Abstract: The present inventors have surprisingly found that (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone can be prepared in high purity and with high yield, by reacting 3-fluoro-4-morpholinyl aniline with (R)-glycidol, or an ester or an ether derivative thereof, to produce a novel 2-hydroxypropyl intermediate, which is then subjected cyclization using a suitable reagent to produce (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone or an ester, or an ether derivative thereof. In one aspect, provided herein are efficient, industrially advantageous and environmentally friendly processes for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone and its derivatives, in high yield and with high purity, using novel intermediates.
IMPROVED PROCESS FOR THE PREPARATION OF LINEZOLID INTERMEDIATE

FIELD OF THE INVENTION

The present invention relates to improved, commercially viable and industrially advantageous processes for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone using novel intermediates, which is useful intermediate in the synthesis of Linezolid.

BACKGROUND OF THE INVENTION

U.S. Patent No. 5,688,792 (hereinafter referred to as the '792 patent), assigned to Pharmacia & Upjohn Company, discloses a variety of oxazine and thiazine oxazolidinone derivatives and their stereochemically isomeric forms, processes for their preparation, pharmaceutical compositions comprising the derivatives, and method of use thereof. These compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms and acid-fast organisms. Among them, Linezolid, a member of the oxazolidinone class of drugs and chemically named as N-[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA). Linezolid is represented by the following structural formula I:

\[
\text{O} \quad \text{N} \quad \text{O} \\
\text{F} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{CH}_3
\]

The main indications of linezolid are infections of the skin and soft tissues and pneumonia (particularly hospital-acquired pneumonia). Linezolid is marketed by Pfizer.
under the trade names Zyvox (in the United States, United Kingdom, Australia, and several other countries), Zyvoxid (in Europe), and Zyvoxam (in Canada and Mexico).


In the preparation of linezolid, (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II:

\[
\text{Scheme 1:}
\]

is a key intermediate.

According to the '792 patent, the (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone intermediate is prepared by a process as depicted in scheme 1:
As per the process described in the '792 patent, (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxazolidinone is prepared by reacting 3-fluoro-4-morpholinyl aniline with benzyl chloroformate in the presence of sodium bicarbonate to produce N-carbobenzyloxy-3-fluoro-4-morpholinyl aniline, which is then reacted with a solution of (R)-glycidyl butyrate in tetrahydrofuran in the presence of n-butyl lithium/hexane at a temperature of -78°C under nitrogen atmosphere, followed by tedious work-up and isolation methods to produce the (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxazolidinone.

As per the process described in the '792 patent, the (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxazolidinone intermediate is subsequently converted to Linezolid by reacting with methanesulfonyl chloride in the presence of triethylamine in methylene chloride under nitrogen atmosphere to produce (5R)-[3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate, which is then reacted with sodium azide to produce (5R)-[3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxo-5-oxazolidinyl]methyl azide. The resulting azide intermediate is hydrogenated in the presence of 10% palladium/carbon, followed by reaction with acetic anhydride to produce Linezolid.

U.S. Patent No. 5,837,870 (hereinafter referred to as the '870 patent) discloses a process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxazolidinone. As per the process described in '870 patent, tetrahydrofuran is mixed with t-amyl alcohol, followed by the addition of butyl lithium in hexanes with agitation to produce a lithium t-amylate mixture, which is then added to solution of N-carbobenzyloxy-3-fluoro-4-morpholinyl aniline [obtained as per the process described in J. Med. Chem., 39(3), 673 (1996)] in tetrahydrofuran while maintaining the temperature at less than 8°C and rinsed in with tetrahydrofuran to produce a lithium anion mixture. Tetrahydrofuran is mixed with S-(+)-3-chloro-1,2-propanediol, the resulting mixture is cooled to -16°C, followed by the addition of potassium t-butoxide in tetrahydrofuran while maintaining the temperature at less than -10°C. The resulting slurry is stirred at -14°C to 0°C for 1 hour and then added to the lithium anion mixture while maintaining both mixtures at 0°C, then rinsed in with tetrahydrofuran. The resulting slurry is stirred for 2 hours at 20-23°C and then cooled to 6°C, followed by the addition of a
mixture of citric acid monohydrate in water. The resultant liquid phases are separated and the lower aqueous phase is washed with ethyl acetate. The organic layers are combined and solvent is removed under reduced pressure. Heptane and water are added to the resulting mass and the solvent is removed by reduced pressure until a total volume of 5 ml remains. The precipitated product is collected by vacuum filtration and washed with water and then dried in a stream of nitrogen to produce (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone.

Chinese Patent Application Publication No. CN 1772750 describes a process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone as depicted in scheme 2:

Scheme 2:

Organic Letters 2003, 5, 963-965 describes a process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone as depicted in scheme 3:

Scheme 3:
PCT Publication No. WO 2012/14355 describes a process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone as depicted in scheme 4:

Scheme 4:

3-Fluoro-4-morpholinyl aniline + (R)-2-(Chloromethyl) oxirane → N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinyl aniline

CDI → (3R)-[(3-Fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidinyl]methyl acetate

Base → (5R)-[(Hydroxymethyl)-3-[3-fluoro-4-morpholinyl]phenyl]-2-oxazolidinone

The processes for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone intermediate described in the aforementioned prior art suffer from disadvantages such as the use of highly flammable, corrosive and pyrophoric reagents like n-butyl lithium in hexanes; use of highly toxic reagents like phosgene, pyridinium p-toluenesulfonate; use of expensive chiral reagents such as (±)-trans-1,2-diaminocyclohexane, in excess amounts, for preparing the starting material 5-(tetrahydro-pyran-2-yloxymethyl)-2-oxazolidinone which is difficult to synthesize; use of multiple solvents and in excess amounts; use of highly flammable and/or hazardous solvents like hexanes, heptane, dioxane and tetrahydrofuran; and involve the use of tedious and cumbersome procedures like prolonged reaction time periods, very low temperature conditions (-78°C or -16°C), multiple process steps, column chromatographic
purifications, multiple isolations/re-crystallizations, and thus resulting in a poor product yield and quality. Methods involving column chromatographic purifications are generally undesirable for large-scale operations, thereby making the process commercially unfeasible.

The major drawback of the processes for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone intermediate described in the aforementioned prior art is that the processes involve the use of highly flammable, corrosive and pyrophoric reagents like n-butyl lithium in hexanes, thereby requiring very strict control of reaction conditions at low temperatures (-78°C or -16°C). Handling of n-butyl lithium is very difficult at lab scale and in commercial scale operations. Moreover, the yields and purities of the product obtained according to the prior art processes are very low.

Based on the aforementioned drawbacks, the prior art processes have been found to be unsuitable for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone at lab scale and in commercial scale operations.

A need remains for an improved, commercially viable and environmentally friendly process of preparing (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone with high yield and purity, to resolve the problems associated with the processes described in the prior art, and that will be suitable for large-scale preparation. Desirable process properties include non-hazardous conditions, environmentally friendly and easy to handle reagents, reduced cost, greater simplicity, increased purity, and increased yield of the product, thereby enabling the production of Linezolid, in high purity and with high yield.

**SUMMARY OF THE INVENTION**

The present inventors have surprisingly found that (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone can be prepared in high purity and with high yield, by reacting 3-fluoro-4-morpholinyl aniline with (R)-glycidol, or an ester or an ether derivative thereof, to produce a novel 2-hydroxypropyl intermediate, which is then subjected cyclization using a suitable reagent to produce (5R)-5-(hydroxymethyl)-3-[3-
fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone or an ester, or an ether derivative thereof.

In one aspect, provided herein are efficient, industrially advantageous and environmentally friendly processes for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone and its derivatives, in high yield and with high purity, using novel intermediates. The processes disclosed herein avoid the tedious and cumbersome procedures of the prior processes, thereby resolving the problems associated with the processes described in the prior art, which is more convenient to operate at lab scale and in commercial scale operations.

In another aspect, provided herein is a novel 2-hydroxypropyl derivative of formula IV:

![Formula IV](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or an hydroxyl protecting group Ri.

In another aspect, the present invention also encompasses the use of the novel 2-hydroxypropyl intermediate compounds of formula IV disclosed herein for preparing Linezolid.

The process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone disclosed herein has the following advantages over the processes described in the prior art:

i) the process involves the use of novel intermediates and which can be carried out in a single pot;

ii) the overall process involves a reduced number of process steps and shorter reactions times;

iii) the process avoids the use of highly flammable or explosive chemicals like n-butyl lithium, hexane and heptane;
iv) the process avoids the use of highly toxic or hazardous chemicals like phosgene, pyridinium p-toluenesulfonate, potassium t-butoxide and dioxane;

v) the process avoids the use of tedious and cumbersome procedures like prolonged reaction time periods, very low temperatures (-78°C or -16°C), multiple process steps, column chromatographic purifications, multiple isolations, additional and excess amounts of solvents;

vi) the process avoids the use of expensive chiral reagents such as (±)-trans-1,2-diaminocyclohexane and 5-(tetrahydro-pyran-2-yloxymethyl)-2-oxazolidinone;

vii) the process involves easy work-up methods and simple isolation processes, and there is a reduction in chemical waste;

viii) the purity of the product is increased without additional purifications; and

ix) the overall yield of the product is increased.

DETAILLED DESCRIPTION OF THE INVENTION

According to one aspect, there is provided an improved process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II:

\[
\text{II}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, which comprises:

a) reacting 3-fluoro-4-morpholinyl aniline of formula V:

\[
\text{V}
\]

or a salt thereof with a compound of formula VI:
or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein \( R \) is hydrogen or a hydroxyl protecting group \( R_1 \), \( L \) represents a leaving group and \( Y \) represents a hydroxy group; or \( L \) and \( Y \) together with the atoms to which they are bonded form an oxirane ring having the structural formula \( \text{VI} \):

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein \( R \) is as defined above;

to produce a 2-hydroxypropyl derivative of formula \( \text{IV} \):

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein \( R \) is as defined in formula \( \text{VI} \);

b) subjecting the compound of formula \( \text{IV} \) to carbonylation using a suitable carbonylating agent to produce the compound of formula \( \text{II} \) or an enantiomeric form or a mixture of enantiomeric forms thereof (when the group \( R \) is hydrogen), or an oxazolidinone compound of formula \( \text{III} \):
or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein R₁ is a hydroxyl protecting group; and

c) optionally, deprotecting the compound of formula III to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

The linezolid intermediate, (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxazolidinone, of formula II contains one chiral centre and thus exists as two optical isomers, i.e. enantiomers (R & S-isomers). The process disclosed herein encompasses the preparation of both enantiomers and mixtures thereof in all proportions.

In one embodiment, the leaving group L in the compound of formula VI is a halogen, or an alkyl or aryl sulfonyloxy group. Specifically, the leaving group L is selected from the group consisting of Cl, Br, I, methanesulfonyloxy, toluenesulfonyloxy and trifluoromethanesulfonyloxy group; and a most specific leaving group is Cl or toluenesulfonyloxy.

In one embodiment, the group R in the compounds of formulae IV, VI and Via is hydrogen.

In another embodiment, the group R in the compounds of formulae IV, VI and Via is a hydroxyl protecting group R₁.

Unless otherwise indicated, the "protecting group for a hydroxyl group" is not particularly limited provided that it can stably protect the hydroxyl group in the reaction, and specifically refers to a protecting group capable of being cleaved by a chemical step such as hydrogenolysis, hydrolysis, electrolysis and photolysis.

Exemplary hydroxyl protecting groups 'R' include, but are not limited to, a substituted or unsubstituted aralkyl, a substituted or unsubstituted trityl, an aliphatic acyl group including an alkanoyl group, an aromatic acyl group including an arylcarbonyl group, a tri(Cı₆ alkyl)silyl (where the alkyl groups may be the same or different), a tri(Cı₆ aryl)silyl, an alkylcarbonyl group substituted with a carboxy group, an alkylcarbonyl group substituted with a halogen atom, a saturated cyclic hydrocarbon-carbonyl group, an alkylcarbonyl group substituted with a lower alkoxy group, an unsaturated alkylcarbonyl group, a halogenoarylcarbonyl group, an arylcarbonyl group substituted with a lower alkyl
group, a lower alkoxylated arylcarbonyl group, an arylcarbonyl group substituted with a carboxy group, a nitrated arylcarbonyl group, an arylcarbonyl group substituted with a lower alkoxycarbonyl group, an arylcarbonyl group substituted with an aryl, and the like.

In one embodiment, the hydroxyl protecting group is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, p-toluoyl, p-anisoyl, 2-carboxybenzoyl, p-nitrobenzoyl, trityl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiofuranyl, o-nitrobenzyl, benzyl, p-methoxybenzyl, trimethylsilyl, triisopropylsilyl and t-butyldiphenylsilyl.

Specific hydroxyl protecting groups are acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, trichloroacetyl, trifluoroacetyl, benzoyl, p-toluoyl, p-anisoyl, trityl, o-nitrobenzyl, benzyl and p-methoxybenzyl; and most specifically butyryl, trityl and benzyl.

The reaction in step-(a) can be carried out in the presence or absence of a reaction inert solvent. In one embodiment, the reaction in step-(a) is carried out in the presence of a solvent or a mixture of solvents.

Exemplary solvents used in step-(a) include, but are not limited to, an alcohol, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, a halogenated hydrocarbon solvent, and mixtures thereof.

Specifically, the solvent used in step-(a) is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, monoglyme, diglyme, acetonitrile, propionitrile, N,N-dimethylformamide, N,N-dimethylethamide, dimethylsulfoxide, dichloromethane, dichloroethane, chloroform, and mixtures thereof. Most specific solvents are methanol, ethanol, isopropanol, and mixtures thereof.
In another embodiment, the reaction in step-(a) is optionally carried out in the presence of a base. Specifically, the base is an organic or inorganic base, and most specifically an inorganic base.

Exemplary bases include, but are not limited to, collidine, trimethylamine, tributylamine, triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine and 1-alkylimidazole; hydroxides, alkoxides, bicarbonates and carbonates of alkali or alkaline earth metals. Specific bases are collidine, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, lithium carbonate, sodium tert-butoxide, sodium isopropoxide and potassium tert-butoxide; and most specifically sodium hydroxide, potassium hydroxide and collidine.

The reaction temperature and time period will ordinarily depend on the starting compounds and the solvent employed in the reaction.

In one embodiment, the reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 25°C to the reflux temperature of the solvent used, and more specifically at the reflux temperature of the solvent used. The reaction time may vary between about 5 hours to about 35 hours, specifically about 8 hours to about 24 hours, and more specifically about 12 hours to about 20 hours.

The reaction mass containing the 2-hydroxypropyl intermediate compound of formula IV obtained in step-(a) may be subjected to usual work up such as a washing, an extraction, a pH adjustment, an evaporation, a layer separation, a decolorization, or a combination thereof. The reaction mass may be used directly in the next step to produce the compound of formula II or formula III, or the compound of formula IV may be isolated and/or recrystallized and then used in the next step.

In one embodiment, the 2-hydroxypropyl compound of formula IV is isolated and/or re-crystallized from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum distillation, or a combination thereof.

The solvent used for isolating and/or recrystallizing the pure 2-hydroxypropyl compound of formula IV is selected from the group consisting of water, an alcohol, a
ketone, an ether, an ester, a hydrocarbon solvent, a halogenated hydrocarbon, and mixtures thereof. Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, acetone, tetrahydrofuran, 2-methyl-tetrahydrofuran, diisopropyl ether, methyl tert-butyl ether, ethyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, dichloromethane, dichloroethane, chloroform, and mixtures thereof.

In one embodiment, a specific 2-hydroxypropyl derivative of formula IV prepared by the process described herein is (2R)-3-[[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-propane-1,2-diol of formula IVa (formula IV, wherein R is hydrogen):

```
O
N
F

H

OH

IVa
```

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

In another embodiment, a specific 2-hydroxypropyl derivative of formula IV prepared by the process described herein is (2R)-3-[[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxy-propyl butanoate of formula IVb (formula IV, wherein R is butyryl):

```
O
N
F

H

OH

IVb
```

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

In another embodiment, a specific 2-hydroxypropyl derivative of formula IV prepared by the process described herein is (2R)-l-Benzylxoy-3-[[3-fluoro-4-(4-morpholinyl)phenyl] amino]-2-propanol of formula IVc (formula IV, wherein R is benzyl):
or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

The 2-hydroxypropyl derivative of formula IV or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, is novel and forms another aspect of the present invention.

The use of the 2-hydroxypropyl derivative of formula IV or a salt thereof in the process for manufacture of Linezolid is novel and forms further aspect of the present invention.

Salts of the compounds of formulae II, III, IV and VIII, as used herein, may include acid addition salts. The acid addition salts are derived from a therapeutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid, phosphoric acid, succinic acid, maleic acid, fumaric acid, citric acid, glutaric acid, tartaric acid, benzenesulfonic acid, toluenesulfonic acid, di-p-toluoyl-L-(+)-tartaric acid, malic acid, ascorbic acid, and the like.

Exemplary salts of the compounds of formulae II, III, IV and VIII include, but are not limited to, hydrochloride, hydrobromide, sulfate, nitrate, phosphate, acetate, propionate, oxalate, succinate, maleate, fumarate, benzenesulfonate, toluenesulfonate, citrate, tartrate, and the like.

In one embodiment, the carbonylation reaction in step-(b) is carried out in the presence of a solvent or a mixture of solvents.

Exemplary solvents used in step-(b) include, but are not limited to, an alcohol, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, a halogenated hydrocarbon solvent, and mixtures thereof.

Specifically, the solvent used in step-(b) is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, diethyl ether,
diisopropyl ether, methyl tert-butyl ether, monoglyme, diglyme, acetonitrile, propionitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, dichloromethane, dichloroethane, chloroform, and mixtures thereof. Most specific solvents are dichloromethane, methanol, ethanol, isopropanol, and mixtures thereof.

The carbonylation reaction in step-(b) is performed using any carbonylating agent commonly known for such purpose.

Exemplary carbonylating agents used in step-(b) include, but are not limited to, N,N'-carbonyldiimidazole, phosgene, diphosgene, triphosgene, dialkyl carbonates, substituted or unsubstituted alkyl chloroformates, substituted or unsubstituted aryl chloroformates, substituted or unsubstituted aralkyl chloroformates, and the like.

Unless otherwise specified, the term "alkyl", as used herein, denotes an aliphatic hydrocarbon group which may be straight or branched having 1 to 12 carbon atoms in the chain. Preferred alkyl groups have 1 to 6 carbon atoms in the chain. The alkyl may be substituted with one or more "cycloalkyl groups". Exemplary alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, and n-pentyl.

The term "cycloalkyl", as used herein, denotes a non-aromatic monocyclic or multicyclic ring system of 3 to 10 carbon atoms, preferably of about 5 to about 10 carbon atoms. Exemplary monocyclic cycloalkyl groups include cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term "aralkyl", as used herein, denotes an aryl-alkyl group wherein the aryl and alkyl are as herein described. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthalenemethyl.

The term "aryl", as used herein; denotes an aromatic monocyclic or multicyclic ring system of 6 to 10 carbon atoms. The aryl is optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Exemplary aryl groups include phenyl, tollyI or naphthyl.

Specific carbonylating agents used in step-(b) are N,N'-carbonyldiimidazole, diethyl carbonate, di-tert-butyl dicarbonate (BOC anhydride), phenyl chloroformate and benzyl chloroformate; and most specifically N,N'-carbonyldiimidazole, diethyl carbonate and di-tert-butyl dicarbonate (BOC anhydride).
In one embodiment, the carbonylating agent in step-(b) is used in a ratio of about 1 to 4 equivalents, specifically about 1 to 1.5 equivalents, with respect to the 2-hydroxypropyl compound of formula IV in order to ensure a proper course of the reaction.

In one embodiment, the reaction in step-(b) is carried out at a temperature of about 10°C to the reflux temperature of the solvent used, specifically at a temperature of about 25°C to the reflux temperature of the solvent used, and most specifically at a temperature of about 30°C to the reflux temperature of the solvent used. The reaction time may vary between about 5 hours to about 48 hours, specifically about 8 hours to about 30 hours, and more specifically about 12 hours to about 24 hours.

The reaction mass containing the oxazolidinone compound of formula III obtained in step-(b) may be subjected to usual work up such as a washing, an extraction, a pH adjustment, an evaporation, a layer separation, a decolorization, or a combination thereof. The reaction mass may be used directly in the next step to produce the compound of formula II, or the compound of formula III may be isolated and/or recrystallized and then used in the next step.

In one embodiment, the oxazolidinone compound of formula III is isolated and/or re-crystallized from a suitable solvent by conventional methods as described hereinabove.

The solvent used for isolating and/or recrystallizing the oxazolidinone compound of formula III is selected from the group consisting of water, an alcohol, a ketone, an ether, an ester, a hydrocarbon solvent, a halogenated hydrocarbon, and mixtures thereof. Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, acetone, tetrahydrofuran, 2-methyl-tetrahydrofuran, diisopropyl ether, methyl tert-butyl ether, ethyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, dichloromethane, dichloroethane, chloroform, and mixtures thereof.

For example, the deprotection in step-(c) is performed by subjecting the N-protected compound of formula VIII to hydrolysis, hydrogenolysis, or a combination thereof.

In one embodiment, the deprotection in step-(c) is carried out by treating the oxazolidinone compound of formula III with a suitable deprotecting agent such as an acid, a base, hydrazine hydrate, and the like, in a reaction inert solvent.

Specifically, the deprotection in step-(c) is carried out by treating the oxazolidinone compound of formula III with a base.

In another embodiment, the deprotection in step-(c) is carried out by subjecting the oxazolidinone compound of formula III to hydrogenolysis using a metal catalyst such as zinc, nickel, platinum, palladium, palladium on carbon, and the like.

The base used for deprotection is an organic or an inorganic base. Exemplary bases include, but are not limited to, trimethylamine, tributylamine, triethylamine, diisopropylethylamine, 4-(N,N-dimethylamino)pyridine and 1-alkylimidazole; hydroxides, alkoxides, bicarbonates and carbonates of alkali or alkaline earth metals. Specific bases are sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, lithium carbonate, sodium methoxide, magnesium methoxide, sodium tert-butoxide, sodium isopropoxide and potassium tert-butoxide; and most specifically sodium methoxide and potassium carbonate.

The acid used for deprotection is an organic or an inorganic acid. Exemplary acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, formic acid, and the like.

In one embodiment, the deprotection in step-(c) is carried out in the presence of a solvent or a mixture of solvents.

Exemplary solvents used for deprotection in step-(c) include, but are not limited to, water, acetic acid, an alcohol, a ketone, a halogenated solvent, an ester, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, and mixtures thereof.

Specifically, the solvent used in step-(c) is selected from the group consisting of water, acetic acid, methanol, ethanol, isopropanol, n-butanol, acetone, methyl isobutyl ketone, dichloromethane, dichloroethane, chloroform, ethyl acetate, methyl acetate,
isopropyl acetate, tert-butyl methyl acetate, ethyl formate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, monoglyme, diglyme, acetonitrile, propionitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, and mixtures thereof. Most specific solvents are water, dichloromethane, methanol, ethanol, isopropanol, and mixtures thereof.

In one embodiment, the deprotection in step-(c) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 20°C to about 50°C, and more specifically at a temperature of about 20°C to about 40°C. The reaction time may vary from about 15 minutes to about 12 hours, specifically from about 20 minutes to about 5 hours, and more specifically from about 30 minutes to about 2 hours.

The reaction mass containing the (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II obtained in step-(b) or step-(c) may be subjected to usual work up, and followed by isolating and/or recrystallizing from a suitable solvent by the methods as described hereinabove, wherein the solvent is selected from the group consisting of water, an alcohol, a ketone, an ester, an aliphatic ether, a hydrocarbon solvent, a chlorinated hydrocarbon, and mixtures thereof. Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, n-propanol, isopropyl alcohol, acetone, tetrahydrofuran, 2-methyl-tetrahydrofuran, diisopropyl ether, methyl tert-butyl ether, ethyl acetate, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, dichloromethane, dichloroethane, chloroform, and mixtures thereof.

In one embodiment, the isolation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II is carried out by cooling the reaction mass while stirring at a temperature below about 30°C and more specifically at about 0°C to about 10°C.

According to another aspect, there is provided an improved process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, which comprises:

a) reacting a 2-hydroxypropyl derivative of formula IV:
or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group \( R_i \); with a suitable activating agent, wherein the activating agent is an anhydride compound of formula \( \text{V ila} \), or a chloroformate compound of formula \( \text{V ilb} \):

\[
\begin{align*}
\text{V ila} & \\
\text{V ilb} & \\
\end{align*}
\]

wherein \( R' \) is \( OR_2 \) or \( CX_3 \), wherein the radical \( R_2 \) is \( C_{1-12} \) straight or branched chain alkyl, cycloalkyl, haloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; and \( X \) is a halogen atom selected from \( F, Cl, Br \) and \( I \); to produce an N-protected compound of formula \( \text{VIII} \):

\[
\begin{align*}
\text{VIII} & \\
\end{align*}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein \( R \) is hydrogen or a hydroxyl protecting group \( R_i \); and \( R' \) is as defined above; and

b) deprotecting the compound of formula \( \text{VIII} \) to produce the compound of formula \( II \) or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.
Advantageously, the above process steps)-(a) and (b) can be carried out in a single pot.

In one embodiment, the group R in the compounds of formulae IV and VIII is hydrogen. In another embodiment, the group R in the compounds of formulae IV and VIII is a hydroxyl protecting group R₁, wherein R₁ is selected from the group as described above.

Specific hydroxyl protecting groups are acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, trichloroacetyl, trifluoroacetyl, benzoyl, p-toluoyl, p-anisoyl, trityl, o-nitrobenzyl, benzyl and p-methoxybenzyl; and most specifically butyryl, trityl and benzyl.

Specifically, the radical R₂ in the compounds of formulae Vila, Vlb and VIII is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, chloromethyl, phenyl, tolyl, benzyl, p-nitrobenzyl, dibromophenyl or p-methoxybenzyl; and most specifically R₂ is ethyl or tert-butyl.

In one embodiment, the reaction in step-(a) is carried out in the presence of a solvent or a mixture of solvents. Exemplary solvents used in step-(a) include, but are not limited to, an alcohol, a hydrocarbon solvent, an ester, a ketone, an ether, a nitrile, a polar aprotic solvent, a halogenated hydrocarbon solvent, and mixtures thereof.

Specifically, the solvent used in step-(a) is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, acetone, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, monoglyme, diglyme, acetonitrile, propionitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, dichloromethane, dichloroethane, chloroform, and mixtures thereof. Most specific solvents are dichloromethane, methanol, ethanol, isopropanol, and mixtures thereof.

In another embodiment, the reaction in step-(a) is optionally carried out in the presence of a base. Specifically, the base is an organic or inorganic base selected from the group as described hereinabove.
In one embodiment, the activating agent in step-(a) is used in a ratio of about 1 to 5 equivalents, specifically about 1.1 to 1.5 equivalents, with respect to the 2-hydroxypropyl compound of formula IV in order to ensure a proper course of the reaction.

In one embodiment, the reaction in step-(a) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 10°C to the reflux temperature of the solvent used, and most specifically at a temperature of about 20°C to about 40°C. The reaction time may vary between about 20 minutes to about 36 hours, specifically about 30 minutes to about 10 hours, and more specifically about 1 hour to about 5 hours.

The reaction mass containing the N-protected compound of formula VHP obtained in step-(a) may be subjected to usual work up methods as described above. The reaction mass may be used directly in the next step to produce the compound of formula II, or the compound of formula VIII may be isolated and/or recrystallized from a suitable solvent by conventional methods, as described hereinabove, and then used in the next step.

In one embodiment, the reaction mass or residue containing the N-protected compound of formula VIII is used directly in the next step to produce the compound of formula II.

The solvent used for isolating and/or recrystallizing the N-protected compound of formula VIII is selected from the group as described hereinabove for such purpose.

In one embodiment, a specific N-protected compound of formula VIII prepared by the process described herein is (2R)-3-[(ethoxycarbonyl)-[3-fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxy-propyl butanoate of formula VIIIa(i) (formula VIII, wherein R is butyryl and R' is ethoxy):

```
O
N
F
```

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.
In another embodiment, a specific N-protected compound of formula VIII prepared by the process described herein is tert-butyl (2R)-(2,3-dihydroxy-propyl)-[3-fluoro-4-(4-morpholinyl)phenyl]-carbamate of formula VIIIb(i) (formula VIII, wherein R is hydrogen and R’ is tert-butoxy):

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

The removal of protecting groups in step-(b) can be achieved by the methods as described hereinabove. For example, the deprotection in step-(b) is performed by subjecting the N-protected compound of formula VIII to hydrolysis, hydrogenolysis, or a combination thereof.

In one embodiment, the deprotection in step-(b) is carried out by treating the N-protected compound of formula VIII with a suitable deprotecting agent such as an acid, a base, hydrazine hydrate, and the like, in a reaction inert solvent.

Specifically, the deprotection in step-(b) is carried out by treating the N-protected compound of formula VIII with a base.

The base used for deprotection in step-(b) is an organic or an inorganic base selected from the group as described above. Most specific bases are sodium methoxide and potassium carbonate.

In another embodiment, the deprotection in step-(b) is carried out by subjecting the N-protected compound of formula VIII to hydrogenolysis using a metal catalyst such as zinc, nickel, platinum, palladium on carbon, and the like.

In one embodiment, the deprotection in step-(b) is carried out in the presence of a solvent or a mixture of solvents.

Exemplary solvents used for deprotection in step-(b) include, but are not limited to, water, acetic acid, an alcohol, a halogenated solvent, as ester, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, and mixtures thereof.
Most specific solvents are water, dichloromethane, methanol, ethanol, isopropanol, and mixtures thereof.

In one embodiment, the deprotection in step-(b) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 20°C to the reflux temperature of the solvent used, and most specifically at the reflux temperature of the solvent used. The reaction time may vary from about 15 minutes to about 5 hours, specifically from about 20 minutes to about 3 hours, and more specifically from about 30 minutes to about 2 hours.

The reaction mass containing (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxazolidinone of formula II obtained in step-(b) may be subjected to usual work up, and followed by isolating and/or recrystallization from a suitable solvent by the methods as described hereinabove. Most specific solvents are water, dichloromethane, methanol, ethanol, isopropanol, and mixtures thereof.

The solids obtained in any of the above process steps may be collected by filtration, filtration under vacuum, decantation, centrifugation, filtration employing a filtration media of a silica gel or celite, or a combination thereof.

The compound of formula II obtained by the processes disclosed herein may be further dried in, for example, a Vacuum Tray Dryer, a Rotocon Vacuum Dryer, a Vacuum Paddle Dryer or a pilot plant Rota vapor, to further lower residual solvents.

In one embodiment, the drying is carried out at atmospheric pressure or reduced pressures, such as below about 200 mm Hg, or below about 50 mm Hg, at temperatures such as about 35°C to about 80°C.

The intermediate compound, (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny1)phenyl]-2-oxazolidinone, of formula II obtained by the processes disclosed herein has a total purity, both chemical and enantiomeric purity, of greater than about 95%, specifically greater than about 98%, more specifically greater than about 99%, and most specifically greater than about 99.5% as measured by HPLC.

Aptly the processes of the invention are adapted to the preparation of oxazolidinone derivatives, preferably Linezolid, in high enantiomeric and chemical purity.
Linezolid can be prepared in high purity by using the substantially pure (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II or a salt thereof obtained by the methods disclosed herein, by known methods.

The use of inexpensive, non-explosive, non-hazardous, readily available and easy to handle reagents and solvents allows the processes disclosed herein to be suitable for preparation of the Linezolid of formula I at lab scale and in commercial scale operations.

The compounds of formulae III, IV, VI, Via and VIII have the right stereochemical configuration to produce the compounds of formula I and II. The stereochemical configuration of the formulae III, IV, VI, Via and VIII are retained throughout the sequence of reactions of the invention. However, it is readily apparent to one skilled in the art that one could easily perform the identical process steps with the opposite enantiomeric form, or a racemic form thereof, to produce the corresponding stereo isomers.

According to another aspect, there is provided a process for the preparation of a 2-hydroxypropyl derivative of formula IV:

![formula IV]

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group R₁;

which comprises reacting 3-fluoro-4-morpholinyl aniline of formula V:

![formula V]

or a salt thereof with a compound of formula VI:

![formula VI]
or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein R is hydrogen or a hydroxyl protecting group Ri, L represents a leaving group and Y represents a hydroxy group; or L and Y together with the atoms to which they are bonded form an oxirane ring having the structural formula Vla:

\[
\text{OR} \quad \text{Vla}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein R is as defined above;

to produce the 2-hydroxypropyl derivative of formula IV or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

In one embodiment, the leaving group L in the compound of formula VI is a halogen, or an alkyl or aryl sulfonyloxy group. Specifically, the leaving group L is selected from the group consisting of CI, Br, I, methanesulfonyloxy, toluenesulfonyloxy and trifluromethanesulfonyloxy group; and a most specific leaving group is CI or toluenesulfonyloxy.

In one embodiment, the group R in the compounds of formulae IV, VI and Vla is hydrogen.

In another embodiment, the group R in the compounds of formulae IV, VI and Vla is a hydroxyl protecting group Ri, wherein the hydroxyl protecting group is selected from the group as described hereinabove.

Specific hydroxyl protecting groups are acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, trichloroacetetyl, trifluoroacetetyl, benzyol, p-toluoyl, p-anisoyl, trityl, o-nitrobenzyl, benzyl and p-methoxybenzyl; and most specifically butyryl, trityl and benzyl.

The process for the preparation of the 2-hydroxypropyl derivative of formula IV described herein is carried out by the methods as described above.

According to another aspect, there is provided an improved process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, which comprises:
a) carbonylating a 2-hydroxypropyl derivative of formula IV:

![Formula IV](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group $R_{15}$ with a suitable carbonylating agent to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof (when the group R is hydrogen), or an oxazolidinone compound of formula III:

![Formula III](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein $R_i$ is a hydroxyl protecting group; and

b) optionally, deprotecting the compound of formula III to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

In one embodiment, the group R in the compound of formula IV is hydrogen. In another embodiment, the group R in the compound of formulae IV is a hydroxyl protecting group $R_i$, wherein the hydroxyl protecting group is selected from the group as described hereinabove.

Specific hydroxyl protecting groups are acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, trichloroacetyl, trifluoroacetyl, benzoyl, p-toluoyl, p-anisoyl, trityl, o-nitrobenzyl, benzyl and p-methoxybenzyl; and most specifically butyryl, trityl and benzyl.

The carbonylating agent used in step-(a) is selected from the group as described hereinabove. Specific carbonylating agents are $N,N'$-carbonyldiimidazole, diethyl...
carbonate, di-tert-butyl dicarbonate (BOC anhydride), phenyl chloroformate and benzyl chloroformate; and most specifically N,N'-carbonyldiimidazole, diethyl carbonate and di-tert-butyl dicarbonate (BOC anhydride).

The process for the preparation of the (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II described herein is carried out by the methods as described above.

According to another aspect, there is provided a 2-hydroxypropyl derivative of formula IV:

![IV](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group Ri.

In one embodiment, the group R in the compound of formula IV is hydrogen. In another embodiment, the group R in the compound of formula IV is a hydroxyl protecting group Ri, wherein the R_i is selected from the group as described above.

Specifically, the hydroxyl protecting group R_i is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, succinoyl, glutamyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, p-toluoyl, p-anisoyl, 2-carboxybenzoyl, p-nitrobenzoyl, trityl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiofuranyl, o-nitrobenzoyl, benzyl, p-methoxybenzyl, trimethylsilyl, triisopropylsilyl and t-butylidiphenylsilyl.

More specifically, the hydroxyl protecting group R_i is selected from the group consisting of acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl,
trichloroacetyl, trifluoroacetyl, benzoyl, p-toluyl, p-anisoyl, trityl, o-nitrobenzyl, benzyl and p-methoxybenzyl; and most specifically butyryl, trityl and benzyl.

In one embodiment, a specific 2-hydroxypropyl derivative of formula IV is (2R)-3-[[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-propane-1,2-diol of formula IVa (formula IV, wherein R is hydrogen):

![IVa](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

In another embodiment, a specific 2-hydroxypropyl derivative of formula IV is (2R)-3-[[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxy-propyl butanoate of formula IVb (formula IV, wherein R is butyryl):

![IVb](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

In another embodiment, a specific 2-hydroxypropyl derivative of formula IV is (2R)-1-Benzylxylo-3-[[3-fluoro-4-(4-morpholinyl)phenyl] amino]-2-propanol of formula IVc (formula IV, wherein R is benzyl):

![IVc](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

According to another aspect, there is provided an N-protected compound of formula Villa:
or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein $R_1$ is a hydroxyl protecting group; and $R'$ is $OR_2$ or $CX_3$, wherein the radical $R_2$ is $C_{1-12}$ straight or branched chain alkyl, cycloalkyl, haloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; and $X$ is a halogen atom selected from F, Cl, Br and I.

In one embodiment, the radical $R_2$ in the compound of formula Villa is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, chloromethyl, phenyl, tolyl, benzyl, $p$-nitrobenzyl, dibromophenyl or $p$-methoxybenzyl; and most specifically $R_2$ is ethyl or tert-butyl.

In another embodiment, the hydroxyl protecting group $R_1$ is selected from the group as described above.

Specifically, the hydroxyl protecting group $R_1$ is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, $p$-toluoyl, $p$-anisoyl, 2-carboxybenzoyl, $p$-nitrobenzoyl, trityl, tetrahydropranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiofuranyl, $o$-nitrobenzyl, benzyl, $p$-methoxybenzyl, trimethylsilyl, triisopropylsilyl and $t$-butyldiphenylsilyl.

More specifically, the hydroxyl protecting group $R_1$ is selected from the group consisting of acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, trichloroacetyl, trifluoroacetyl, benzoyl, $p$-toluoyl, $p$-anisoyl, trityl, $o$-nitrobenzyl, benzyl and $p$-methoxybenzyl; and most specifically butyryl, trityl and benzyl.
In one embodiment, a specific N-protected compound of formula Villa is (2R)-3-
([ethoxycarbonyl]-[3-fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxy-propyl butanoate of formula VIIIa(i) (formula Villa, wherein R₁ is butyryl and R' is ethoxy):

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

According to another aspect, there is provided an N-protected compound of formula VIIIb:

or a salt thereof, wherein R'' is OR₃ or CX₃, wherein the radical R₃ is C₃₋₁₂ straight or branched chain alkyl, cycloalkyl, haloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; and X is a halogen atom selected from F, Cl, Br and I.

In one embodiment, the radical R₃ in the compound of formula VIIIb is propyl, isopropyl, isobutyl, tert-butyl, chloromethyl, phenyl, tolyl, benzyl, p-nitrobenzyl, dibromophenyl or p-methoxybenzyl; and most specifically R₃ is tert-butyl.

In another embodiment, a specific N-protected compound of formula VIIIb is tert-butyl (2R)-(2,3-dihydroxy-propyl)-[3-fluoro-4-(4-morpholinyl)phenyl]-carbamate of formula VIIIb(i) (formula VIIIb, wherein R'' is tert-butoxy):
or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitation on the scope or spirit of the invention.

EXAMPLES

Example 1

Preparation of (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone

Step-1: (2R)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-propane-l,2-diol

(R)-Glycidol (7.4 g, 0.1 mol) was added to a solution of 3-fluoro-4-morpholinyl aniline (19.6 g, 0.1 mol) in methanol (200 ml) and the resulting solution was heated to reflux (64-66°C), followed by maintaining at the same temperature for 14 hours. The solvent was removed completely by distillation under reduced pressure to produce 27 g of (2R)-3-[3-fluoro-4-(4-morpholinyl)phenyl]amino]-propane-l,2-diol as a residue (Yield: 100%).

Step-2: (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone

(2R)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-propane-l,2-diol (27 g, obtained in step-1) and methanol (100 ml) were taken into a reaction flask, followed by the addition of di-tert-butyl dicarbonate (BOC anhydride) (22.8 g, 0.11 mol) and stirring the resulting mixture for 4 hours at 40-45°C to produce a reaction mass containing tert-butyl (2R)-(2,3-dihydroxy-propyl)-[3-fluoro-4-(4-morpholinyl)phenyl]-carbamate. After completion of the reaction, anhydrous sodium methoxide (5.4 g, 0.1 mol) was added to the reaction mass and the resulting mass was heated for 2 hours at reflux (64-66°C). After completion of the
reaction, the solvent was distilled off completely under vacuum to produce (5R)-5-
(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl) phenyl]-2-oxazolidinone as a semi-solid. 
Methanol (25 ml) and water (100 ml) were added to the resulting solid, followed by 
heating for 1 hour at 50-55°C. The resulting mass was initially cooled to 25-30°C, 
followed by slowly cooling to 0-5°C and then stirring for 1 hour at 0-5°C. The separated 
solid was filtered and then washed with methanol (20 ml) to produce 24.1 g of the titled 
compound as off-white crystalline solid (Yield: 81.5%; Melting Point: 111 to 112.8°C; 
Purity by HPLC: 99.1%).

Example 2

Preparation of (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxyazolidinone

Step-1: (2R)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxy-propyl butanoate

(R)-Glycidyl butyrate (14.4 g, 0.1 mol) was added to a solution of 3-fluoro-4-morpholinyl aniline (19.6 g, 0.1 mol) in isopropyl alcohol (200 ml) and the resulting mixture was 
refluxed (80-85°C) for about 16 hours. The reaction mass was distilled to remove the 
solvent completely to produce 34 g of (2R)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-
2-hydroxy-propyl butanoate as a crude product, which is used directly in the next step 
without further purification (Yield: 100%).

Step-2: (5R)-[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl butanoate

N,N'-Carbonyldiimidazole (17.82 g, 0.11 mol) was added to a solution of (2R)-3-[3-fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxy-propyl butanoate (34 g, 0.1 mol) in 
dichloromethane (175 ml), and the resulting solution was stirred for 24 hours at 30-35°C. 
The reaction mass was quenched by adding water (150 ml), followed by layer separation and 
then concentrating the resulting organic layer under vacuum to produce 34 g of (5R)-
[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl butanoate (Yield: 
92.9%).

Step-3: (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-
oxazolidinone
Sodium methoxide (0.5 g, 0.0093 mol) was added to a solution of (5R)-[[3-[3-fluoro-4-(4-morpholiny)phenyl]-2-oxo-5-oxazolidinyl]methyl butanoate (34 g, 0.0936 mol) in methanol (170 ml), the resulting mixture was stirred for 1 hour at 25-35°C and then distilled off the solvent completely. Isopropyl alcohol (100 ml) was added to the resulting residue, followed by adjusting the pH to 2 with isopropanolic-HCl solution. The resulting solid was cooled and maintained for 1 hour at 0-5°C. The separated solid was filtered and washed with cold isopropyl alcohol (25 ml) to produce 24.5 g of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone as off-white crystalline solid (Yield: 89.1%; Melting Range: 111.7 - 113.9°C; Purity by HPLC: 99.6%).

Example 3
Preparation of (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny)phenyl]-2-oxazolidinone

Step-1: (2R)-3-[(ethoxycarbonyl)-[3-fluoro-4-(4-morpholiny)phenyl]amino]-2-hydroxy-propyl butanoate

N-Ethyl diisopropylamine (19.35 g, 0.15 mol) was added to a solution of (2R)-3-[[3-fluoro-4-(4-morpholiny)phenyl]amino]-2-hydroxy-propyl butanoate (obtained in step-1 of example 2, 34 g, 0.1 mol) in dichloromethane (340 ml) and the resulting mixture was stirred for 10 minutes at 25-30°C. Ethyl chloroformate (11.9 g, 0.111 mol) was added drop-wise to the resulting solution and then stirred for 2 hours at 25-30°C. The reaction mass was washed with water (100 ml) and the solvent was distilled off completely under reduced pressure to produce 38.1 g of (2R)-3-[(ethoxycarbonyl)-[3-fluoro-4-(4-morpholiny)phenyl]amino]-2-hydroxy-propyl butanoate as an oily residue (Yield: 92.5%).

Step-2: (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholiny)phenyl]-2-oxazolidinone

Potassium carbonate (1.28 g, 0.00925 mol) was added to a solution of (2R)-3-[(ethoxycarbonyl)-[3-fluoro-4-(4-morpholiny)phenyl]amino]-2-hydroxy-propyl butanoate (38.1 g, 0.0925 mol) in methanol (190 ml). The resulting mixture was refluxed (64-66°C) for 2 hours, followed by distillation off the solvent under reduced pressure to obtain a residue. Methanol (20 ml) and water (100 ml) were added to the resulting residue, followed by stirring for 30 minutes at 25-30°C and then for 1 hour at 0-5°C. The separated
solid was filtered and washed with cold methanol (10 ml) to produce 21 g of the (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (Yield: 77%; Melting Range: 109.5 to 111 °C; Purity by HPLC: 98.5%).

Example 4

Preparation of (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone

Step-1: (2R)-1-Benzyl-3-[[3-fluoro-4-(4-morpholinyl)phenyl] amino]-2-propanol

Potassium carbonate (27.6 g, 0.2 mol) and (S)-l-0-benzyl-3-p-toluenesulfonyl synglycerol (25.2 g, 0.075 mol) [prepared as per the process described in Tetrahedron Letters 30(21), 2751, (2001)] were added to a solution of 3-fluoro-4-morpholinyl aniline (19.6 g, 0.1 mol) in dimethylformamide (100 ml). The resulting mixture was heated to 80-85 °C and maintained for 12 hours at the same temperature. The reaction mass was cooled to 25-30°C and then poured into water (300 ml), followed by stirring for 1 hour. The separated solid was filtered and washed with water (25 ml) to produce 19.9 g of (2R)-1-Benzyl-3-[[3-fluoro-4-(4-morpholinyl)phenyl] amino]-2-propanol as a light yellowish solid (Yield: 55.3%; Purity by HPLC: 96.5%).

Step-2: (5R)-5-(BenzyloxymethyI)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone

N,N'-carbonyldiimidazole (9.85 g, 0.06 mol) was added to a solution of (2R)-1-Benzyl-3-[[3-fluoro-4-(4-morpholinyl)phenyl] amino]-2-propanol (19.9 g, 0.055 mol) in dichloromethane (200 ml) and the resulting mixture was stirred for 32 hours at 25-30°C. Water (100 ml) was added to the reaction mass, the resulting organic layer was separated and then distilled off the solvent completely to produce 20.3 g of (5R)-5-(benzyloxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (Yield: 95.5%), which is directly used for next step.

Step-3: (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone

Palladium on charcoal (4 g, 10% w/w) was added to a suspension of (5R)-5-(benzyloxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (21.2 g, 0.055 mol) in ethanol (200 ml) and the resulting mixture was hydrogenated in an autoclave at 45 °C.
50°C under a pressure of 4 to 5 Kg of hydrogen. After completion of the reaction, the catalyst was filtered and the reaction mass was distilled under reduced pressure until the volume of solvent reaches to half of its initial volume. The resulting mass was slowly cooled to 0-5°C, followed by stirring for 1 hour at the same temperature. The separated solid was filtered and washed with ethyl alcohol (30 ml) to produce 12 g of (5R)-5-(Hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl) phenyl]-2-oxazolidinone (Yield: 73.7%; Melting Range: 111 to 114.2°C; Purity by HPLC: 99.7%).

All ranges disclosed herein are inclusive and combiable. While the invention has been described with reference to a preferred embodiment, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment disclosed as the best mode contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the appended claims.
We claim:

1. A process for the preparation of (5R)-5-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone of formula II:

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, which comprises:

a) reacting 3-fluoro-4-morpholinyl aniline of formula V:

or a salt thereof with a compound of formula VI:

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein R is hydrogen or a hydroxyl protecting group R1, L represents a leaving group and Y represents a hydroxy group; or L and Y together with the atoms to which they are bonded form an oxirane ring having the structural formula Via:

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein R is as defined above;

to produce a 2-hydroxypropyl derivative of formula IV:
or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is as defined in formula VI;
b) subjecting the compound of formula IV to carbonylation using a suitable carbonylating agent to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof (when the group R is hydrogen), or an oxazolidinone compound of formula III:

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein R₁ is a hydroxyl protecting group; and
c) optionally, deprotecting the compound of formula III to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

2. The process of claim 1, wherein the leaving group L in the compound of formula VI is a halogen, or an alkyl or aryl sulfonyloxy group; and wherein the group R in the compounds of formulae IV, VI and Via is a hydroxyl protecting group R₁.

3. The process of claim 2, wherein the leaving group L is selected from the group consisting of Cl, Br, I, methanesulfonyloxy, toluenesulfonyloxy and trifluoromethanesulfonyloxy group; and wherein the hydroxyl protecting group R₁ is selected from the group consisting of a substituted or unsubstituted aralkyl, a substituted or unsubstituted trityl, an aliphatic acyl group including an alkanoyl group, an aromatic acyl group including an arylcarbonyl group, a tri(C₁₋₆ alkyl)silyl, a tri(C₆₋₁₀ aryl)silyl, an alkylcarbonyl group substituted with a carboxy group, an alkylcarbonyl
group substituted with a halogen atom, a saturated cyclic hydrocarbon-carbonyl group, an alkylcarbonyl group substituted with a lower alkoxy group, an unsaturated alkylcarbonyl group, a halogenoarylcarbonyl group, an arylcarbonyl group substituted with a lower alkyl group, a lower alkoxylated arylcarbonyl group, an arylcarbonyl group substituted with a carboxy group, a nitrated arylcarbonyl group, an arylcarbonyl group substituted with a lower alkoxy carbonyl group, and an arylcarbonyl group substituted with an aryl.

4. The process of claim 3, wherein the hydroxyl protecting group R₁ is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methyl nonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, p-toluoyl, p-anisoyl, 2-carboxybenzoyl, p-nitrobenzoyl, trityl, tetrahydropranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiofuranyl, o-nitrobenzyl, benzyl, p-methoxybenzyl, trimethylsilyl, triisopropylsilyl and t-butyldiphenylsilyl.

5. The process of claim 4, wherein the hydroxyl protecting group R₁ is selected from the group consisting of butyryl, trityl and benzyl.

6. The process of claim 1, wherein the reaction in step-(a) is carried out in the presence of a solvent or a mixture of solvents, wherein the solvent is selected from the group consisting of an alcohol, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, a halogenated hydrocarbon solvent, and mixtures thereof; and wherein the reaction in step-(a) is optionally carried out in the presence of a base, wherein the base is an organic or inorganic base.

7. The process of claim 6, wherein the solvent used in step-(a) is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, monoglyme, diglyme, acetonitrile, propionitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, dichloromethane, dichloroethane, chloroform, and mixtures thereof; and wherein the base is selected from the group consisting of collidine, trimethylamine,
tributylamine, triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, 4-
(N,N-dimethylamino)pyridine and 1-alkylimidazole; hydroxides, alkoxides, bicarbonates, and carbonates of alkali or alkaline earth metals.

8. The process of claim 7, wherein the solvent used in step-(a) is selected from the group consisting of methanol, ethanol, isopropanol, and mixtures thereof; and wherein the base is selected from the group consisting of collidine, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, lithium carbonate, sodium tert-butoxide, sodium isopropoxide and potassium tert-butoxide.

9. The process of claim 1, wherein the carbonylation in step-(b) is carried out in the presence of a solvent or a mixture of solvents, wherein the solvent is selected from the group consisting of an alcohol, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, a halogenated hydrocarbon solvent, and mixtures thereof; and wherein the carbonylating agent used in step-(b) is selected from the group consisting of N,N'-carbonyldimidazole, phosgene, diphosgene, triphosgene, dialkyl carbonates, substituted or unsubstituted alkyl chloroformates, substituted or unsubstituted aryl chloroformates, and substituted or unsubstituted aralkyl chloroformates.

10. The process of claim 9, wherein the solvent used in step-(b) is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, monoglyme, diglyme, acetonitrile, propionitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, dichloromethane, dichloroethane, chloroform, and mixtures thereof; and wherein the carbonylating agent is selected from the group consisting of N,N'-carbonyldimidazole, diethyl carbonate, di-tert-butyl dicarbonate (BOC anhydride), phenyl chloroformate and benzyl chloroformate.

11. The process of claim 1, wherein the deprotection in step-(c) is carried out in the presence of a solvent or a mixture of solvents, wherein the solvent used for deprotection in step-(c) is selected from the group consisting of water, acetic acid, an alcohol, a ketone, a halogenated solvent, an ester, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, and mixtures thereof; and wherein the deprotection in
step-(c) is carried out by treating the oxazolidinone compound of formula III with a deprotecting agent or by subjecting the compound of formula III to hydrogenolysis using a metal catalyst, or a combination thereof, wherein the deprotecting agent is an acid, a base or hydrazine hydrate.

12. The process of claim 11, wherein the solvent used in step-(c) is selected from the group consisting of water, dichloromethane, methanol, ethanol, isopropanol, and mixtures thereof; and wherein the deprotecting agent is a base, wherein the base is selected from the group consisting of trimethylamine, tributylamine, triethylamine, diisopropylethylamine, 4-(N,N-dimethylamino)pyridine, 1-alkylimidazole, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, lithium carbonate, sodium methoxide, magnesium methoxide, sodium tert-butoxide, sodium isopropoxide and potassium tert-butoxide.

13. A process for the preparation of \((5R)-5\)-(hydroxymethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone\) of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, which comprises:

a) reacting a 2-hydroxypropyl derivative of formula IV:

\[
onumber \text{IV}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group Ri;

with a suitable activating agent, wherein the activating agent is an anhydride compound of formula Vila, or a chloroformate compound of formula VIIb:

\[
onumber \text{VIIa}
\]

(or)

\[
onumber \text{VIIb}
\]
wherein R’ is OR₂ or CX₃, wherein the radical R₂ is C₁₋₁₂ straight or branched chain alkyl, cycloalkyl, haloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; and X is a halogen atom selected from F, Cl, Br and I; to produce an N-protected compound of formula VIII:

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group R₁; and R’ is as defined above; and

b) deprotecting the compound of formula VIII to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

14. The process of claim 13, wherein the radical R₂ in the compounds of formulae Vila, VIIb and VIII is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, chloromethyl, phenyl, tolyl, benzyl, p-nitrobenzyl, dibromophenyl or p-methoxybenzyl; and wherein the group R in the compounds of formulae IV and VIII is a hydroxyl protecting group Ri, wherein the hydroxyl protecting group Ri is selected from the group consisting of a substituted or unsubstituted aralkyl, a substituted or unsubstituted trityl, an aliphatic acyl group including an alkanoyl group, an aromatic acyl group including an arylcarbonyl group, a tri(C₁₋₆ alkyl)silyl, a tri(C₆₋₁₀ aryl)silyl, an alkylcarbonyl group substituted with a carboxy group, an alkylcarbonyl group substituted with a halogen atom, a saturated cyclic hydrocarbon-carbonyl group, an alkylcarbonyl group substituted with a lower alkoxy group, an unsaturated alkylcarbonyl group, a halogenoarylcarbonyl group, an arylcarbonyl group substituted with a lower alkyl group, a lower alkoxylated arylcarbonyl group, an arylcarbonyl group substituted with a carboxy group, a nitrated arylcarbonyl group, an arylcarbonyl group substituted with a lower alkoxy group, and an arylcarbonyl group substituted with an aryl.
15. The process of claim 14, wherein the radical \( R_2 \) is ethyl or tert-butyl; and wherein the hydroxyl protecting group \( R_1 \) is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, p-toluoyl, p-anisoyl, 2-carboxybenzoyl, p-nitrobenzoyl, 2-carboxybenzoyl, p-nitrobenzoyl, benzyl, p-methoxybenzyl, trimethylsilyl, triisopropylsilyl and t-butyldiphenylsilyl.

16. The process of claim 15, wherein the hydroxyl protecting group \( R_1 \) is butyryl, trityl or benzyl.

17. The process of claim 13, wherein the reaction in step-(a) is carried out in the presence of a solvent or a mixture of solvents, wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl methyl acetate, ethyl formate, acetone, n-pentane, n-hexane, n-heptane, cyclohexane, toluene, xylene, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, methyl tert-butyl ether, monoglyme, diglyme, acetonitrile, propionitrile, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, dichloromethane, dichloroethane, chloroform, and mixtures thereof; and wherein the reaction in step-(a) is optionally carried out in the presence of a base, wherein the base is an organic or inorganic base.

18. The process of claim 13, wherein the deprotection in step-(b) is carried out in the presence of a solvent or a mixture of solvents, wherein the solvent is selected from the group consisting of water, acetic acid, an alcohol, a halogenated solvent, as ester, a hydrocarbon solvent, an ether, a nitrile, a polar aprotic solvent, and mixtures thereof; and wherein the deprotection in step-(b) is carried out by treating the \( N \)-protected compound of formula VIII with a deprotecting agent or by subjecting the compound of formula VIII to hydrogenolysis using a metal catalyst, or a combination thereof, wherein the deprotecting agent is an acid, a base or hydrazine hydrate.
19. The process of claim 18, wherein the solvent used in step-(b) is selected from the group consisting of water, dichloromethane, methanol, ethanol, isopropanol, and mixtures thereof; and wherein the deprotection in step-(b) is carried out by treating the N-protected compound of formula VIII with a base, wherein the base is selected from the group consisting of trimethylamine, tributylamine, triethylamine, diisopropylethylamine, 4-(N,N-dimethylamino)pyridine, 1-alkylimidazole, sodium hydroxide, calcium hydroxide, magnesium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, lithium carbonate, sodium methoxide, magnesium methoxide, sodium tert-butoxide, sodium isopropoxide and potassium tert-butoxide.

20. A process for the preparation of a 2-hydroxypropyl derivative of formula IV:

\[
\begin{align*}
\text{N} & \quad \text{OR} \\
\text{F} & \\
\text{OH} &
\end{align*}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group \( R_1 \);

which comprises reacting 3-fluoro-4-morpholinyl aniline of formula V:

\[
\begin{align*}
\text{N} & \quad \text{NH}_2 \\
\text{F} &
\end{align*}
\]

or a salt thereof with a compound of formula VI:

\[
\begin{align*}
\text{L} & \quad \text{OR} \\
\text{Y} &
\end{align*}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein R is hydrogen or a hydroxyl protecting group \( R_1 \), L represents a leaving group and Y represents a hydroxy group; or L and Y together with the atoms to which they are bonded form an oxirane ring having the structural formula Via:-
or an enantiomeric form or a mixture of enantiomeric forms thereof; wherein R is as defined above;
to produce the 2-hydroxypropyl derivative of formula IV or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

21. The process of claim 20, wherein the leaving group L in the compound of formula VI is a halogen, or an alkyl or aryl sulfonyloxy group; and wherein the group R in the compounds of formulae IV, VI and Via is a hydroxyl protecting group R₁.

22. The process of claim 21, wherein the leaving group L is selected from the group consisting of Cl, Br, I, methanesulfonyloxy, toluenesulfonyloxy and trifluoromethanesulfonyloxy group; and wherein the hydroxyl protecting group R₁ is selected from the group consisting of a substituted or unsubstituted aralkyl, a substituted or unsubstituted trityl, an aliphatic acyl group including an alkanoyl group, an aromatic acyl group including an arylcarbonyl group, a tri(C₆₋₁₀ aryl)silyl, an alkylcarbonyl group substituted with a carboxy group, an alkylcarbonyl group substituted with a halogen atom, a saturated cyclic hydrocarbon-carbonyl group, an alkylcarbonyl group substituted with a lower alkoxy group, an unsaturated alkylcarbonyl group, a halogenoarylcarbonyl group, an arylcarbonyl group substituted with a lower alkyl group, a lower alkoxylated arylcarbonyl group, an arylcarbonyl group substituted with a carboxy group, a nitrated arylcarbonyl group, an arylcarbonyl group substituted with a lower alkoxy carbonyl group, and an arylcarbonyl group substituted with an aryl.

23. The process of claim 22, wherein the hydroxyl protecting group R₁ is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl; furany1, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl,
24. The process of claim 23, wherein the hydroxyl protecting group \( R_i \) is selected from the group consisting of butyryl, trityl and benzyl.

25. A process for the preparation of \((5R)-5-(hydroxymethyl)-3-[3\text{-}fluoro-4-(4-morpholinyl)phenyl]-2\text{-}oxazolidinone\) of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, which comprises:

a) carbonylating a 2-hydroxypropyl derivative of formula IV:

\[
\text{IV} \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{F} \\
\text{N} \\
\text{OH} \\
\text{OR}
\end{array}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein \( R \) is hydrogen or a hydroxyl protecting group \( R_i \);

with a suitable carbonylating agent to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof (when the group \( R \) is hydrogen), or an oxazolidinone compound of formula III:

\[
\text{III} \quad \begin{array}{c}
\text{O} \\
\text{N} \\
\text{F} \\
\text{N} \\
\text{OR} \quad R_i
\end{array}
\]

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein \( \text{R}_i \) is a hydroxyl protecting group; and

b) optionally, deprotecting the compound of formula III to produce the compound of formula II or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

26. The process of claim 25, the group \( R \) in the compound of formula IV is hydrogen.
27. The process of claim 25, wherein the group R in the compound of formulae IV is a hydroxyl protecting group Ri, wherein the hydroxyl protecting group Ri is selected from the group consisting of a substituted or unsubstituted aralkyl, a substituted or unsubstituted trityl, an aliphatic acyl group including an alkanoyl group, an aromatic acyl group including an arylcarbonyl group, a tri(C6-IO aryl)silyl, an alkylcarbonyl group substituted with a carboxy group, an alkylcarbonyl group substituted with a halogen atom, a saturated cyclic hydrocarbon-carbonyl group, an alkylcarbonyl group substituted with a lower alkoxy group, an unsaturated alkylcarbonyl group, a halogenoarylcarbonyl group, an arylcarbonyl group substituted with a lower alkyl group, a lower alkoxylated arylcarbonyl group, an arylcarbonyl group substituted with a carboxy group, a nitrated arylcarbonyl group, a lower alkoxyarylcarbonyl group, and an arylcarbonyl group substituted with an aryl.

28. The process of claim 27, wherein the hydroxyl protecting group Ri is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, p-toluoyl, p-anisoyl, 2-carboxybenzoyl, p-nitrobenzoyl, trityl, tetrahydropyranyl, tetrahydrothiopropanyl, tetrahydrofuranyl, tetrahydrothiofuranyl, o-nitrobenzyl, benzyl, p-methoxybenzyl, trimethylsilyl, triisopropylsilyl and t-butyldiphenylsilyl.

29. The process of claim 28, wherein the hydroxyl protecting group Ri is selected from the group consisting of butyryl, trityl and benzyl.

30. The process of claim 25, wherein the carbonylating agent used in step-(a) is selected from the group consisting of N,N'-carbonyldiimidazole, phosgene, diphenylphosphine, triphosgene, dialkyl carbonates, substituted or unsubstituted alkyl chloroformates, substituted or unsubstituted aryl chloroformates, and substituted or unsubstituted aralkyl chloroformates.
31. The process of claim 30, wherein the carbonylating agent is selected from the group consisting of N,N'-carbonyldiimidazole, diethyl carbonate, di-tert-butyl dicarbonate (BOC anhydride), phenyl chloroformate and benzyl chloroformate.

32. A 2-hydroxypropyl derivative of formula IV:

![Chemical structure](image)

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof, wherein R is hydrogen or a hydroxyl protecting group Ri.

33. The compound of claim 32, wherein the group R in the compound of formula IV is hydrogen.

34. The compound of claim 32, wherein the group R in the compound of formula IV is a hydroxyl protecting group Ri selected from the group consisting of a substituted or unsubstituted aralkyl, a substituted or unsubstituted trityl, an aliphatic acyl group including an alkanoyl group, an aromatic acyl group including an arylcarbonyl group, a tri(Ci₆₋₉ alkyl)silyl, a tri(C6-aryl)silyl, an alkylcarbonyl group substituted with a carboxy group, an alkylcarbonyl group substituted with a halogen atom, a saturated cyclic hydrocarbon-carbonyl group, an alkylcarbonyl group substituted with a lower alkoxy group, an unsaturated alkylcarbonyl group, a halogenoarylcarbonyl group, an arylcarbonyl group substituted with a lower alkyl group, a lower alkoxylated arylcarbonyl group, an arylcarbonyl group substituted with a carboxy group, a nitrated arylcarbonyl group, an arylcarbonyl group substituted with a lower alkoxyarylcarbonyl group, and an arylcarbonyl group substituted with an aryl.

35. The compound of claim 34, wherein the hydroxyl protecting group Ri is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-
naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, p-toluoyl, p-anisoyl, 2-carboxybenzoyl, p-nitrobenzoyl, trityl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiofuranyl, o-nitrobenzyl, benzyl, p-methoxybenzyl, trimethylsilyl, triisopropylsilyl and t-butyldiphenylsilyl.

36. The compound of claim 35, wherein the hydroxyl protecting group $R_i$ is selected from the group consisting of butyryl, trityl and benzyl.

37. The compound of claim 32, wherein the 2-hydroxypropyl derivative of formula IV is (2R)-3-[[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-propane-1,2-diol of formula IVa (formula IV, wherein R is hydrogen):

$$\text{IVa}$$

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

38. The compound of claim 32, wherein the 2-hydroxypropyl derivative of formula IV is (2R)-3-[[3-Fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxy-propyl butanoate of formula IVb (formula IV, wherein R is butyryl):

$$\text{IVb}$$

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

39. The compound of claim 32, wherein the 2-hydroxypropyl derivative of formula IV is (2R)-1-Benzyl oxy-3-[[3-fluoro-4-(4-morpholinyl)phenyl]amino]-2-propanol of formula IVc (formula IV, wherein R is benzyl):
or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

40. An N-protected compound of formula Villa:

or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein \( R_1 \) is a hydroxyl protecting group; and \( R' \) is \( OR_2 \) or \( CX_3 \), wherein the radical \( R_2 \) is \( C_{i-2} \) straight or branched chain alkyl, cycloalkyl, haloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; and \( X \) is a halogen atom selected from F, Cl, Br and I.

41. The compound of claim 40, wherein the radical \( R_2 \) is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, chloromethyl, phenyl, tolyl, benzyl, p-nitrobenzyl, dibromophenyl or p-methoxybenzyl.

42. The compound of claim 40, wherein the hydroxyl protecting group \( R_1 \) is selected from the group consisting of a substituted or unsubstituted aralkyl, a substituted or unsubstituted trityl, an aliphatic acyl group including an alkanoyl group, an aromatic acyl group including an arylcarbonyl group, a tri(\( C_{i-6} \) alkyl)silyl, a tri(C6-io aryl)silyl, an alkylcarbonyl group substituted with a carboxy group, an alkylcarbonyl group substituted with a halogen atom, a saturated cyclic hydrocarbon-carbonyl group, an alkylcarbonyl group substituted with a lower alkoxy group, an unsaturated alkylcarbonyl group, a halogenoarylcarbonyl group, an arylcarbonyl group substituted with a lower alkyl group, a lower alkoxylated arylcarbonyl group, an arylcarbonyl group substituted with a carboxy group, a nitrated arylcarbonyl group, an arylcarbonyl...
group substituted with a lower alkoxy carbonyl group, and an aryl carbonyl group substituted with an aryl.

43. The compound of claim 42, wherein the hydroxyl protecting group $R_i$ is selected from the group consisting of formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methyl nonanoyl, succinoyl, glutaroyl, adipoyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, cyclopropylcarbonyl, cyclobutylcarbonyl, methoxyacetyl, benzoyl, a-naphthoyl, b-naphthoyl, pyridoyl, furoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethyl benzoyl, p-toluoyl, p-anisoyl, 2-carboxybenzoyl, p-nitrobenzoyl, trityl, tetrahydropyranoyl, tetrahydrothiopryanoyl, tetrahydrofuranyl, tetrahydrothiofuranyl, o-nitro benzyl, benzyl, p-methoxy benzyl, trimethylsilyl, triisopropylsilyl and t-butyldiphenylysilyl.

44. The compound of claim 43, wherein the hydroxyl protecting group $R_i$ is selected from the group consisting of butyryl, trityl and benzyl.

45. The compound of claim 40, wherein the N-protected compound of formula Villa is (2R)-3-[(ethoxycarbonyl)-[3-fluoro-4-(4-morpholinyl)phenyl]amino]-2-hydroxypropyl butanoate of formula VIHa(i) (formula Villa, wherein $R_i$ is butyryl and $R'$ is ethoxy):

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.

46. An N-protected compound of formula Vlllb:
or an enantiomeric form or a mixture of enantiomeric forms thereof, wherein $R^{\prime \prime}$ is $OR_3$ or $CX_3$, wherein the radical $R_3$ is $C_3H_7$ straight or branched chain alkyl, cycloalkyl, haloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl; and $X$ is a halogen atom selected from F, Cl, Br and I.

47. The compound of claim 46, wherein the radical $R_3$ in the compound of formula VIIIb is propyl, isopropyl, isobutyl, tert-butyl, chloromethyl, phenyl, tolyl, benzyl, p-nitrobenzyl, dibromophenyl or p-methoxybenzyl.

48. The compound of claim 46, wherein the N-protected compound of formula VIIIb is tert-butyl (2R)-(2,3-dihydroxy-propyl)-[3-fluoro-4-(4-morpholinyl)phenyl]-carbamate of formula VIIIb(i) (formula VIIIb, wherein $R^{\prime \prime}$ is tert-butoxy):

or an enantiomeric form or a mixture of enantiomeric forms thereof, or a salt thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 413/10 (2013.01)
USPC - 544/137

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07D 265/30, 413/10 (2013.01)
USPC - 544/1 11, 137, 139

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C07D 295/04, 073, 413/10

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 2011/137222 A1 (MCCARTHY) 03 November 2011 (03.11.2011) entire document</td>
<td>1-48</td>
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Further documents are listed in the continuation of Box C.

Special categories of cited documents:
“X” 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
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“Z” 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 January 2013
Date of mailing of the international search report 12 FEB 2013

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