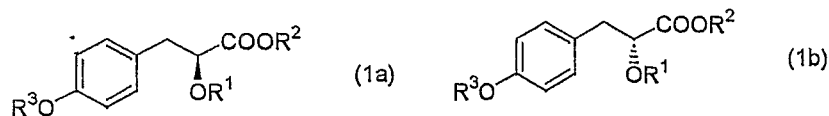


PROCESS FOR PREPARING 3-ARYL-2-ALKOXY PROPANOIC ACID DERIVATIVES WITHOUT RESOLUTION

Field of invention

- 5 The present invention relates to a process for the preparation of S (-) & R (+) isomers of 3-aryl-2-alkoxy propanoic acid derivatives of the structural formula (1a) & (1b) respectively,

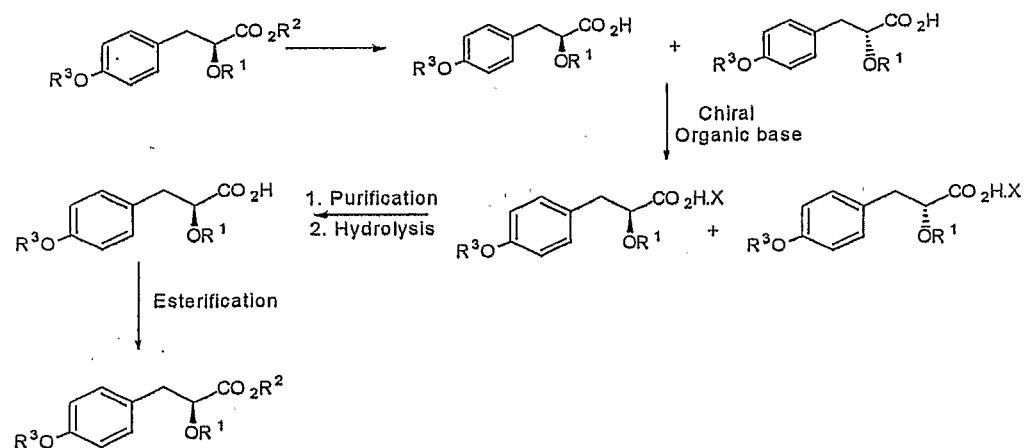


The compound of formula (1a) & (1b) where $R^3 = -H$, is useful as an intermediate for the preparation of many pharmaceutically active compounds.

10 Background & prior art

S (-)-3-aryl-2-alkoxy propanoic acid derivatives are essential intermediates for the preparation of a number of promising drugs. These compounds also have been considered useful for the treatment of eating disorders. They are also used as sweetening agents, in photosensitive materials and also in liquid crystals.

- 15 S (-)-3-aryl-2-alkoxy propanoic acid derivatives have been prepared by several methods in the literature such as by classical resolution i.e. by crystallization of diastereomeric salts of the racemates or by using chiral precursor. However, in all the processes resolution has been carried out in atleast one step to obtain optically pure S (-) isomer of structural formula (1a) (where $R^3 = H$). Such processes are described in WO 0026200, WO 0140159, WO 0224625, WO 9962871 and WO 0063189. The processes described in WO 0026200 (Rao et. al.) uses benzyl bromide for benzylation, which is highly lachrymatory. Again, in the processes described, the debenylation of the final intermediate was done by using Pd/C under pressure. Such a process is costly and not very efficient at a large scale. WO 0224625 describes a process for preparing chirally pure S (-) alkyl-2-alkoxy-3-(4-benzyloxyphenyl) propanoate.
- 20 However, the process for obtaining the chirally pure product involves the following steps:



Thus, the process of obtaining the chirally pure product from the partially racemized (S) isomer involves 5 extra steps thereby increasing the manufacturing cost and reducing the overall yield.

Deussen et al. (Organic Process Research & Development, 7, 82-88 (2003)) describes the enantioselective enzymatic hydrolysis of Ethyl-2-ethoxy-3-(4-hydroxyphenyl)propanoate for the large scale production of S (-) & R (+) isomers of structural formula (1a) & (1b), where $R^3=H$.

The preparation of the R (+) isomer [1(b)] has also been reported in WO 0111072 & WO 0111073 (Deussen et al).

WO 0140159 (Andersson et. al.) describes a process for preparing compounds of formula (1a), when $R^3 = H$, using alkylthiol and base at higher temperature as the deprotecting agent. Also the pure (S) isomer was obtained by a sequence of steps similar to those used in WO 0224625 thereby affecting the manufacturing cost & yield.

The problems indicated above, apparently depicts that there is a need to develop a process, which obviates these difficulties. The present invention relates to a process for the preparation of S (-) & R (+) 3-aryl-2-alkoxy propanoic acid derivatives of the structural formula (1a) & (1b) respectively, which not only overcomes the draw backs of prior art, but also provides an improved process which possess several advantages like operational simplicity, cost effectiveness and easily implementable on a large scale. The present invention relates to an improved process of preparation of S (-) & R (+) 3-aryl-2- alkoxy propanoic acid derivatives of the structural formula (1a) & (1b) respectively, of high chemical and chiral purity.

Objectives of present invention

The main objective of the present invention is to provide an improved process for the preparation of S (-) & R (+) 3-aryl-2-alkoxy propanoic acid derivatives of formula (1a) & (1b) respectively, with high chemical and chiral purity.

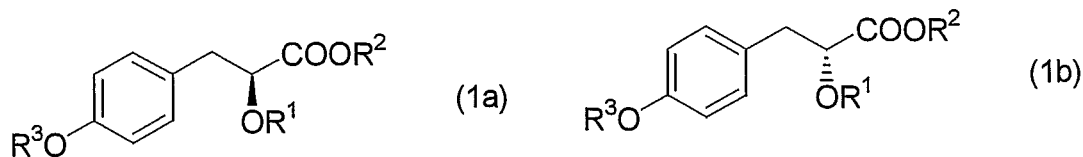
A further objective is to prepare compounds of formula (1a), where $R^3 = H$, having more than or equal to 99 % e.e. by HPLC analysis without any resolution.

Another objective of is to provide a cost-effective, safe and efficient process for obtaining chirally pure compounds of formula (1a) & (1b) respectively.

A further objective of the present invention is to provide a process for the large scale production of compound of formula (1a) & (1b) in a chirally pure form.

Detailed description of the invention

Accordingly, the present invention describes an improved process for the preparation of compound of the general formula (1a) and (1b).



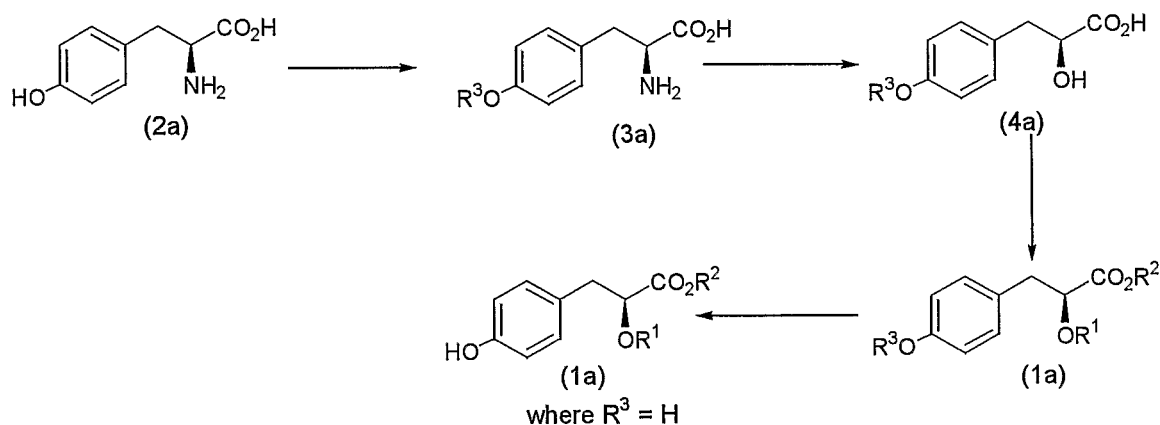
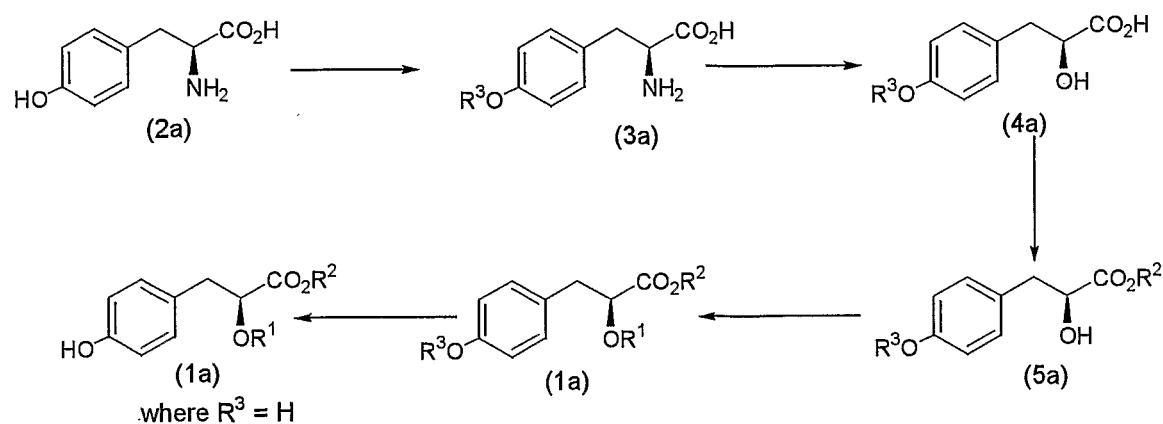
5 Wherein, R^1 represent H or ($\text{C}_1\text{-C}_6$) alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl and the like.

R^2 represents ($\text{C}_1\text{-C}_6$) alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl and the like.

R^3 represents H, protecting groups such as benzyl, substituted benzyl, ($\text{C}_1\text{-C}_3$) alkyl and like.

10 **Preparation of compound (1a):**

Compound of general formula (1a) can be prepared according to the following schemes:

Scheme 1**Scheme 2**

Step 1: Selective O-alkylation or O-aralkylation of L-Tyrosine of formula (2a) using a base, a chelating agent, an alkyl or aralkyl halide in the presence of solvents to obtain the

compound of formula (3a) (according to the general method described in "The practice of peptide synthesis", Bodanszky et. al., pp 50)

The selective O-alkylation or O-aralkylation of compound of formula (2a) can be carried out by reacting a base such as NaOH, KOH, K₂CO₃ and the like, a chelating agent such as
5 CuSO₄, Cu (OAc)₂ and the like, and an alkyl or aralkyl halide in the presence of solvents such as aq. methanol, ethanol, DMF and the like or their combination thereof, at 25 °C-65 °C. The bases may be present in 2-2.5 equivalents, the chelating agent in 0.5-0.7 equivalents, alkyl or aralkyl halide in 1-1.5 eq. and the solvent may be present in 4-20 times to the weight of L-tyrosine. In a preferred embodiment, the base used is KOH (2 to 2.2 eq.), the chelating agent
10 is CuSO₄ (0.5 to 0.65 eq.), Benzyl chloride is the aralkylating agent and the solvent used is aq. DMF at 50 °C-60 °C, to afford the copper complex of O-benzyl-L-tyrosine. Thus by substituting aqueous methanol (WO 0026200 & WO 0224625) with DMF as the solvent, the rate of reaction is enhanced resulting in higher yield and better purity. Also, the volume of solvent required is reduced substantially (from ~20 times of the starting compound in case of
15 MeOH to 4 times the starting compound in case of DMF).

The crude Cu complex obtained above was purified by treating it with methanol at reflux temperature. Cleavage of the Cu complex using dil. HCl yielded the compound (3a) in high chemical & chiral purity (e.e. ≥ 99%).

Step 2: Diazotisation of the compound of the formula (3a) using a diazotising agent, in
20 suitable solvents in acidic media to obtain the compound of formula (4a).

Diazotisation of the compound of formula (3a) is carried out with sodium nitrite in 2-5 equivalents, preferably 3-4 equivalents and strong acids such as sulfuric acid, orthophosphoric acid, conc. HCl in 2-8 equivalents, KHSO₄, preferably sulfuric acid in 3-5 equivalents at 0 °C to 25 °C. Solvents such as dioxane, acetone, methyl ethyl ketone and the
25 like or their mixtures, preferably dioxane, may be used. [Tetrahedron Lett., **25**, 2287-2290(1971) & US 5,747,448 which are incorporated herein as reference]. The hydroxy acid (4a) was obtained in high chemical & chiral purity (e.e. ≥ 98 %) with retention of configuration.

Step 3: Dialkylation of the compound of formula (4a) using an excess of alkylating agent and
30 excess base, in presence of suitable solvent to obtain optically pure compound of formula (1a).

Alternatively, compound of formula (4a) may be selectively esterified to obtain compound of formula (5a), which is subsequently O-alkylated to obtain compound of formula (1a) (Scheme 2)

Dialkylation of the compound of formula (4a) to get the dialkylated compound of formula (1a) with high chemical and chiral purity, was carried out by suitably modifying the process reported by Robert A.W. Johnstone et.al.(Tetrahedron, **35**, 2169-2173, (1979)), which describes the alkylation of aliphatic alcohols and acids with alkylating agents at ambient temperature i.e.18-20 °C using an excess of potassium hydroxide as a base and DMSO as a solvent.

According to the modified procedure, dialkylation of the compound of formula (4a) was carried out using an excess of base w.r.to the starting compound, with a suitable alkylating agent in presence of a solvent to obtain the compound of formula (1a). Suitable alkylating agents may be alkyl sulfates such as diethyl sulfate, dimethyl sulfate and the like; alkyl halides may be methyl iodide, ethyl iodide, ethyl bromide, propyl bromide, isopropyl bromide and the like. The solvent used is DMSO. The base may be present in 2 to 7 equivalents, preferably in 5 to 7 equivalents, the alkylating agent is present in equal moles w.r.to the base, and the solvent volume may be 4-10 times w.r.to the weight of the intermediate of formula (4a). Suitable base may be selected from NaH, KOH, t-BuOK and the like. The compound (4a) is obtained with high chemical (> 98 %) and chiral (e. e > 97 %) purity. Prior art for this conversion reports the formation of ~20 % byproduct and upto 4 % racemization. (Deussen et. al. *Organic Process Research & Development*, **2003**, 7, 82-88)

Selective esterification of compound of formula (4a) to obtain (5a) (Scheme 2) may be carried out using corresponding alcohols such as MeOH, EtOH, propanol, isopropanol, butanol, isobutanol, tert-butanol and the like, in the presence of acids such as H₂SO₄, p-TSA and the like or mixture thereof or activating reagent such as SOCl₂. Alternatively, the esterification may be carried out in the presence of a suitable base selected from Na₂CO₃, K₂CO₃, KOH, NaOMe, NaOEt and the like or mixture thereof in the presence of corresponding alkylating agents such as methyl iodide, ethyl iodide, dimethyl sulfate, diethyl sulfate and the like in solvents selected from DMF, DMSO and the like or mixtures thereof.

The alkylation of compound of formula (5a) to obtain compound of formula (1a) may be carried out using an excess of base w.r.to the starting compound, with a suitable alkylating agent in the presence of a solvent to obtain compound of formula (1a). Suitable alkylating agents may be alkyl sulfates such as diethyl sulfate, dimethyl sulfate and the like; alkyl halides selected from methyl iodide, ethyl iodide, ethyl bromide, propyl bromide, isopropyl bromide and the like. The solvent used is DMSO. The base may be present in 2 to 7 equivalents, preferably in 5 to 7 equivalents, the alkylating agent is present in equal moles w.r.to the base, and the solvent volume may be 4-10 times w.r.to the weight of the

intermediate of formula (5a). Suitable base may be selected from NaH, KOH, t-BuOK and the like.

The crude product of formula (1a) was purified by removal of excess alkyl halide or alkyl sulfate to obtain chemically pure and high chirally pure (e.e $\geq$ 97%) compound of formula (1a) without resolution. Removal of excess alkyl halide from the product can be done by vacuum distillation or by reacting with trialkyl amines like triethyl amine. If alkyl sulfate is used, the excess alkyl sulfate, may be removed by treating with an organic base such as, trialkyl amines preferably with triethylamine and diisopropyl ethylamine (1-2 equivalents to alkyl sulfate) in suitable alcohol at a temp. ranging from 25-30 °C to reflux temperature of the solvent. Use of tertiary amine, instead of alkali which is normally used to remove excess of dialkyl sulfates, prevented the hydrolysis of the ester group.

Step 4: Deprotection of the protecting group of compound of formula (1a) to obtain further compound of formula [(1a), where $R^3 = H$].

The protecting group may be removed using a hard acid and soft nucleophile, optionally in the presence of a solvent at 0 °C-40 °C to obtain the chirally pure (e. e $\geq$ 99 %) compound of formula (1a), (where $R^3 = H$). The deprotection may be carried out in the presence of an ester group. Suitable acids for carrying out such deprotection may be Lewis acids such as $AlCl_3$, BF_3 etherate, BF_3 acetate and the like, preferably BF_3 etherate in 1.5 to 6 equivalents. Suitable nucleophiles may be alkylthiols like ethanethiol, propanethiol, ethanedithiol, and the like, or suitable alkyl aryl sulphides or dialkyl sulfides, preferably alkyl aryl sulfides more preferably thioanisole, in 1.5-7 equivalents. Solvents, if required may be selected from CH_2Cl_2 , $CHCl_3$ and like or mixtures thereof. The product contains less than or equal to 0.3 % of the rearranged product S (-) alkyl-2-alkoxy-3-(3-benzyl-4-hydroxyphenyl) propanoate. Suitable proportion of the Lewis acid and nucleophile may be used to minimize or remove the rearranged side product.

Alternatively, the deprotection can be carried out by catalytic transfer hydrogenation in a suitable solvent using metal catalysts such as Pd/C (5-10 %) in the presence of a hydrogen donor reagent, at atmospheric pressure and at a temperature ranging from 25 °C to the reflux temperature of the solvent used, to obtain the compound of formula (1a), (where $R^3 = H$). Suitable solvents include ethyl acetate, THF, dioxane, glacial acetic acid, aqueous or non aqueous alcohols such as methanol, ethanol, isopropanol and the like or their mixtures. Preferably, ethyl acetate in 5-10 volumes is used. Suitable hydrogen donor reagent may be ammonium formate, cyclohexene, 1,4-cyclohexadiene and the like, preferably, ammonium formate in 3-6 equivalent. The compound of formula (1a), where $R^3 = H$, is obtained in high

optical purity (having $\geq 99\%$ e.e) after suitable work up, and chemical purity of more than or equal to 98 % by HPLC analysis. The product often contains less than or equal to 0.3 % of the rearranged product S (-) alkyl-2-alkoxy-3-(3-benzyl-4-hydroxyphenyl) propanoate.

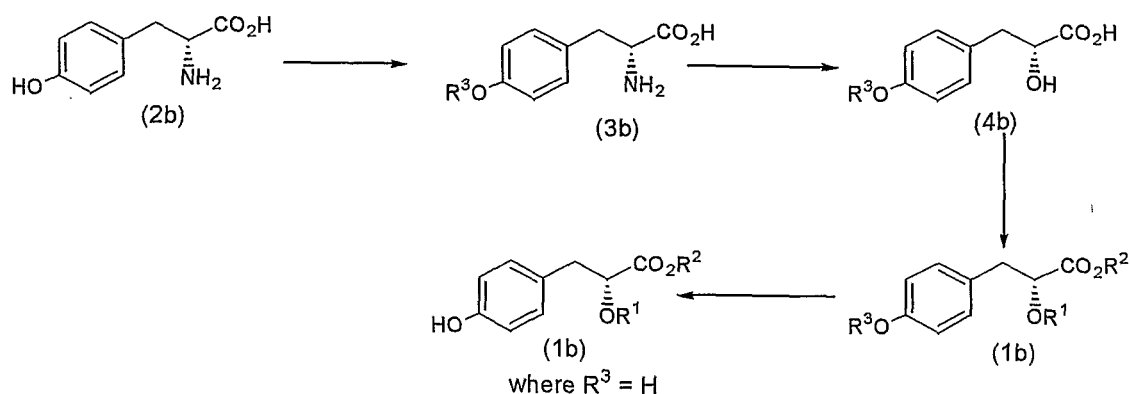
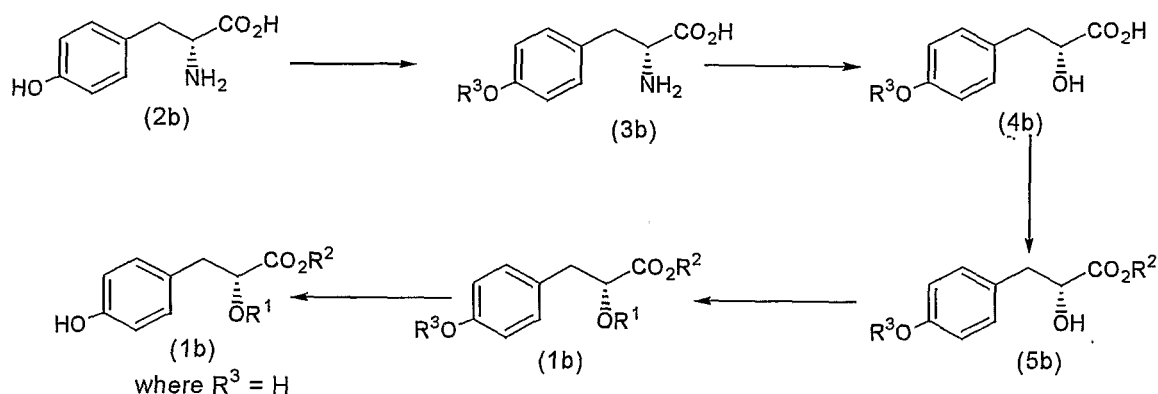
One skilled in the art may appreciate that minor differences in the temperature and reaction times may produce the same result and the other temperatures and time may produce the same result under other condition.

Advantages of the present process:

1. The present invention provides a novel process for the preparation of chemically & chirally pure S (-) 3-aryl-2-alkoxy propanoic acid derivatives of formula (1a).
2. The present invention provides a manufacturing process for the preparation of chemically and optically pure compounds of formula (1a), without using resolution at any stage.
3. The invention also describes a process of converting compound of formula (2a) to compound of formula (3a) using DMF as the solvent. This has the benefit of enhancing the reactivity; thereby the reaction goes to completion and the product is obtained in high yield (55 %) with high chemical and chiral purity.
4. It provides a novel process for the debenzylation or dealkylation of compound of formula (1a) to obtain further compound of formula (1a), (where $R^3 = H$).
5. The present invention provides a very mild and cost effective method for debenzylation of compound of formula (1a) to give further compounds of formula (1a), where $R^3 = H$, unlike Pd/C under high pressure conditions that are normally used in prior art.
6. Another advantage is the reduction of reaction time (4-6 hours) during conversion of compound of formula (4a) to (1a) compared to that reported in some of the literature (24 - 36 hours, WO 0224625).
7. This invention provides a method to obtain compound of formula (3a) in high assay and purity.
8. This invention provides a method to remove excess dialkyl sulfate in the presence of sensitive ester functional group during the conversion of compound of formula (4a) to (1a) ($R^3 \neq H$).
9. The present invention provides an industrial process for the manufacture of compound of formula (1a) which is practical, safe and cost effective.

Preparation of compound (1b):

The corresponding R (+) isomer can be prepared by using D-tyrosine and following a process similar to those described in schemes 1 & 2 above, as shown in **scheme 3 & scheme 4** below:

Scheme 3:**Scheme 4:****Scheme 3:**

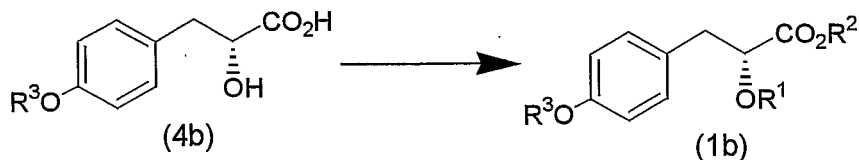
- Selective O-alkylation or O-aralkylation of D-tyrosine of formula (2b) by reacting
 - a base and a chelating agent to obtain the copper complex;
 - reacting the chelated product with an alkylating agent in the presence of solvents to obtain the compound of formula (3b), where R^3 represents suitable protective groups, by a process similar to that disclosed for the preparation of compound of formula (3a), scheme 1;



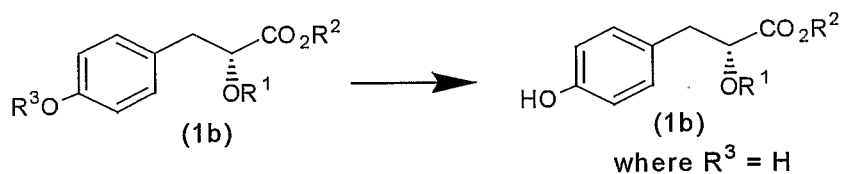
- Diazotisation of the compound of the formula (3b) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4b), by a process similar to that disclosed for the preparation of compound of formula (4a), scheme 1;



- (iii) Dialkylation of the compound of formula (4b) using an excess of alkylating agent and excess base, in presence of a solvent to obtain optically and chemically pure compound of formula (1b), without resolution, by a process similar to that disclosed for the preparation of compound of formula (1a), scheme 1;



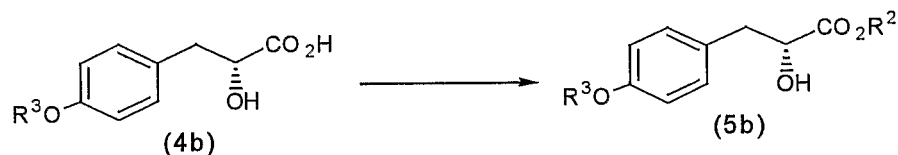
- (iv) Optionally, removing the excess alkylating agent;
- (v) Deprotection of the protecting group of compound of formula (1b) to obtain further compound of formula (1b), where $\text{R}^3 = \text{H}$, without resolution, by a process similar to that disclosed for the preparation of further compound of formula (1a), scheme 1.



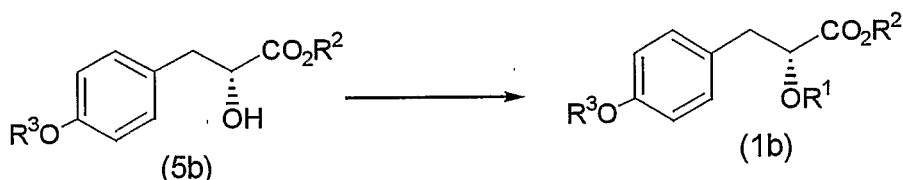
Scheme 4:

Alternatively, the compound of formula (1b), where all symbols are as defined earlier, is obtained by the process comprising

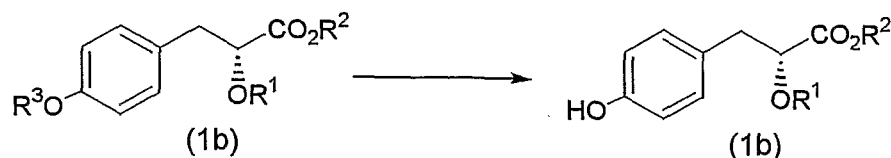
- (i) converting the compound of formula (4b) to compound of formula (5b), by a process similar to that disclosed for the preparation of compound of formula (5a), scheme 2;



- (ii) subsequently, converting the compound of formula (5b) to compound of formula (1b), by a process similar to that disclosed for the preparation of compound of formula (1a), scheme 2;



- (iii) optionally, converting the compound of formula (1b), to further compounds of formula (1b), where $\text{R}^3 = \text{H}$, without resolution, by a process similar to that disclosed for the preparation of further compounds of formula (1a), scheme 2;

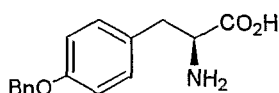


The process of preparing compounds of formula (1b) has similar advantages over earlier processes as discussed for compound (1a) above.

The process described in the present invention is demonstrated in the examples illustrated below. These examples are provided as illustration and should not be considered as limiting the scope of invention in any way.

Example1

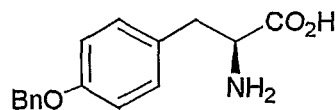
Preparation of O-Benzyl-L-Tyrosine



In a dry, 50 L glass assembly was charged water (6L) and potassium hydroxide pellets (2.409 kg, 36.56 mol) and cooled to ca. 26-28 °C. To this solution L-tyrosine (3 kg, 16.57 mol) and copper sulfate pentahydrate (2.565 kg, 10.3 mol) was added at ca. 26-28 °C with stirring. The mixture was heated to 60 °C-65 °C with stirring and cooled. DMF (12 L) was added to it. Benzyl chloride (2.516 kg, 19.88 mol) was added slowly between 50 °C to 60 °C with stirring. Gray coloured solid copper complex of O-benzyl-L-tyrosine precipitates out. The mixture was cooled to ca. 26-28 °C, stirred and resulting solids were collected by filtration, washed with water and drained well under vacuum.

The wet cake of O-benzyl-L-tyrosine copper complex (18.2 kg) was stirred with methanol in a 50 L glass assembly at reflux temperature. The solids were filtered hot through filter cloth using nutch filter, drained well and washed with methanol. It was dried in an oven at 65 °C-70 °C. The copper complex of O-benzyl-L-tyrosine weighed about 4.6 kg.

The Cu complex of O-benzyl-L-tyrosine was added into water in a 30 lit S.S. tank. It was stirred at ca. 26-28 °C. To this slurry 35 % conc. HCl (3.32 L) was added with stirring, and the solids obtained were filtered and drained well followed by washing with water and 10 % ammonia solution. The wet cake was centrifuged and again washed with water. The solids were dried in an oven at 65 °C-70 °C. The off white O-benzyl-L-tyrosine was obtained in 56 % yield (2.63 kg) with 95.8 % assay by HPLC and 100 % e.e.

Example 2**Preparation of O-Benzyl-L-Tyrosine**

In a dry 100 L glass assembly was charged water (10 L) and potassium hydroxide pellets (4 kg, 71.5 mol) and cooled to room temperature. To this solution L-tyrosine (5 kg, 27.62 mol) and copper sulfate pentahydrate (4.3 kg, 17.17 mol) was added at ca 26-28 °C with stirring. The mixture was heated to 60 °C-65 °C with stirring and cooled. DMF (20 L) was added to it. Benzyl chloride (4.2 kg, 33.14 mol) was added slowly between 50 °C to 60 °C with stirring. Gray coloured solid copper complex of O-benzyl-L-tyrosine precipitates out. The mixture was cooled to ca 26-28 °C, stirred, and resulting solids were collected by filtration, washed with water and drained well under vacuum.

The wet cake of O-benzyl-L-tyrosine copper complex (25.6 kg) was stirred with methanol in a 100 L glass assembly at reflux temperature. The solids were filtered hot through filter cloth using nutch filter, drained well and washed with methanol. It was dried in an oven at 65 °C-70 °C. The copper complex of O-benzyl-L-tyrosine weighed about 8.2 kg.

The Cu complex of O-benzyl-L-tyrosine was added into water in a 50 lit S. S. tank and stirred at ca 26-28 °C. To this slurry 35 % conc. HCl (5.8 L) was added with stirring, the solids obtained were filtered, drained well followed by washing with water and 10 % ammonia solution. The wet cake was centrifuged and again was washed with water. The solids were dried in an oven at 65 °C-70 °C. The off white O-benzyl-L-tyrosine was obtained in 54.7 % yield (4.3 kg) with 95 % assay by HPLC and 100 % e.e.

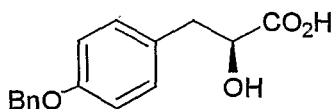
Following processes similar to those disclosed above, Cu complex of O-benzyl-L-tyrosine were prepared under different reaction conditions and solvents as given below. Purification by methanol is not always essential. The complex was subsequently broken to get O-benzyl-L-tyrosine by the process described above.

Ex. No.	Solvent for Preparation of O-Bn-L-Tyrosine Cu complex	Reagent	Base	Condition/ Reaction time	Assay (%)	% ee	% Yield
3	MeOH (4 Vol.)	Benzyl chloride	KOH	50-60 °C 2h	79.8	100	46
4	DMF (4. Vol.)	Benzyl chloride	KOH	50-60 °C 2h	79.2	100	50.6
5	DMF (4. Vol.)	Benzyl chloride	KOH	50-60 °C 2h	88.2	100	50.2
6	MeOH	Benzyl	NaOH	25-30 °C	90.3	100	49.4

	(20 Vol.)	bromide		2h			
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Example 7

S (-) 2-hydroxy-3- (4-benzyloxyphenyl) propanoic acid

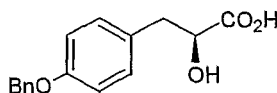


5 To a 2 L round bottom three necked flask, 1,4 dioxane (625 mL) was added followed by O-benzyl-L-tyrosine (50 g, 0.184 mol). To this suspension dilute aqueous sulfuric acid solution (54 g, 0.553 mol, in 175 mL water) was added at ca 26-28 °C. It was cooled to 0 °C-2 °C in an ice salt bath. At 0 °C, aqueous sodium nitrite solution (63.6 g, 0.922 mol) was added dropwise. After the addition, it was stirred for an extended period of time (~ upto 24 hours)
 10 below 30 °C. It was diluted with water and extracted with ethyl acetate. Extracts were combined and washed with water. Organic layer was collected and dried over anhydrous sodium sulfate. It was filtered and filtrate was concentrated below 45 °C to dryness under reduced pressure to obtain crude semi-solid product (58.9 g).

The crude product was purified by stirring in a mixture of diisopropyl ether & ethyl acetate
 15 and filtered and washed with diisopropyl ether. The product obtained was dried in an oven at 55 °C-60 °C. The product weighs about 25.7 g (51 % yield). The HPLC assay was 92.3 % and enantiomeric excess was 100 %.

Example 8

S (-) 2-hydroxy-3- (4-benzyloxyphenyl) propanoic acid



20 To a 20 L round bottom three necked flask, 1,4 dioxane (6.25 L) was added followed by O-benzyl-L-tyrosine (500g, 1.84 mol). To this suspension dilute aqueous sulfuric acid solution (540 g, 5.53 mol, in 2.5 L water) was added at RT. It was cooled to 0 °C-2 °C in an ice salt bath. At 0 °C, aqueous sodium nitrite solution (636 g, 9.22 mol) was added. After the addition, it was stirred for extended period of time (~ upto 24 hours) below 30 °C. It was
 25 diluted with water and extracted with ethyl acetate. Extracts were combined and washed with water. Organic layer was collected and dried over anhydrous sodium sulfate. It was filtered and filtrate was concentrated below 45 °C to dryness under reduced pressure to obtain crude semi-solid product (820 g).

The crude product was purified by stirring in a mixture of diisopropyl ether & ethyl acetate. It
 30 was filtered and washed with diisopropyl ether. The dark yellowish product obtained was

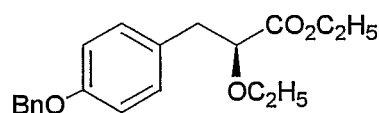
dried in an oven at 55 °C-60 °C. The product weighs about 235 g (47 % yield). The HPLC assay was 98.4 % and enantiomeric excess was 98 %.

Following processes similar to those disclosed in example 7 & 8, S (-) 2-hydroxy-3- (4-benzyloxyphenyl) propanoic acid was prepared using different reagents and solvents as given below.

Ex. No.	Reagent/ (equivalent)	NaNO ₂ equivalent	Reaction condition/ reaction time	% purity	% e.e.	% yield
9	Phosphoric acid (2.5)	2.74	1h, 0-5 °C 4h, <30 °C	92.8	96.6	42
10	Potassium hydrogen Sulfate (2.5)	2.74	1h, 0-5 °C 4h, <30 °C	95.4	97.6	50

Example 11

S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate:



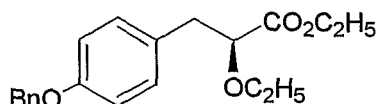
To a dry, three necked round bottom flask dimethyl sulfoxide (DMSO, 5 L) was added followed by potassium hydroxide pellets (811 g, 12.3 mol). It was cooled in an ice-cold water-bath and to it was added 4-benzyloxy phenyl lactic acid obtained above, (500 g, 1.83 mole) with stirring. To the reaction mixture diethyl sulfate (1.9 kg, 12.31 mol) was added through a dropping funnel between 8 °C to 10 °C and the mixture was stirred till completion of the reaction. It was diluted with toluene and dumped into ice cold water with stirring at 10-20 °C. The layers were separated, the organic layer was collected and aqueous layer again extracted with toluene. The combined organic layers were washed with water and brine. The organic layer after drying over anhydrous sodium sulfate and distilling under reduced pressure gave reddish brown liquid product. The liquid product weighs 1 kg which contains 38.39 % diethyl sulfate (GC). The chemical purity of the product was 98.0 % by HPLC.

The crude liquid product was taken in a three-necked round bottom flask. To the product ethanol (2.2 L) and triethylamine (440 ml) were added. It was heated to reflux temperature and stirred. The excess ethanol was distilled out at reduced pressure. The liquid residue was dumped into ice-cold water and extracted with ethyl acetate. The organic layer after drying over anhydrous sodium sulfate was distilled out at reduced pressure to obtain title compound in a liquid form. The liquid product weighs 500g which contains 0 % diethyl sulfate by GC.

The chemical purity of the product is 98.6 % by HPLC and enantiomeric purity was 97.36 % by HPLC.

Example 12

S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate:



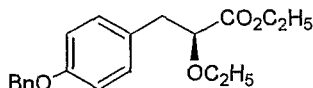
5

To a dry, 100 mL three necked round bottom flask a mixture of dimethyl sulfoxide (DMSO, 2.0 mL) and toluene (18.0 mL) was added followed by crushed potassium hydroxide pellets (0.6 g, 9.1 mmol). Then 4-benzyloxy phenyl lactic acid (1.0 g, 3.67 mmol) was added with stirring. It was heated upto reflux temperature. After 6h it was cooled to 25 °C to 30 °C. To this reaction mixture diethyl sulfate (1.4 g, 9.1 mmol) was added. The reaction mixture was heated to reflux temp. in an oil-bath. After completion of the reaction, it was cooled to RT. The mixture was diluted with water and extracted twice with toluene. The combined organic layers were washed with water and brine. The organic layer after drying over anhydrous sodium sulfate and distilling under reduced pressure gave reddish brown liquid product. The liquid product weighs 1.2 g The chemical purity of the product was 90.6 % by HPLC.

15

Example 13

S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate



To a dry, three necked round bottom flask dimethyl sulfoxide (DMSO, 10 L) was added followed by crushed potassium hydroxide pellets (1.6 kg, 24.6 mol). It was cooled in an ice-cold water-bath and to it was added 4-benzyloxy phenyl lactic acid obtained above, (1 kg, 3.67 mole) with stirring. To the reaction mixture diethyl sulfate (3.8 kg, 24.7 mol) was added through a dropping funnel between 8 °C to 10 °C and the mixture was stirred till completion of the reaction. It was diluted with toluene and dumped into ice cold water with stirring at 10-20 °C. The layers were separated, the organic layer was collected and aqueous layer again extracted with toluene. The combined organic layers were washed with water and brine. The organic layer after drying over anhydrous sodium sulfate and distilling under reduced pressure gave reddish brown liquid product. The liquid product weighs 2.628 kg which contains 48.3 % diethyl sulfate by GC. The chemical purity of the product was 97.9 % by HPLC.

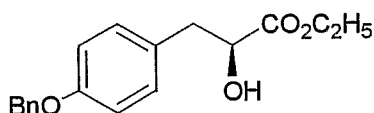
30

The crude liquid product was taken in a three necked round bottom flask. To the product ethanol (10 L) and triethylamine (1.4 l) were added. It was heated to reflux temperature and stirred. The excess ethanol was distilled out at reduced pressure. The liquid residue was dumped into ice-cold water and extracted with ethyl acetate. The organic layer after drying over anhydrous sodium sulfate was distilled out at reduced pressure to obtain title compound in a liquid form. The liquid product weighs 1.1 kg which contains 0 % diethyl sulfate by GC. The chemical purity of the product is 98.5 % by HPLC and enantiomeric purity was 97.5 % by HPLC.

The S (-) 2-hydroxy-3-(4-benzyloxyphenyl) propanoic acid obtained in examples 7-10 was alternatively esterified and subsequently alkylated according to the process described in Scheme 2 to obtain the o-alkylated product of formula (1a), where R³ = a protective group. Representative examples are given below:

Example 14

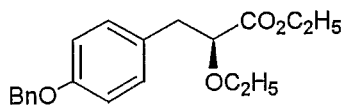
S (-) ethyl-2-hydroxy-3-(4-benzyloxyphenyl) propanoate



To a dry, three necked round bottom flask ethanol (500 mL) and conc. H₂SO₄ (2mL)) was added. Then S (-) 2-hydroxy-3-(4-benzyloxyphenyl) propanoic acid (100g) was added with stirring. It was heated to reflux temp. in an oil-bath. After completion of the reaction ethanol was distilled out at reduced pressure. Thick liquid product was dumped into cold water and extracted with toluene. The organic layer was washed with water, saturated NaHCO₃ solution and brine. The organic layer after drying over anhydrous sodium sulfate and distilling under reduced pressure gave reddish brown liquid product. The liquid product weighs 110 g. The liquid product was stirred with n-hexane (500 mL) at RT. The solid product was separated. It was filtered and washed with n-hexane, dried till constant weight obtained. The solid product weighs 89.2 g The chemical purity of the product was 99.1 % by HPLC.

Example 15

S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate



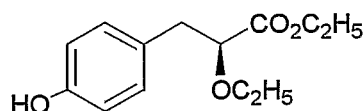
To a dry, three necked round bottom flask dimethyl sulfoxide (DMSO, 100 mL) was added followed by potassium hydroxide pellets (14.7 g, 223.3 mmol). Then S (-) ethyl-2-hydroxy-

3-(4-benzyloxyphenyl) propanoate (10 g, 33.33 mmol, obtained in Example 14) was added with stirring at ca 26-28 °C to which diethyl sulfate (29.2 mL, 223.3 mmol) was added, mixture stirred till completion of reaction. The reaction mixture was dumped into water. Product was extracted with toluene. The organic layer was washed with water, satd. NaHCO₃ solution and brine. The organic layer after drying over anhydrous sodium sulfate was distilled out at reduced pressure to obtain title compound in a liquid form. The liquid product weighs 33.2 g which contains 68 % diethyl sulfate by GC. The chemical purity of the product is 93.0 % by HPLC.

The crude liquid product was taken in a three necked round bottom flask. To the product ethanol (150 mL) and triethylamine (23.0 ml) were added. It was heated to reflux temperature with stirring. The excess ethanol was distilled out at reduced pressure. The liquid residue was dumped into ice-cold water and extracted with ethyl acetate. The organic layer was washed with brine. The organic layer after drying over anhydrous sodium sulfate was distilled out at reduced pressure to obtain title compound in a liquid form. The liquid product weighs 10.1 g which contains 0 % diethyl sulfate by GC. The chemical purity of the product is 97.5 % by HPLC

Example 16

S (-) ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate

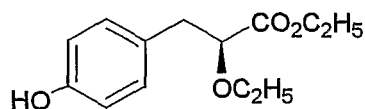


To a three necked flask S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate (15.0 g, 45.7 mmol) and ethanethiol (25.35 mL, 343 mmol) were added. It was stirred and cooled to 0-5°C. To this mixture boron trifluoride etherate (15.83 mL, 125.76 mmol) was added at 0-5 °C. After the addition is complete, it was stirred below 30 °C. After completion of the reaction, the mixture was dumped into ice-cold water with stirring and extracted with ethyl acetate. The extracts were combined and washed with water and brine. The organic layer was collected and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude liquid product.

The crude liquid product was stirred with diisopropyl ether at ca. 25-30 °C to extract the desired product. The diisopropyl ether was removed to obtain the crude liquid product, which was stirred with n-heptane at ca. 25-30 °C to obtain the solid product in 70 % yield (7.6 g). The chemical purity was 96.7 % by HPLC and enantiomeric excess was 100 % by HPLC.

Example 17

S (-) ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate

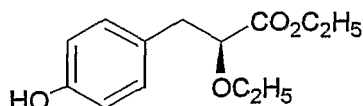


To a three necked flask S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate (25 g, 76.2 mmol) and thioanisole (67 mL, 571.6 mmol) were added. It was stirred and cooled to 0-5 °C. To this mixture borontrifluoride etherate (26.5 mL, 209.6 mmol) was added at 0-5 °C. Once the addition was complete, it was stirred below 30 °C. After completion of the reaction, the mixture was dumped into ice-cold water with stirring and extracted with ethyl acetate. The extracts were combined and washed with water and brine. The organic layer was collected and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude liquid product.

The crude liquid product was stirred with diisopropyl ether at ca. 25-30 °C to extract the desired product. The diisopropyl ether was removed to obtain the crude liquid product, which was stirred with n-heptane at ca. 25-30 °C to obtain the solid product in 60 % yield (11 g). The chemical purity was 99 % by HPLC and enantiomeric excess was 100 % by HPLC.

Example 18

S (-) ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate

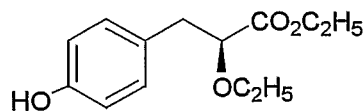


To a three necked flask S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate (2.0 g, 6.0 mmol) and octanethiol (3.96 mL, 22.86 mmol) were added. It was stirred and cooled to 0-5 °C. To this mixture borontrifluoride etherate (1.0 mL, 8.34 mmol) was added at 0-5 °C. Once the addition was complete, it was stirred below 30 °C. After completion of the reaction, the mixture was dumped into an ice-cold water with stirring, extracted with ethyl acetate. The extracts were combined and washed with water and brine. The organic layer was collected and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain the crude liquid product.

The crude liquid product was stirred with diisopropyl ether at ca. 25-30 °C to extract the desired product. The diisopropyl ether was removed to obtain the crude liquid product, which was stirred with n-heptane at ca. 25-30 °C to obtain the solid product in 50.8 % yield (0.74 g). The chemical purity was 92.4 % by HPLC.

Example 19

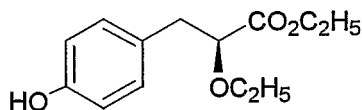
S (-) ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate



To a three necked flask ethyl acetate (1.0 L) and S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate (200 g, 304.8 mmol) were added with stirring. To this mixture 5 % Pd-C paste containing 50 % water (100 g, 23.58 mmol) was added. To this suspension ammonium formate (156 g, 1219.5 mmol) was added. After completion of the reaction it was filtered through hyflo-bed using filter cloth, hyflo-bed was washed with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure to obtain a light yellowish solid product. The solid product was obtained in 83.0 % yield (120 g). The chemical purity was 99.7 % by HPLC and enantiomeric excess was 99 % by HPLC.

Example 20

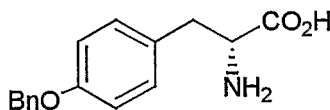
S (-) ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate



To a three necked flask S (-) ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate (5.0 g, 15.2 mmol, obtained in Example No. 15) and thioanisole (13.4 g, 114.3 mmol) were added. It was stirred and cooled to 0-5 °C. To this mixture borontrifluoride etherate (5.3 g, 41.9 mmol) was added. The mixture was stirred below 30 °C. After completion of the reaction, it was dumped into ice-cold water with stirring and extracted with ethyl acetate. The extracts were combined and washed with satd. NaHCO₃, water and brine. The organic layer was collected and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain a crude liquid product.

The liquid product was stirred with diisopropyl ether at RT to extract the product. The diisopropyl ether was removed, stirred with n-heptane to obtain the solid product in 40 % yield (1.45 g). The chemical purity was 99.38 % by HPLC and enantiomeric excess was 99.16 % by HPLC.

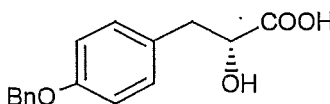
The corresponding R (+) ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate was prepared by a processes similar to those disclosed above starting from D-Tyrosine, as per scheme 3 & 4. Representative examples of the process of preparation are as under:

Example 21**Preparation of O-Benzyl-D-Tyrosine**

5 In a dry, 1L three necked round bottom flask was charged water (200 mL) and potassium hydroxide pellets (80.3 g, 1.22 mol) and cooled to ca.26-28 °C. To this solution D-tyrosine (100 g, 0.55 mol) and copper sulfate pentahydrate (85.5 g, 0.34 mol) was added at ca. 26-28 °C with stirring. The mixture was heated to 60 °C-65 °C with stirring and cooled. DMF (400 mL) was added to it. Benzyl chloride (83.8 g, 0.66 mol) was added slowly between 50 °C to
 10 60 °C with stirring. Gray coloured solid copper complex of O-benzyl-D-tyrosine precipitates out. The mixture was cooled to ca. 26-28 °C, stirred and resulting solids were collected by filtration, washed with water and drained well under vacuum.

The wet cake of O-benzyl-D-tyrosine copper complex (200 g) was stirred with methanol at reflux temperature. The solids were filtered and washed with methanol. It was dried in an
 15 oven at 65 °C-70 °C. The copper complex of O-benzyl-D-tyrosine weighed about 150 g.

The Cu complex of O-benzyl-D-tyrosine was added into water in a 30 lit S.S. tank. It was stirred at ca.26-28 °C. To this slurry 35 % conc. HCl (3.32 L) was added with stirring, and the solids obtained were filtered and drained well followed by washing with water and 10 % ammonia solution. The wet cake was centrifuged and again washed with water. The solids
 20 were dried in an oven at 65 °C-70 °C. The off white O-benzyl-D-tyrosine was obtained in 73 % yield (110 g).

Example 22**R (+)-2-hydroxy-3-(4-benzyloxyphenyl) propanoic acid**

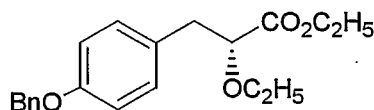
25 In a 3 L round bottom three necked flask, 1,4 dioxane (1.25 L) was added followed by O-benzyl-D-tyrosine (100 g, 0.37 mol). To this suspension dilute aqueous sulfuric acid solution (108 g, 1.1 mol, in 350 mL water) was added at ca. 26-28 °C. It was cooled to 0 -2 °C in an ice salt bath. At 0 °C, aqueous sodium nitrite solution (127.2 g, 1.84 mol) was added
 30 dropwise. After the addition, it was stirred for an extended period of time (~ upto 24 hours) below 30 °C. It was diluted with water and extracted with ethyl acetate. Extracts were combined and washed with water. Organic layer was collected and dried over anhydrous

sodium sulfate. It was filtered and filtrate was concentrated below 45 °C to dryness under reduced pressure to obtain crude semi-solid product (115 g).

The crude product was purified by stirring in a mixture of diisopropyl ether & ethyl acetate, filtered and washed with diisopropyl ether. The product obtained was dried in an oven at 55 °C-60 °C. The product weighs about 40 g (40 % yield).

Example 23

R (+)-ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate

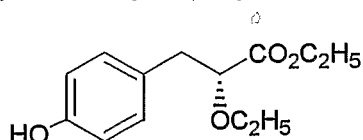


In a dry, three necked round bottom flask dimethyl sulfoxide (DMSO, 96 mL) was added followed by potassium hydroxide pellets (39 g, 0.59 mol). It was cooled in an ice-cold water-bath and to it was added R (+) 4-benzyloxy phenyl lactic acid obtained above, (24 g, 0.09 mole) with stirring. To the reaction mixture diethyl sulfate (91 g, 0.59 mol) was added through a dropping funnel between 8 °C to 10 °C and the mixture was stirred till completion of the reaction. It was diluted with toluene and dumped into ice cold water with stirring at 10-20 °C. The layers were separated, the organic layer was collected and aqueous layer again extracted with toluene. The combined organic layers were washed with water and brine. The organic layer after drying over anhydrous sodium sulfate and distilling under reduced pressure gave reddish brown liquid product. The liquid product weighs 45 g

The crude liquid product was taken in a three-necked round bottom flask. To the product ethanol (450 mL) and triethylamine (13.8 ml) were added. It was heated to reflux temperature and stirred. The excess ethanol was distilled out at reduced pressure. The liquid residue was dumped into ice-cold water and extracted with ethyl acetate. The organic layer after drying over anhydrous sodium sulfate was distilled out at reduced pressure to obtain title compound in a liquid form. The liquid product weighs 16 g. The chemical purity of the product is 93.3 % by HPLC

Example 24

R (+)-ethyl-2-ethoxy-3-(4-hydroxyphenyl) propanoate



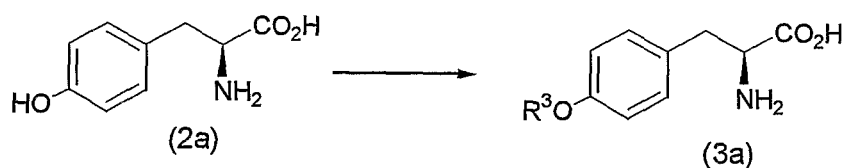
In a three necked flask ethyl acetate (25 mL) and R (+)-ethyl-2-ethoxy-3-(4-benzyloxyphenyl) propanoate (5 g, 15 mmol) were added with stirring. To this mixture 10 % Pd-C (1.3 g) was added. To this suspension ammonium formate (4 g, 63 mmol) was added.

After completion of the reaction it was filtered through hyflo-bed using filter cloth, hyflo-bed was washed with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure to obtain a light yellowish solid product. The solid product was obtained in 85 %
5 yield (3.1 g). The chemical purity was 97 % by HPLC and enantiomeric excess was 99 % by HPLC.

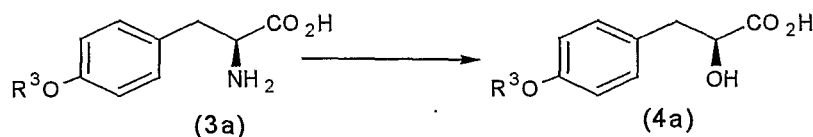
We Claim:

1. A process for the preparation of of S (-) 3-aryl-2-alkoxy propanoic acid derivatives of the formula (1a), wherein R¹ represents H or (C₁-C₆) alkyl group; R² represents (C₁-C₆) alkyl groups; R³ represents H, protecting groups such as benzyl, substituted benzyl, or (C₁-C₃) alkyl group, comprising steps of:

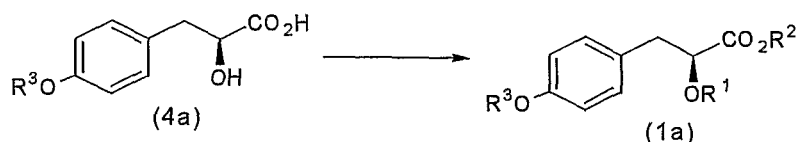
- (i) Selective O-alkylation or O-aralkylation of L-tyrosine of formula (2a) by
- Reacting a base and a suitable chelating agent to obtain the copper complex,
 - Reacting the copper complex with an alkylating or aralkylating agent in the presence of suitable solvents and a base to obtain the compound of formula (3a), where R³ represents the corresponding alkyl or aralkyl group;



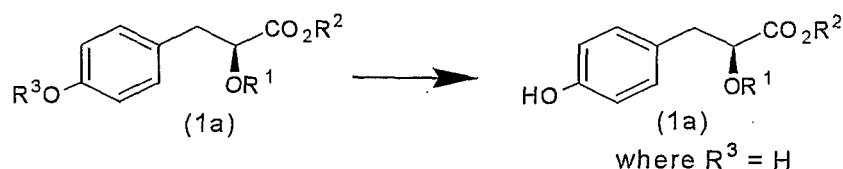
- (ii) Diazotisation of the compound of the formula (3a) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4a)



- (iii) Dialkylation of the compound of formula (4a) using an excess of alkylating agent and excess base, in presence of suitable solvent to obtain optically and chemically pure compound of formula (1a), without resolution.



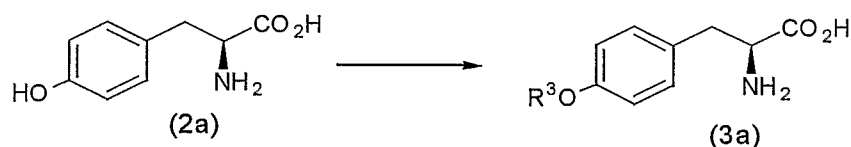
- (iv) Optionally, removing the excess alkylating agent
- (v) Deprotection of the protecting group of compound of formula (1a) to obtain further compound of formula (1a), where R³ = H, without resolution.



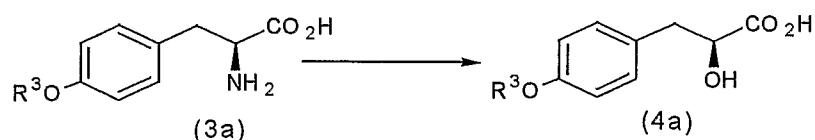
2. A process as claimed in claim 1 wherein the said base used in step (i) is selected from NaOH, KOH, K₂CO₃.
3. A process as claimed in claim 1 wherein the said chelating agent used in step (i) is selected from CuSO₄, Cu(OAc)₂.

4. A process as claimed in claim 1 wherein the said alkylating agent used in step (i) is selected from suitable (C₁-C₃)alkyl halides and suitable aralkylating agent is selected from suitable benzyl or substituted benzyl halides.
5. A process as claimed in claim 1 wherein the said solvent used in step (i) is selected from methanol, ethanol, DMF or mixture thereof.
6. A process as claimed in claim 1 wherein the said diazotising agent used in step (ii) is sodium nitrite in presence of reagents selected from sulfuric acid, orthophosphoric acid, potassium hydrogen sulfate.
7. A process as claimed in claim 1 wherein the said solvent used in step (ii) is selected from dioxane, acetone, methyl ethyl ketone or mixture thereof.
8. A process as claimed in claim 1 wherein the said alkylating agent used in step (iii) is selected from suitable alkyl sulfates, alkyl halides, the base is selected from NaH, KOH, t-BuOK and the solvent used is DMSO.
9. A process for the preparation of S (-) 3-aryl-2-hydroxy propanoic acid derivatives of the formula (1a), wherein R¹, R² & R³ are as described in claim 1, comprising steps of:

- (i) Selective O-alkylation or O-aralkylation of L-tyrosine of formula (2a) by
 - a) Reacting a base and a suitable chelating agent to obtain the copper complex,
 - b) Reacting the copper complex with an alkylating or aralkylating agent in the presence of suitable solvents and a base to obtain the compound of formula (3a), where R³ represents the corresponding alkyl or aralkyl group;



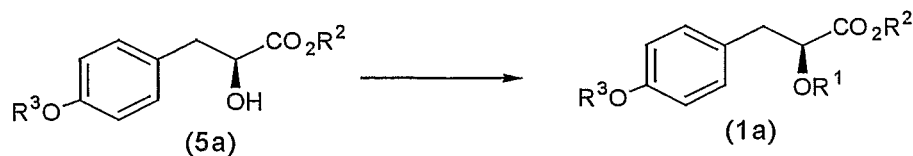
- (ii) Diazotisation of the compound of the formula (3a) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4a)



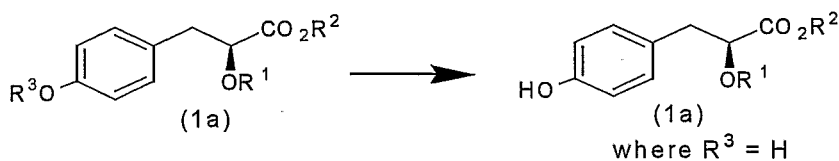
- (iii) Selective esterification of compound of formula (4a) to obtain compound of formula (5a)



- (iv) O-alkylation of compound of formula (5a) using suitable alkylating agents in the presence of suitable bases to obtain compound of formula (1a),



- (v) optionally, removing the excess alkylating agent
- (vi) Deprotection of the protecting group of compound of formula (1a) to obtain further compound of formula (1a), where $\text{R}^3 = \text{H}$, without resolution.



10. A process as claimed in claim 9 wherein the said base used in step (i) is selected from NaOH, KOH, K_2CO_3 .
11. A process as claimed in claim 9 wherein the said chelating agent used in step (i) is selected from CuSO_4 , $\text{Cu}(\text{OAc})_2$.
12. A process claimed in claim 9 wherein the said alkylating agent used in step (i) is selected from suitable $(\text{C}_1\text{-C}_3)$ alkyl halides and suitable aralkylating agent is selected from suitable benzyl or substituted benzyl halides.
13. A process as claimed in claim 9 wherein the said solvent used in step (i) is selected from methanol, ethanol, DMF or mixture thereof.
14. A process as claimed in claim 9 wherein the said diazotising agent used in step (ii) is sodium nitrite in presence of reagents selected from sulfuric acid, orthophosphoric acid, potassium hydrogen sulfate.
15. A process as claimed in claim 9 wherein the said solvent used in step (ii) is selected from dioxane, acetone, methyl ethyl ketone or mixture thereof.
16. A process as claimed in claim 9 wherein selective esterification of (4a) to obtain compound of formula (5a), in step (iii), is carried out using corresponding alcohols such as MeOH, EtOH, propanol, isopropanol, butanol, isobutanol, tert-butanol in the presence of reagents selected from H_2SO_4 , SOCl_2 , p-TSA or mixtures thereof.
17. An alternate process for the selective esterification of (4a) to obtain compound of formula (5a), as claimed in claim 9, in basic conditions using suitable bases selected from Na_2CO_3 , K_2CO_3 , KOH, NaOMe, NaOEt or mixtures thereof in the presence of

corresponding alkylating agents such as methyl iodide, ethyl iodide, dimethyl sulfate, diethyl sulfate in solvents selected from DMF, DMSO or mixtures thereof.

18. A process as claimed in claim 9, wherein the O-alkylation of compound of formula (5a) in step (iv) is carried out using suitable alkylating agents selected from alkyl sulfates such as diethyl sulfate, dimethyl sulfate; alkyl halides selected from methyl iodide, ethyl iodide, ethyl bromide, propyl bromide and isopropyl bromide. The solvent used is DMSO.

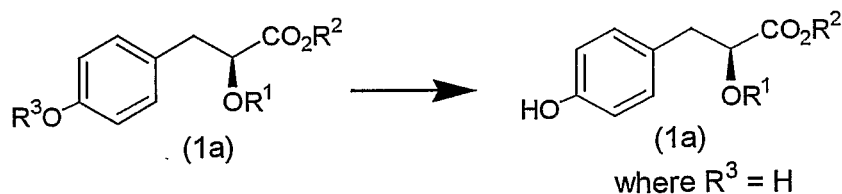
19. A process as claimed in claim 9, step (iv) wherein suitable bases are NaH, KOH, t-BuOK.

20. A process as claimed in claims 1 and 9 wherein the deprotection of compound of formula (1a) where R^3 = protective group, to obtain further compounds of formula (1a), where R^3 = H, is carried by treating with suitable Lewis acids selected from $AlCl_3$, BF_3 etherate, BF_3 acetate and suitable nucleophiles selected from suitable alkylthiols such as ethanethiol, propanethiol, ethanedithiol, alkyl aryl sulfides and dialkyl sulfides, preferably aryl alkyl sulfides, more preferably thioanisole.

21. A process as claimed in claims 1 and 9 wherein the deprotection of compound of formula (1a), where R^3 = protective group, to obtain further compounds of formula (1a), where R^3 = H, is alternatively carried by catalytic transfer hydrogenation using metal catalysts such as Pd/C at atmospheric pressure in the presence of a hydrogen donor reagent, in a suitable solvent selected from ethyl acetate, THF, dioxane, glacial acetic acid, methanol, ethanol, propanol, isopropanol or mixtures thereof.

22. A process as claimed in claim 21 wherein suitable hydrogen donor reagent is selected from ammonium formate, cyclohexene, 1,4-cyclohexadiene.

23. A process for the preparation of compound of formula (1a), where R^3 = H, with chiral purity $\geq 99\%$, by deprotecting compound of formula (1a), when R^3 represents a protective group as defined earlier, by treating with suitable Lewis acids selected from $AlCl_3$, BF_3 etherate, BF_3 acetate and suitable nucleophiles selected from ethanethiol, propanethiol, ethanedithiol, alkyl aryl sulfides and dialkyl sulfides.



24. A process as claimed in claims 1 & 9 wherein the excess alkyl halide is removed by vacuum distillation or reacting with trialkyl amines preferably triethyl amine.

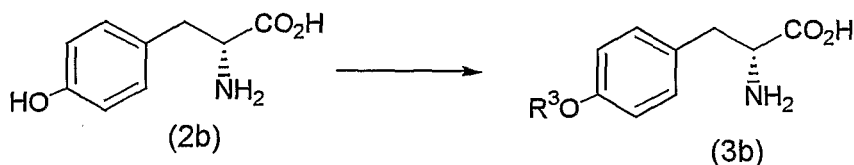
25. A process as claimed in claims 1 & 9 wherein the excess alkyl sulfate is removed by treating with organic base such as trialkylamines preferably, triethylamine and diisopropyl ethylamine.

26. A process for the preparation of R (+) 3-aryl-2-alkoxy propanoic acid derivatives of the formula (1b), wherein R¹ represent H or (C₁-C₆) alkyl; R² represents (C₁-C₆) alkyl group; R³ represents H, protecting groups such as benzyl, substituted benzyl, or (C₁-C₃) alkyl group, comprising:

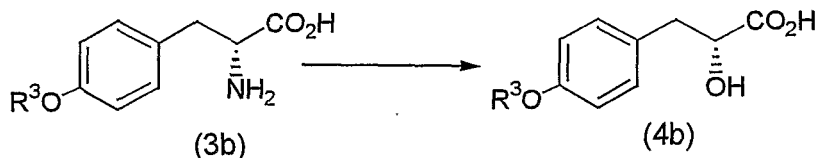
(i) Selective O-alkylation or O-arylation of D-tyrosine of formula (2b) by

a) Reacting a base and a suitable chelating agent to obtain the copper complex,

b) Reacting the copper complex with an alkylating or aralkylating agent in the presence of suitable solvents and base to obtain the compound of formula (3b), where R³ represents corresponding alkyl or aralkyl group;



(ii) Diazotisation of the compound of the formula (3b) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4b)

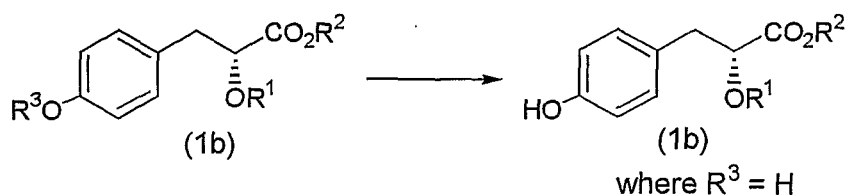


(iii) Dialkylation of the compound of formula (4b) using an excess of alkylating agent and excess base, in presence of suitable solvent to obtain optically and chemically pure compound of formula (1b), without resolution.



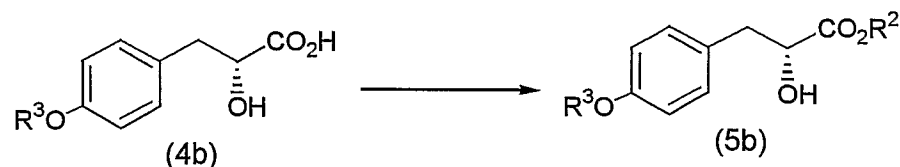
(iv) Optionally, removing the excess alkylating agent

(v) Deprotection of the protecting group of compound of formula (1b) to obtain further compound of formula (1b), where R³ = H, without resolution.

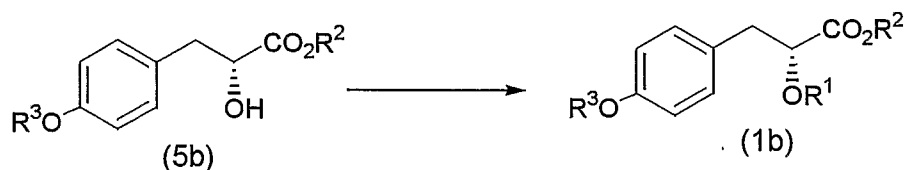


27. A process for the preparation of R (+) 3-aryl-2-alkoxy propanoic acid derivatives of the formula (1b), where all symbols are as defined earlier, the process comprising

- (i) converting the compound of formula (4b) to compound of formula (5b),



- (ii) subsequently, converting the compound of formula (5b) to compound of formula (1b),



- (iii) optionally, converting the compound of formula (1b), to further compounds of formula (1b), where $\text{R}^3 = \text{H}$, without resolution

