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(54) Title: PROCESS FOR PREPARING LINEZOLID

(57) Abstract: The present invention relates to a new process for preparing the oxazolidinone antibacterial agent linezolid which comprises the reaction of an (S)-I -chloro-3- (benzylidenylamino)-propan-2-ol with a morpholinyl fluorophenyl carbamate to afford a protected imine intermediate which, upon hydrolysis and acylation, yields linezolid in high yield.

PROCESS FOR PREPARING LINEZOLID

FIELD OF INVENTION

The present invention relates to a novel process to prepare an oxazolidinone antibacterial agent. Particularly, the present invention relates to a novel process to prepare linezolid.

BACKGROUND OF THE INVENTION

Antibacterial resistance is a global clinical and public health problem that has emerged with alarming rapidity in recent years and undoubtedly will increase in the near future. Resistance is a problem in the community as well as in health care settings, where transmission of bacteria is greatly amplified. Because multiple drug resistance is a growing problem, physicians are now confronted with infections for which there is no effective therapy. As a result, structurally novel antibacterial agents with a new mode of action have become increasingly important in the treatment of bacterial infections.

Among newer antibacterial agents, linezolid is a recent synthetic class of antimicrobials active against a number of pathogenic microorganisms. Linezolid [(S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide] is disclosed in U.S. Patent No. 5,688,792. It is marketed in the United States by Pfizer, Inc. as an injection, tablets, and oral suspensions under the name ZYVOX®. Processes for preparation of linezolid are described in U.S. Patent No. 5,688,792, U.S. Patent No. 5,837, 870, PCT publication WO 99/24393, PCT publication WO 2006/004922, J. Med. Chem. 39(3), 673-679, 1996 and Tetrahedron Lett., 40(26), 4855, 1999.

We have discovered and developed a novel process to prepare linezolid. The process has the potential to significantly lower the cost of commercial production of linezolid. It is a highly convergent three-step process with a much shorter cycle time. It is environmentally friendly because it reduces the large solvent volumes used in the currently known processes. We also discovered rapidly crystallized key intermediates for the process of the present invention.

INFORMATION DISCLOSURE

US 4,150,029, 4,250,318, 4,476,136, 4,340,606 and 4,461,773 disclose the synthesis of 5-hydroxymethyloxazolidinones from amines.

J. Med. Chem., 32, 1673 (1989), *Tetrahedron* 45, 1323 (1989) and US Patent 4,948,801 disclose a method of producing oxazolidinones.

PCT Publications WO93/09103, WO93/09103, WO95/07271 and WO93/23384; PCT applications PCT/US95/12751 and PCT/US95/10992 disclose the reaction of a

carbamate with *n*-butyllithium, lithium diisopropylamide or lithium hexamethyldisilazide.

International Publication WO95/07271 discloses the ammonolysis of 5R-methylsulfonyloxymethyl substituted oxazolidinones.

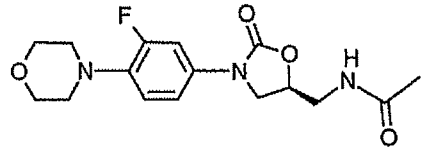
US Patent 4,476,136 discloses a method of transforming 5-hydroxymethyl substituted oxazolidinones to the corresponding 5(S)-aminomethyl substituted oxazolidinones.

US patent 5,332,754 discloses racemic oxazolidinone-CH_2-NH-Ac can be synthesized in one step by condensation of a carbamate with racemic glycidyl acetamide.

US patent 3,654,298 discloses the synthesis of 5-alkoxymethyl-3-aryl-substituted oxazolidinones by sodium ethoxide induced cyclization of chlorocarbamates.

SUMMARY OF THE INVENTION

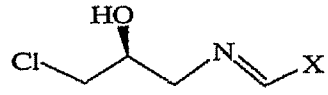
The present invention provide a process to prepare linezolid



Linezolid

which comprises:

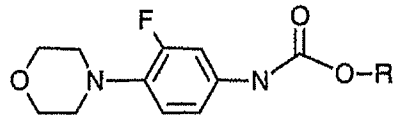
a) reacting a compound of structure (**1**)



(**1**)

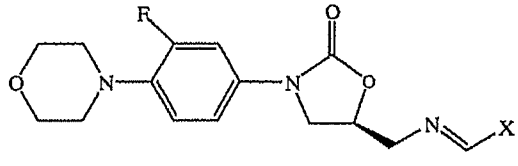
wherein X is chlorophenyl, bromophenyl, or 2,4-dichlorophenyl;

with a compound of structure (**2**)



(**2**)

at a temperature in a range from ambient temperature to about 65°C, wherein R is benzyl or $C_{1\text{-}8}$alkyl to provide a compound of structure (**3**);



(**3**)

where X is chlorophenyl, bromophenyl, or 2,4-dichlorophenyl;

b) hydrolyzing the compound of structure (3) and subsequent acylation to provide linezolid.

Other aspects of the present invention are the compounds of structures (1) and (3) as shown above, their crystal structures, and their methods of crystallizations.

DETAILED DESCRIPTION OF THE INVENTION

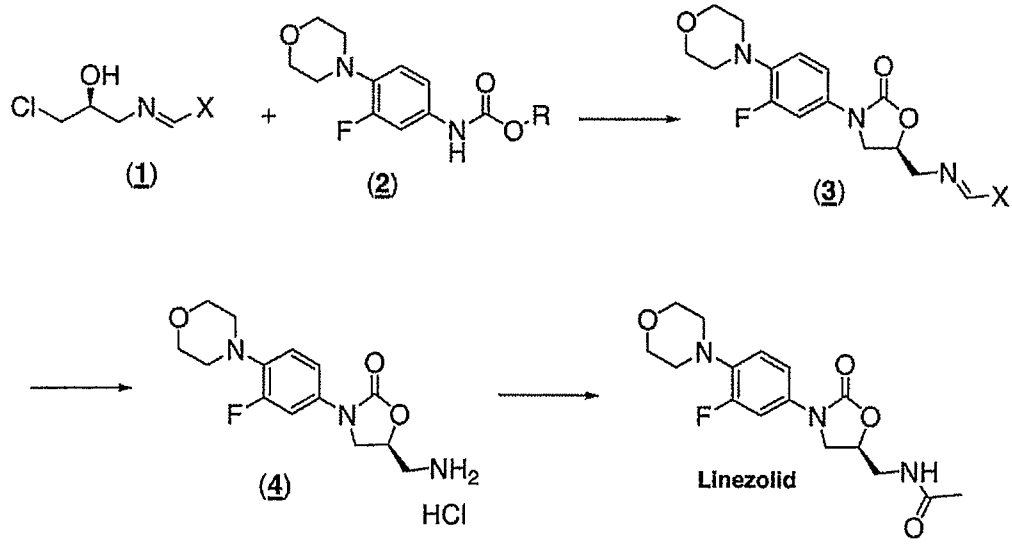
Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1-8} alkyl refers to alkyl of one to eight carbon atoms, inclusive.

The term alkyl refers to both straight and branched groups, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Specifically, alkyl is C_{1-4}alkyl. More specifically, alkyl is *tert*-butyl.

The term "ambient temperature" refers to a temperature in a range from about 20 °C to 30 °C.

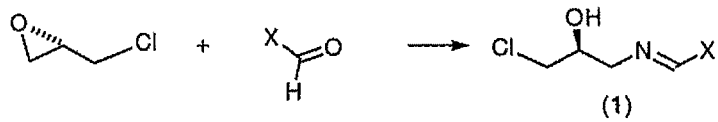
SCHEME I



As shown in Scheme I (wherein X and R are defined above), the synthesis begins with coupling the substituted imine moiety (1) (preferably 1 to 3 eq, most preferably 1.5 to 2 eq) with a carbamate (2) to provide the corresponding (S)-oxazolidinone imine (3). The reaction is carried out preferably at a temperature in a range from ambient temperature to about 65°C in the presence of a base with pKa greater than 12, preferably a tertiary alkoxide base, most preferably lithium t-butoxide and an aprotic non-nucleophilic solvent (preferably

DMF, DMAc, THF, Acetonitrile, C_{1-6} linear, branched and cyclic ethers and/ or chlorinated solvents and/ or mixtures of these solvents, most preferably MTBE or methylene chloride). Most preferably, the temperature is from about 30-60 °C and the reaction time is 2 to 24 hours. Preferably, the (S)-oxazolidinone imine (2), after an aqueous extractive workup, is crystallized and isolated by filtration from a weakly polar organic solvent, such as an alcohol (including C_{1-6} branched and linear alcohols and polyols) or ether (including MTBE, THF, and other C_{1-6} linear, branched and cyclic ethers); most preferably isopropanol. Hydrolysis of compound (**3**) with an aqueous acidic solution and subsequent acylation provides crude linezolid. Compound (3) is best hydrolyzed with a mixture of water and a strong acid such as hydrochloric acid and the substituted benzaldehyde byproduct removed by extraction with a water immiscible organic solvent (preferably toluene, MTBE, methylene chloride and ethyl acetate), most preferably ethyl acetate. The resulting aqueous solution of Amine hydrochloride (4) is preferably acylated with acetic anhydride, preferably in the presence of water and a water immiscible organic solvent (most preferably methylene chloride). The conversion of Amine hydrochloride (4) to linezolid is well known in the literature (Brickner, S.J.; et. al. *J. Med. Chem.* **1996** 39 (3) 673-679, US Patent 5,837,870, US 5,688,792).

SCHEME II



(1)

As shown in Scheme II (wherein X is defined above), the key strating material (**1**) can be prepared by reacting (S)-epichlorohydrin with a mixture of the appropriately substituted benzaldehyde derivative (preferably 0.5 to 2 eq, most preferably 1 eq) and aqueous ammonia (preferably 0.5 to 3 eq, most preferably 1.5 eq). The reaction is best performed in both protic and aprotic non-nucleophilic and non-electrophilic solvents such as alcohols (including C_{1-6} branched and linear alcohols and polyols), ethers (including MTBE, THF, and other C_{1-6} linear, branched and cyclic ethers) as well as chlorinated solvents such as methylene chloride. MTBE is a preferred solvent. Temperatures can be in a range from about 15 to about 60 °C are preferred, preferably between 30 to 50 °C most preferred. After extractive isolation and concentration, the imine moiety (**1**) is obtained. It is then crystallized from a second liquid phase, in the presence of non-polar aprotic hydrocarbon solvents such as, but not limited to, alkanes, mixtures of alkanes (hexane, heptane, octane, isooctane and commercially available alkane mixtures), optionally in the presence of aprotic polar solvents, preferably ethereal solvents such as MTBE or aromatic solvents such as toluene or chlorinated solvents such as methylene chloride or mixtures thereof. Preferred solvents are a

mixture of MTBE and heptane or a mixture of toluene and heptane. The crystallization process can be conducted in a temperature in a range from ambient temperature (about 18-25 °C) to about 55 °C, preferably in a range of 30 to 50 °C, more preferably in a range of 38 to 45 °C. This crystallization provides surprisingly high yield and with significantly improved enantiomeric purity after isolation by filtration.

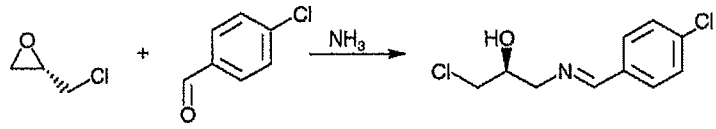
EXAMPLES

In the discussion above and in the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

bm	=	broad multiplet
BOC	=	*tert*-butoxycarbonyl
bd	=	broad doublet
bs	=	broad singlet
CDI	=	1,1*O*-carbodiimidazole
d	=	doublet
dd	=	doublet of doublets
dq	=	doublet of quartets
dt	=	doublet of triplets
DMF	=	dimethylformamide
DMAP	=	dimethylaminopyridine
DMSO	=	dimethyl sulfoxide
eq.	=	equivalents
g	=	grams
h	=	hours
HPLC	=	high pressure liquid chromatography
HATU	=	N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide
LG	=	leaving group
m	=	multiplet
M	=	molar
M%	=	mole percent
max	=	maximum
meq	=	milliequivalent
mg	=	milligram
mL	=	milliliter
mm	=	millimeter
mmol	=	millimol
MTBE	=	methyl t-butyl ether
q	=	quartet
s	=	singlet
t or tr	=	triplet
TBS	=	tributylsilyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
p-TLC	=	preparative thin layer chromatography
µL	=	microliter

	N	=	normality
	MeOH	=	methanol
	DCM	=	dichloromethane
	HCl	=	hydrochloric acid
	ACN	=	acetonitrile
	MS	=	mass spectrometry
	rt	=	room temperature
	EtOAc	=	ethyl acetate
	EtO	=	ethoxy
	Ac	=	acetate
	NMP	=	1-methyl-2-pyrrolidinone
	µL	=	microliter
	J	=	coupling constant
	NMR	=	Nuclear magnetic resonance
	MHz	=	megahertz
	Hz	=	hertz
	m/z	=	mass to charge ratio
	min	=	minutes
	Boc	=	*tert*-butoxycarbonyl
	CBZ	=	benzyloxycarbonyl
	DCC	=	1,3-dicyclohexylcarbodiimide
	PyBop	=	benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate

Example 1 Preparation of (S)-1-chloro-3-[(4-chloro-E-benzylidene)-amino]-propan-2-ol

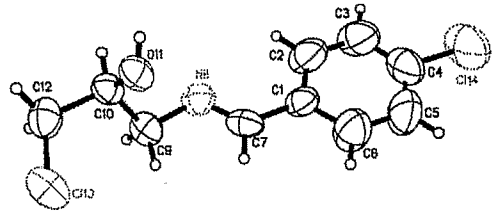


Method A

A 5L three neck round bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser and heating mantel is charged with 4-chlorobenzaldehyde (351. g, 2.5 mol, 1.0 eq.). MTBE (1.5 L) is then charged into the round bottom to give a homogeneous solution. Aqueous ammonia (28 wt%, 252.98 mL, 3.75 mol, 1.5 eq.) is added in a single portion resulting in a white precipitate that turned into a thin slurry within 15 minutes of stirring. (S)-(+)-epichlorohydrin (> 99 % ee, 196.0 mL, 2.5 mol, 1.0 eq.) is then slowly charged into the vessel. After 40 minutes, the contents are then slowly heated to 43°C. The reaction is stirred at 40°C for 18 hours at which time 8.4% area of epichorohydrin remained by GC. Upon cooling to rt, the reaction mixture is transferred to a separatory funnel and the layers are separated. The lower aqueous layer is discarded. The organic layer is transferred to a 3L round bottom flask, concentrated *in vacuo* to about half the volume (800-900 mL) at which time iso-octanes is slowly added from a feed tube (~750 mL) until cloudiness is observed. The biphasic mixture is seeded with ~ 4 mgs of the title compound. The reaction is cooled with an ice bath for 45 minutes while stirring. The precipitate is collected and rinsed with cold iso-octane (500 mL). The solid is dried for 18 hours at 50°C

under vacuum to give the title compound as a white crystalline in solid. GC assay: 100%, 99.7% ee by Chiral SFC). GC (conditions: column - 30 meter HP-1, 0.25mm ID and 0.25 micron film and 15 psi head pressure, 1.0µl injection size; T_{ini} = 70 °C, ramp of 20 °C/min) T_R (epichlorohydrin) = 2.4 min, T_R (4-chlorobenzaldehyde) = 4.8 min and T_R (title compound) = 9.7min; HPLC conditions: Chiralpak AD-H 250 nm X 4.6 nm column, eluting with 70% CO_2/ 30%MeOH at 3.0 mL/min, detecting at 255 nm. T_R [title compound] = 3.9 min; T_R (enantiomer of title compound) = 2.8 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (bs, 2 H), 3.80 (m, 2 H), 4.15 (s, 1 H), 7.41 (d, J = 8 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 8.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.05, 63.09, 70.82, 128.93, 129.39, 134.08, 137.07, 162.30; IR (KBr Pellet) 1630 cm^{-1};

X-ray crystal structure: crystal system = monoclinic, space group = P2(1), unit cell dimensions a = 8.791(2) Å, b = 4.6556(11) Å, c = 14.372(3) Å, α= 90°, β= 106.819(4)°, γ = 90°, Volume = 563.0(2) Å^3; Z =2; F(000) = 240; Ortep Drawing:



Method B

A 5L three neck round bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser and heating mantel is charged with 4-chlorobenzaldehyde (375 g, 2.67 mol, 1.0 eq.). Methanol or THF is added and mixture warmed from 10 to 23 °C. Aqueous ammonia (28.4 wt%, 264 mL, 3.95 mol, 1.5 eq.) is added in a single portion resulting in a biphasal solution forming after stirring for 15 minutes at 23 to 26 °C. (S)-(+)-epichlorohydrin (99.3 % ee, 207 mL, 2.64 mol, 1.0 eq.) is then added in one portion. The reaction mixture is stirred at 23-24 °C for 18 h, then warmed to 40 to 45 °C and stirred for 2.5 h at which time 0.26% area of S-epichorohydrin remains by GC (GC conditions, 0.050 ml reaction mixture in 1 ml acetonitrile, inject 1 microliter; 15 M DB-1 column, 0.25mm ID and 0.25 micron film and 15 psi head pressure, 1.0µl injection size; T_{ini} = 38°C, ramp of 10 °C/min) T_R (epichlorohydrin) = 1.1 min, T_R (4-chlorobenzaldehyde) = 6.9 min and T_R (title compound) = 16.0 min). The mixture is concentrated in vacuo to a total volume of 1250 ml. Toluene (250 ml) is added and the mixture concentrated in vacuo to a total volume of 1250 ml. Toluene (250 ml) is added and the mixture concentrated in vacuo to a total volume of 1145 ml. Toluene (355 ml) is added and the mixture concentrated in vacuo to a total volume of 900 ml. Toluene (600 ml) is added and the mixture concentrated in vacuo to a total

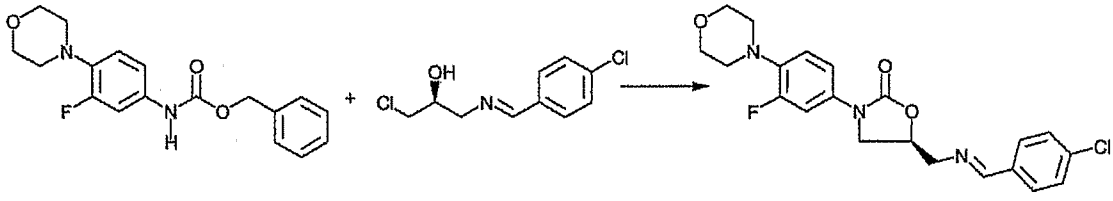
volume of 1120 ml. While maintaining 45 to 50 °C, heptane (1500 ml) is added. The resulting biphasal solution is cooled to 45 °C and seeded. The mixture is then further cooled to 38 °C over 1/2 h while seeding after every 1 degree of cooling. The mixture is then further allowed to slowly cool to 23 °C over 16 h. The white crystals are then collected by vacuum filtration and washed with room temperature heptane (180 ml). The product is dried in a nitrogen stream to give the title compound. HPLC 95 area% [Kromasil 150 mm X 4.6 mm column, 254 nm, flow rate 1.5 ml/ min; A = 1000 ml water + 0.52 ml trifluoroacetic acid + 1.20 ml triethylamine; B = acetonitrile; Isocratic 47: 53 A: B for 5 min then gradient to 100% B over 5 min T_R [title compound] = 2.1 min,; T_R (4-chlorobenzaldehyde) = 2.3 min]; 99.72% ee by Chiral SFC. Chiral HPLC conditions: Chiralpak AD-H 250 nm X 4.6 nm column, eluting with 70% CO_2/ 30%MeOH at 3.0 mL/min, detecting at 255 nm. T_R [title compound] = 3.9 min; T_R (enantiomer of title compound) = 2.8 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (bs, 2 H), 3.80 (m, 2 H), 4.15 (s, 1 H), 7.41 (d, J = 8 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 8.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.05, 63.09, 70.82, 128.93, 129.39, 134.08, 137.07, 162.30.

Method C

A 5L three neck round bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser and heating mantel is charged with 4-chlorobenzaldehyde (375 g, 2.67 mol, 1.0 eq.). MTBE (1.50 L) is then added to give a homogeneous solution after warming from 9 to 24 °C. Aqueous ammonia (28.4 wt%, 265 mL, 3.97 mol, 1.5 eq.) is added in a single portion resulting in a biphasal solution forming after stirring for 15 minutes at 23 to 26 °C. (S)-(+)-epichlorohydrin (99.3 % ee, 209 mL, 2.67 mol, 1.0 eq.) is then added in one portion. The reaction mixture is stirred at 23-24 °C for 3 days. The phases are separated and the upper phase concentrated under atmospheric pressure from 2000 to 1000 ml total volume (boiling point 58 to 67 °C). While maintaining 45 to 50 °C, heptane (1700 ml) is added. The resulting biphasal solution is cooled to 45 °C and seeded. The mixture is then further cooled to 38 °C over 1/2 h while seeding after every 1 degree of cooling. The mixture is then further allowed to slowly cool to 23 °C over 1 h. The white crystals are then collected by vacuum filtration and washed with room temperature heptane (180 ml). The product is dried in a nitrogen stream to give the title compound. HPLC 94 area% [Kromasil 150 nm X 4.6 nm column, 254 nm, flow rate 1.5 ml/ min; A = 1000 ml water + 0.52 ml trfluoroacetic acid + 1.20 ml triethylamine; B = acetonitrile Isocratic 47: 53 A: B for 5 min then gradient to 100% B over 5 min T_R [title compound] = 2.1 min,; T_R (4-chlorobenzaldehyde) = 2.3 min]; 99.92% ee by Chiral SFC. Chiral HPLC conditions: Chiralpak AD-H 250 nm X 4.6 nm column, eluting with 70% CO_2/ 30%MeOH at 3.0 mL/min, detecting at 255 nm. T_R [title compound] = 3.9 min; T_R (enantiomer of title

compound) = 2.8 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (bs, 2 H), 3.80 (m, 2 H), 4.15 (s, 1 H), 7.41 (d, J = 8 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 8.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.05, 63.09, 70.82, 128.93, 129.39, 134.08, 137.07, 162.30.

Example 2 Preparation of (S)-5-{[(4-chloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one



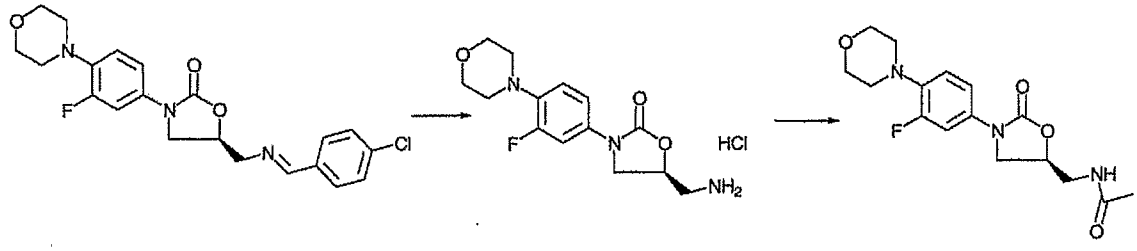
Method A

To (3-fluoro-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester (20 g, 60.05 mmoles, 1 eq) is added lithium t-butoxide (12.11 g, 151.4 mmoles, 2.5 eq), followed by methylene chloride (80 mL) and the mixture stirred at room temperature. To the resultant suspension is added (S)-1-chloro-3-[(4-chloro-benzylidene)-amino]-propan-2-ol (21.07 g, 90.81 mmoles, 1.5 eq) in methylene chloride (40 mL) in one portion. The resulting thin suspension is heated to reflux (41°C) for 5h. After cooling to room temperature, the organic layer is washed with water (1 x 100 mL, 1 x 50 mL), these aqueous washes are then discarded. The organic phase is concentrated *in vacuo* to about ½ volume, at which time isopropyl alcohol (200 mL) is added and the concentration continued to a volume of less than 200 mL. The resultant suspension is cooled to -10°C to -20°C and the solids isolated by filtration and washed with cold isopropyl alcohol (less than 100 mL) then dried at 55°C under vacuum to afford the title compound as a crystalline in solid. SFC achiral assay indicates a purity of 99.4 area% and SFC chiral assay identified 0.11% of the (R) enantiomer. HPLC conditions: YMC 5μ ODS-AM 150 nm X 4.6 nm column, eluting with CH_3CN /water + 0.1% TFA from 20% CH_3CN to 80% CH_3CN in 8 min at 0.5 mL/min, detecting at 254nm. T_R [(3-fluoro-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester] = 8.5 min; T_R (title compound) = 7.9 min; HPLC conditions: Chiralcel OJ-H 250 nm X 4.6 nm column, eluting with 75% CO_2/ 25%MeOH at 3.0 mL/min, detecting at 255 nm. T_R [title compound] = 3.8 min; T_R (enantiomer of title compound) = 4.4 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (d, J = 4 Hz, 4 H), 3.87 (d, J = 4 Hz, 4 H), 3.90 (m, 2 H), 4.12 (m, 2 H), 4.95 (m, 1 H), 6.92 (t, J = 8 Hz, 1 H), 7.12 (d, J = 2 Hz, 1 H), 7.36 (d, J = 8 Hz, 2 H), 7.44 (dd, J = 16, 4 Hz, 1 H); 7.63 (d, J = 8 Hz, 2 H), 8.34 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 48.23, 51.00, 63.19, 66.94, 71.69, 107.42 (d, J = 27 Hz), 113.88, 118.74, 128.93, 129.50, 133.36 (d, J = 11 Hz),133.94, 136.30,137.22, 154.46, 155.48 (d, J = 244 Hz), 163.46.

Method B

To (3-fluoro-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester (372 g, 1.13 mol, 1 eq) is added lithium t-butoxide (225 g, 2.81 mol, 2.5 eq), followed by methylene chloride (2.2 L) and the mixture stirred at room temperature. To the resultant suspension is added (S)-1-chloro-3-[(4-chloro-benzylidene)-amino]-propan-2-ol (400 g, 1.72 mol, 1.5 eq) in one portion. The resulting thin suspension is heated to reflux (41°C) for 10 h. The resultant slurry is added to a solution of acetic acid (85.2 g, 1.42 mol, 1.26 eq) in methanol (800 ml) while maintaining reflux and rinsed in with methanol (40 ml). The resultant slurry is concentrated via atmospheric distillation to a total volume of 3200 ml. Methanol (2500 ml) is added while concentrating via atmospheric distillation to maintain a total volume of 3200-3800 ml. The resultant slurry is cooled to 3 °C and the precipitate collected by vacuum filtration, washed with methanol and dried in a nitrogen stream to give the title compound as crystalline in solid. (HPLC conditions: Kromasil C18 3.5 micron 250 mm X 4.6 mm column, mobile phase A = 0.52 ml TFA, 1.20 ml triethylamine, 1000 ml water; mobile phase B = acetonitrile, isocratic 53: 47 A:B for 5 min then gradient to 100% B over 5 min at 1.5 mL/min, detecting at 254 nm; T_R [title compound] = 6.66 min.

Example 3 Preparation of (S)-N-[3-(3-fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide (Linezolid)

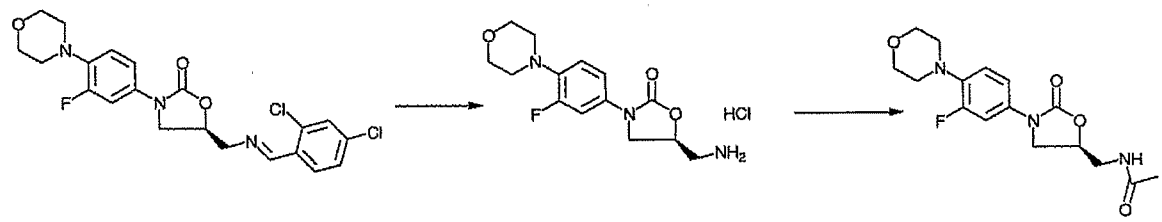


Method A

To (S)-5-{[(4-chloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one (129.5g, 31 mmol, 1.0 eq.) is added ethyl acetate (935 mL) and water (935 mL). To the heterogeneous mixture is added 12M aq. HCl (51.58 mL, 620 mmol, 2.0 eq.). Within minutes, the solid went into solution and the reaction mixture is biphasic. After stirring the emulsion at ambient temperature for 2 hours, HPLC assay showed the hydrolysis reaction to be complete (HPLC conditions: YMC 5µ ODS-AM 150 nm X 4.6 nm column, eluting with CH_3CN /water + 0.1% TFA from 20% CH_3CN to 80% CH_3CN in 8 min at 0.5 mL/min, detecting at 254nm. Retention time of (S)-N-[3-(3-fluoro-4-morpholin-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-amine is 3.2 min). The phases are separated, the organic layer is discarded, and the aqueous layer is washed with ethyl acetate (500 mL).

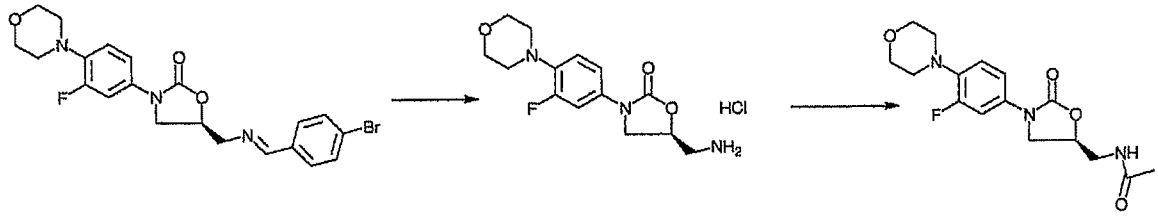
CH_2Cl_2 (900 mL) is added and the pH is adjusted to 6.7 with ~ 25 mL aq. 50% aq. NaOH. With constant stirring, Ac_2O (58.49 mL, 620 mmol, 2.0 eq.) is added in one portion and the pH dropped to 2. The pH is then readjusted to 6 using 50% aq. NaOH. The pH is adjusted to ca. 7.1 with 50% aq. NaOH and the phases separated. The aqueous phase is extracted with CH_2Cl_2 (800 mL) and the organics are combined and concentrated to ~1L in volume. Ethyl acetate (1L) is added and the volume is reduced to 1.5 L under vacuum. Another 1L of ethyl acetate is added and volume is reduced again to 1L under vacuum. The resultant slurry is cooled to 0°C and the precipitate collected by vacuum filtration. The resulting solid is washed with ethyl acetate (250 mL). The crude product is dried under vacuum at 50°C for 2 hours to give the title compound as linezolid crystalline Form I.

Method B



Following the general procedure of method A and making non-critical variations, but substituting (S)-5-{[2,4-dichloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one (example 11) for (S)-5-{[(4-chloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one, the title compound is obtained.

Method C

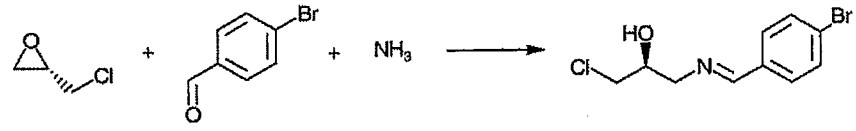


Following the general procedure of method B and making non-critical variations, but substituting (S)-5-{[4-bromo-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one (example 9) for (S)-5-{[(4-chloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one, the title compound is obtained.

Example 4 Trituration (convert linezolid crystalline Form I to linezolid crystalline Form II) The product from Example (89.18 g) is transferred to a 3L round bottom flask equipped with a mechanical stirrer, thermocouple and heating mantel. Ethyl acetate (2.23 L, 15 mL/g) is added and seeded with Linezolid form II crystals and the slurry is heated to ca. 50°C. A

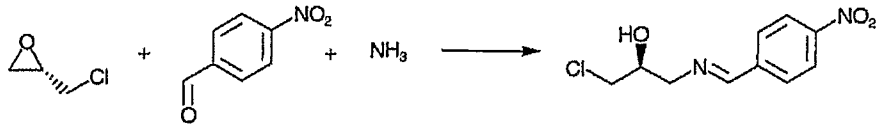
slight exotherm of 3°C is observed. After 30 minutes of heating the form change is observable as the solid is changing to long needles. Stirring is continued for 2 hours at 50°C, at which time the contents are cooled to ambient temperature and stirred for an additional 30 minutes. The contents are then cooled to 3°C for 1.5 hours, filtered and washed with cold ethyl acetate (300 mL total). The resultant solids are dried under vacuum at 50°C for 18 hours to give Linezolid (78.12 g) Form II by XRD, 99.8 wt%, 99.9% ee. HPLC conditions: YMC 5μ ODS-AM 150 nm X 4.6 nm column, eluting with CH_3CN /water + 0.1% TFA from 20% CH_3CN to 80% CH_3CN in 8 min at 0.5 mL/min, detecting at 254nm. T_R (Linezolid) = 4.4 min; HPLC conditions: Chiralcel OJ-H 250 nm X 4.6 nm column, eluting with 90% CO_2/ 10%MeOH at 3.0 mL/min, detecting at 255 nm. T_R [title compound] = 3.6 min; T_R (enantiomer of title compound) = 4.1 min.

Example 5 Preparation of (S)-1-chloro-3-[(4-bromo-benzylidene)-amino]-propan-2-ol



To a solution of 4-bromobenzaldehyde (20.8 g, 112 mmol) in MTBE (48 g) is added ammonia (28 wt%, 10.9 ml, 167 mmol, 1.54 eq) at room temperature. The biphasal mixture is stirred for 15 minutes and (S)-(+)-epichlorohydrin (>97 % ee, 8.5 mL, 108 mmol, 1.0 eq.) is added. The mixture is stirred for 3 days at room temperature and the phases separated. The organics layer is dried on $MgSO_4$ (2 g) clarified with an MTBE rinse (10 ml) and isopar C (100 ml) is added to the filtrate. The solution is concentrated in vacuo to 75 ml total volume and the resultant precipitate collected by vacuum filtration at room temperature and washed with isooctanes. Drying in a nitrogen stream afforded the title compound as crystalline in solid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (m, 2 H), 3.77 (dd, J = 6, 13 Hz, 1 H), 3.84 (dd, J = 13, 5 Hz, 1 H), 4.15 (m, 1 H), 7.57 (d, J = 8 Hz, 2 H), 7.62 (d, J = 8 Hz, 2 H), 8.31 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.05, 63.11, 70.80, 129.60, 131.89, 134.49, 137.36, 162.41.

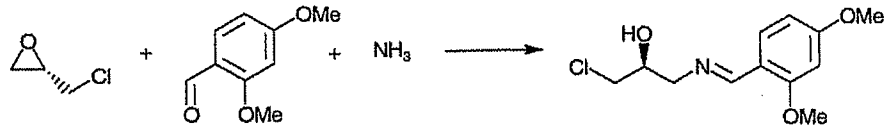
Example 6 Preparation of (S)-1-chloro-3-[(4-nitro-benzylidene)-amino]-propan-2-ol



To a mixture of 4-nitrobenzaldehyde (2.69 g, 17.8 mmol), THF (10 ml), and aqueous ammonia (28%, 1.80 ml, 26.7 mmol, 1.5 eq) at 18 °C is added (S)-(+)-epichlorohydrin (> 99 % ee, 1.39 mL, 17.8 mmol, 1.0 eq.). The mixture is stirred at 40 °C for 18 h then

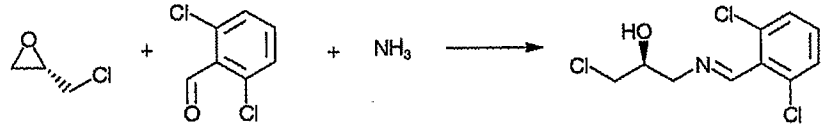
concentrated to in vacuo to provide the title compound as oil. GC (column - 30 meter HP-1, 0.25mm ID and 0.25 micron film and 15 psi head pressure, 1.0µl injection size; T_{ini} = 70 °C, ramp of 20 °C/min) T_R (title compound) = 11.16 min, 64 area%.

Example 7 Preparation of (S)-1-chloro-3-[(2,4-dimethoxy-benzylidene)-amino]-propan-2-ol



To a solution of 2,4-dimethoxybenzaldehyde (18.0 g, 112 mmol) in MTBE (48 g) is added ammonia (28 wt%, 10.9 ml, 167 mmol, 1.54 eq) at room temperature. The biphasal mixture is stirred for 15 minutes and (S)-(+)-epichlorohydrin (>97 % ee, 8.5 mL, 108 mmol, 1.0 eq.) is added. The mixture is stirred for 3 days at room temperature and the phases separated. The organics layer is dried on $MgSO_4$ (2 g) clarified with an MTBE rinse (10 ml) and isopar C (100 ml) is added to the filtrate. The solution is concentrated in vacuo to 75 ml total volume. The resultant biphasal mixture is allowed to stand at room temperature for 24 hours. The resultant waxy solid is collected by vacuum filtration at room temperature and washed with isooctanes. Drying in a nitrogen stream to provide the title compound ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (m, 4 H), 3.85 (s, 6 H), 4.11 (m, 1 H), 6.44 (s, 1 H), 6.53 (q, J = 12 Hz, 1 H), 7.89 (d, J = 8 Hz, 1 H), 8.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.11, 55.44, 55.46, 63.39; ^{13}C NMR ($CDCl_3$) δ 71.07, 97.94, 105.32, 117.40, 128.45, 159.13, 160.20, 163.35.

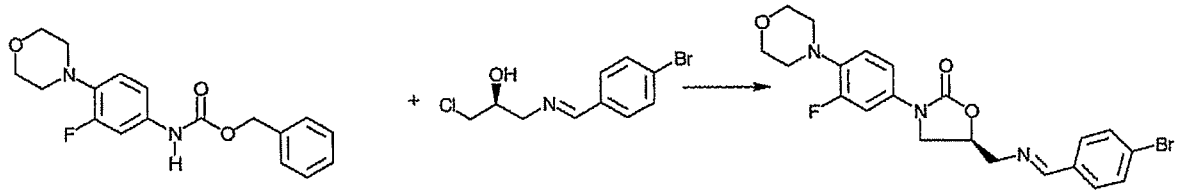
Example 8 Preparation of (S)-1-chloro-3-[(2,6-dichloro-benzylidene)-amino]-propan-2-ol



To a solution of 2,6-dichlorobenzaldehyde (18.9 g, 112 mmol) in MTBE (48 g) is added ammonia (28 wt%, 10.9 ml, 167 mmol, 1.54 eq) at room temperature. The biphasal mixture is stirred for 15 minutes and (S)-(+)-epichlorohydrin (>97 % ee, 8.5 mL, 108 mmol, 1.0 eq.) is added. The mixture is stirred for 3 days at room temperature and the phases separated. The organics layer is dried on $MgSO_4$ (2 g) clarified with an MTBE rinse (10 ml) and isopar C (100 ml) is added to the filtrate. The solution is concentrated in vacuo to give the title compound as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (m, 4 H), 3.85 (s, 6 H), 4.11 (m, 1 H), 6.44 (s, 1 H), 6.53 (q, J = 12 Hz, 1 H), 7.89 (d, J = 8 Hz, 1 H), 8.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.11, 55.44, 55.46, 63.39; ^{13}C NMR ($CDCl_3$) δ 71.07, 97.94, 105.32, 117.40,

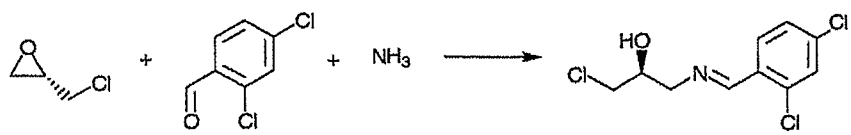
128.45, 159.13, 160.20, 163.35.

Example 9 Preparation of (S)-5-{[4-bromo-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one



To (3-fluoro-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester (7.51 g, 22.7 mmol, 1 eq) is added lithium t-butoxide (4.64 g, 57.9 mmol, 2.55 eq), followed by methylene chloride (45 ml) and the mixture stirred at room temperature. To the resultant suspension is added (S)-1-chloro-3-[(4-bromo-benzylidene)-amino]-propan-2-ol (8.55 g, 30.9 mmol, 1.36 eq) in one portion. The resulting thin suspension is heated to reflux (41°C) for 21 h. The resultant slurry is added to a solution of acetic acid (1.76 g, 29.3 mmol, 1.29 eq) in methanol (46 g) and rinsed in with methanol (24 g). The resultant slurry is concentrated via atmospheric distillation to a total volume of 100 ml. The resultant slurry is cooled to 3 °C and the precipitate collected by vacuum filtration, washed with methanol and dried in a nitrogen stream to give the title compound as crystalline in solid. 1H NMR ($CDCl_3$) δ 3.05 (t, J = 5 Hz, 4 H), 3.87 (t, J = 5 Hz, 4 H), 3.90 (dd, J = 5, 14 Hz, 1 H), 3.96 (dd, J = 5, 13 Hz, 1 H), 4.04 (dd, J = 6, 9 Hz, 1 H), 4.12 (t, J = 9 Hz, 1 H), 4.95 (p, J = 5 Hz, 1 H), 6.92 (t, J = 9 Hz, 1 H), 7.13 (dd, J = 10, 2 Hz, H), 7.43 (dd, J = 14, 3 Hz, 1 H), 7.52 (d, J = 9 Hz, 2 H), 7.56 (d, J = 9 Hz, 2 H), 8.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 48.05, 50.84 (J_{C-F} = 4 Hz), 63.03, 66.77, 71.49, 107.25 (J_{C-F} = 26 Hz), 113.70 (J_{C-F} = 4 Hz), 118.60, 125.56, 129.54, 131.72, 133.18 (J_{C-F} = 10 Hz), 134.20, 136.09 (J_{C-F} = 6 Hz), 154.30, 155.32 (J_{C-F} = 245 Hz), 163.41.

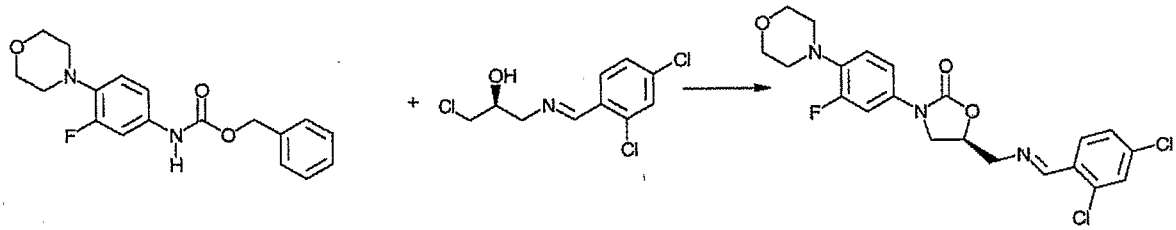
Example 10 Preparation of (S)-1-chloro-3-[(2,4-dichloro-benzylidene)-amino]-propan-2-ol



To a solution of 2,4-dichlorobenzaldehyde (112 g, 639 mmol) in MTBE (267 g) is added ammonia (28 wt%, 63.0 ml, 943 mmol, 1.48 eq) at room temperature. The biphasal mixture is stirred for 15 minutes and (S)-(+)-epichlorohydrin (>97 % ee, 50.0 mL, 639 mmol, 1.0 eq.) is added. The mixture is stirred for 3 days at room temperature and the phases separated. The organics layer is dried on $MgSO_4$ (2 g) clarified with an MTBE rinse (50 ml) and the solution concentrated to 200 ml. Heptane (300 ml) is added and the resultant

precipitate collected by vacuum filtration at room temperature and washed with heptane. Drying in a nitrogen stream to provide the title compound as crystalline in solid. ^{1}H NMR ($CDCl_3$) δ 3.66 (dd, J = 6, 11 Hz, 1 H), 3.70 (dd, J = 5, 11 Hz, 1 H), 3.80 (ddd, J = 1, 6, 13 Hz, 1 H), 3.86 (ddd, J = 2, 5, 13 Hz, 1 H), 4.14 (p, J = 6 Hz, 1 H), 7.28 (dd, J = 2, 8 Hz, 1 H), 7.40 (d, J = 2 Hz, 1 H), 7.96 (d, J = 8 Hz, 1 H), 8.71 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 46.98, 63.21, 70.66, 127.37, 128.95, 129.49, 131.06, 135.64, 137.22, 159.13.

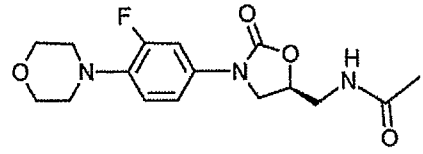
Example 11 Preparation of (S)-5-{[2,4-dichloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one



To (3-fluoro-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester (7.59 g, 23.0 mmol, 1 eq) is added lithium t-butoxide (4.69 g, 58.5 mmol, 2.55 eq), followed by methylene chloride (45 ml) and the mixture stirred at room temperature. To the resultant suspension is added (S)-1-chloro-3-[(2,4-dichloro-benzylidene)-amino]-propan-2-ol (8.24 g, 30.9 mmol, 1.35 eq) in one portion. The resulting thin suspension is heated to reflux (41°C) for 21 h. The resultant slurry is added to a solution of acetic acid (1.76 g, 29.3 mmol, 1.27 eq) in methanol (46 g) and rinsed in with methanol (24 g). The resultant mixture is concentrated via atmospheric distillation to 51 g net weight. The resultant slurry is cooled to 0 °C and the precipitate collected by vacuum filtration, washed with methanol and dried in a nitrogen stream to give the title compound as crystalline in solid. ^{1}H NMR ($CDCl_3$) δ 3.05 (t, J = 4 Hz, 4 H), 3.87 (t, J = 4 Hz, 4 H), 3.98 (t, J = 4 Hz, 1 H), 4.04 (dd, J = 6, 9 Hz, 1 H), 4.13 (t, J = 9 Hz, 1 H), 4.97 (p, J = 5 Hz, 1 H), 6.92 (t, J = 9 Hz, 1 H), 7.14 (dd, J = 2, 9 Hz, 1 H), 7.22 (dd, J = 2, 9 Hz, 1 H), 7.39 (d, J = 2 Hz, 1 H), 7.44 (dd, J = 3, 14 Hz, 1 H), 7.87 (d, J = 2 Hz, 1 H), 8.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 48.03, 50.83, 63.16, 66.78, 71.44, 107.20 (J_{C-F} = 26 Hz), 113.62, 118.59, 127.37, 129.05, 129.46, 130.93, 133.16 (J_{C-F} = 11 Hz), 135.71, 136.09 (J_{C-F} = 9 Hz), 137.38, 154.26, 155.32 (J_{C-F} = 245 Hz), 160.24.

CLAIMS

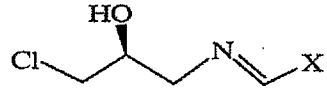
1. A process to prepare linezolid



Linezolid

which comprises:

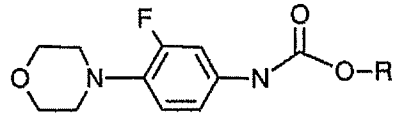
a) reacting a compound of structure (**1**)



(**1**)

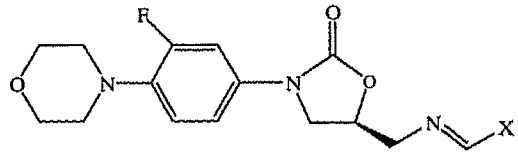
wherein X is chlorophenyl, bromophenyl, or 2,4-dichlorophenyl;

with a compound of structure (**2**)



(**2**)

at a temperature in a range from ambient temperature to about 65°C, wherein R is benzyl or C_{1-8}alkyl to provide a compound of structure (**3**);



(**3**)

wherein X is chlorophenyl, bromophenyl, or 2,4-dichlorophenyl;

b) hydrolyzing the compound of structure (**3**) and subsequently acylation to provide linezolid.

2. A compound of structure (**1**) in claim 1 which is (S)-1-chloro-3-[(4-chloro-E-benzylidene)-amino]-propan-2-ol.

3. A compound of structure (**1**) in claim 1 which is (S)-1-chloro-3-[(4-bromo-E-benzylidene)-amino]-propan-2-ol.

4. A compound of structure (**1**) in claim 1 which is (S)-1-chloro-3-[(2,4-dichloro-

benzylidene)-amino]-propan-2-ol.

5. A compound of structure (3) in claim 1 which is (S)-5-{[(4-chloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one.

6. A compound of structure (3) (S)-5-{[4-bromo-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one

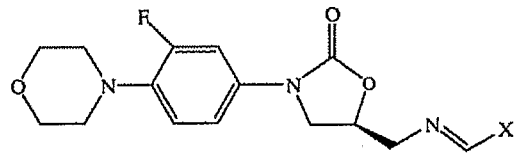
7. A compound of structure (3) in claim 1 which is (S)-5-{[2,4-dichloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one.

8. The temperature of claim 1 which is in a range from about 30-65 °C.

9. A compound of structure (2) in claim 1 where R is benzyl.

10. A compound of structure (2) in claim 1 where R is *tert-butyl*.

11. A process to prepare a compound of structure (3)

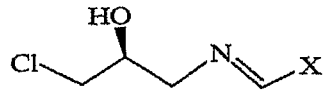


(3)

wherein X is chlorophenyl, bromophenyl, or 2,4-dichlorophenyl;

which comprises

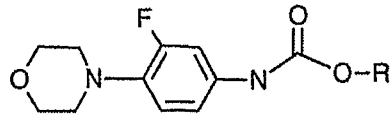
a) reacting a compound of structure (1)



(1)

wherein X is chlorophenyl, bromophenyl, or 2,4-dichlorophenyl;

with a compound of structure (2)

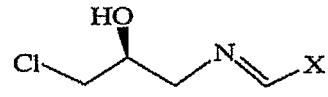


(2)

at a temperature in a range from ambient temperature to about 65°C, wherein R is benzyl or C_{1-8}alkyl.

12. The temperature of claim 8 which is in a range from about 30-65 °C.

13. A compound of structure (**1**)



(**1**)

Wherein X is chlorophenyl, bromophenyl, or 2,4-dichlorophenyl.

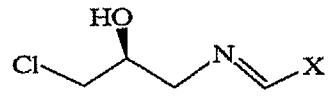
14. A compound of claim 12 which is (S)-1-chloro-3-[(4-chloro-E-benzylidene)-amino]-propan-2-ol.

15. A compound of claim 12 which is (S)-1-chloro-3-[(4-bromo-E-benzylidene)-amino]-propan-2-ol.

16 A compound of claim 12 which is (S)-1-chloro-3-[(2,4-dichloro-benzylidene)-amino]-propan-2-ol.

17. (S)-5-{[(4-chloro-benzylidene)-amino]-methyl}-3-(3-fluoro-4-morpholin-4-yl-phenyl)-oxazolidin-2-one.

18. A method of crystallization a compound of structure (**1**)



(**1**)

which comprises

a) liquefying a compound of structure (**1**) in the presence of a non-polar aprotic hydrocarbon solvent at a temperature in a range from ambient temperature to about 55 °C, optionally in the presence of an aprotic polar solvent; and

b) Slowly cooling the temperature to ambient temperature or lower.

19. The method of claim 18 wherein the hydrocarbon solvent is an alkane or mixtures of alkanes.

20. The method of claim 18 wherein the hydrocarbon solvent is hexane, heptane, octane, isooctane, or mixtures thereof.

21. The method of claim 18 wherein the aprotic polar solvent is an ethereal solvent, a chlorinated solvent, an aromatic solvent, or mixtures thereof.

22. The method of claim 18 wherein the aprotic plar solvent is MTBE.

23. The method of claim 18 wherein the aprotic plar solvent is toluene.

24. The method of claim 18 wherein the aprotic plar solvent is methylene chloride.

25. The method of claim 18 wherein the temperature is in a range from about 30 to 50 °C.

26. The method of claim 18 wherein the temperature is in a range from about 38 to 45 °C.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/000882

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D263/20 C07D295/12 C07C251/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/24393 A (UPJOHN CO [US]; PEARLMAN BRUCE A [US]) 20 May 1999 (1999-05-20) cited in the application the whole document	1-26
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2007	14/08/2007

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/000882

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	BRICKNER S J ET AL: "SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF U-100592 AND U-100766, TWO OXAZOLIDINONE ANTIBACTERIAL AGENTS FOR THE POTENTIAL TREATMENT OF MULTIDRUG-RESISTANT GRAM-POSITIVE BACTERIAL INFECTIONS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 3, 1996, pages 673-679, XP002070209 ISSN: 0022-2623 cited in the application the whole document	1-26

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Information on patent family members

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