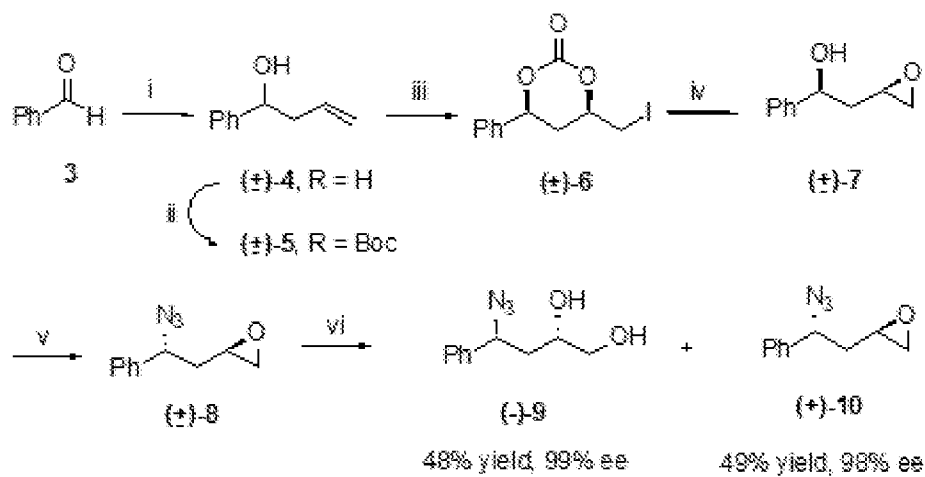
Formula 17

- n) oxidizing of alkyl group protected product of formula 17 of step (m) using reagents to obtain (2*S*,4*R*)-4-hydroxypipericolic acid of formula 1.

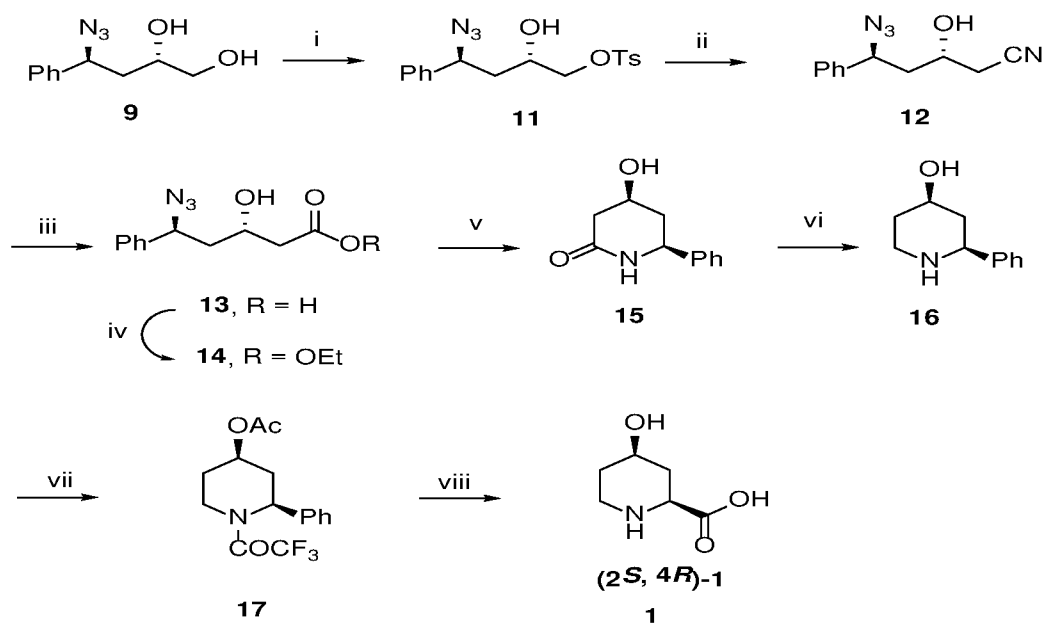
2. The process as claimed in claim 1, wherein said reagents of step (b) are di-*tert*-butyl dicarbonate, 4-dimethylaminopyridine and acetonitrile.
3. The process as claimed in claim 1, wherein said reagents of step (c) are N-Iodosuccinimide and acetonitrile.
4. The process as claimed in claim 1, wherein said reagents of step (d) are Potassium Carbonate and methanol.
5. The process as claimed in claim 1, wherein said reagents of step (g) are selected from the group consisting of 4-Toluenesulfonyl chloride, trimethylamine, dibutyltin oxide and 4-dimethylaminopyridine.
6. The process as claimed in claim 1, wherein the said reagents of step (l) is selected from LiAlH₄/THF.
7. The process as claimed in claim 1, wherein said alkyl piperidine-4-ol of step (l) is 2-Phenylpiperidine-4-ol.

8. The process as claimed in claim 1, wherein said reagents of step (m) are selected from the group consisting of TFAA/Et₃N and K₂CO₃/THF, K₂CO₃/THF, Ac₂O/Et₃N/DMAP either alone or in combination.
- 5 9. The process as claimed in claim 1, wherein said reagents of step (n) are selected from the group consisting of NaIO₄/RuCl₃/CCl₄/MeCN/H₂O, K₂CO₃, Dowex 50 X8 resin (79%).

1/2



Scheme 1



Scheme 2

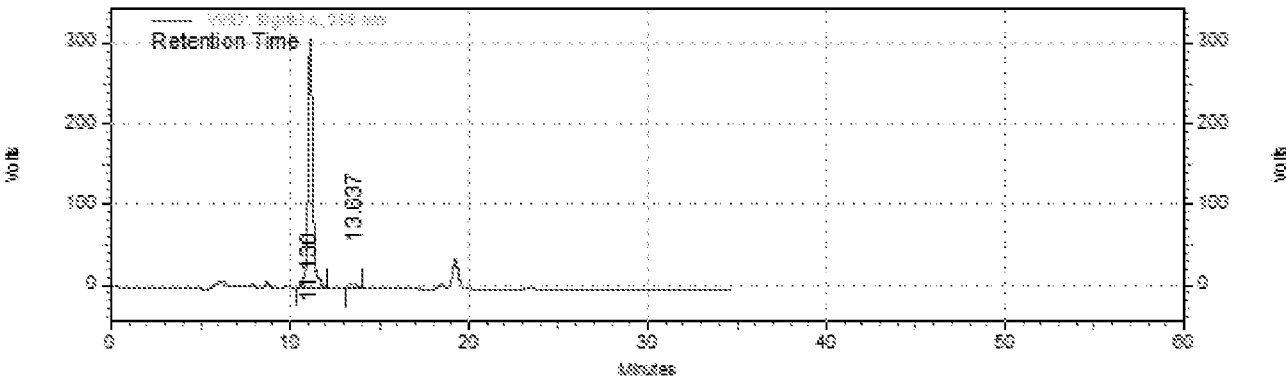


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2016/050029

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/60
ADD.

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAMBLE R. B. ET AL.: "A formal asymmetric synthesis of (2S,4R)-4-hydroxypipicolinic acid via Co(III)(salen)-catalysed two stereocentered HKR of racemic azido epoxide", TETRAHEDRON LETTERS, vol. 56, 22 January 2015 (2015-01-22), pages 1263-1265, XP002757139, schemes 1 and 2 -----	1-9
A	DAVIS F A ET AL: "Asymmetric synthesis of the four stereoisomers of 4-hydroxypipicolinic acid", SYNTHESIS, GEORG THIEME VERLAG, STUTTGART, DE, no. 14, 1 January 2000 (2000-01-01), pages 2106-2112, XP003019746, ISSN: 0039-7881, DOI: 10.1055/S-2000-8710 scheme 3 -----	1-9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 April 2016

Date of mailing of the international search report

13/05/2016

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