Title: PROCESS TO CHIRAL BETA AMINO ACID DERIVATIVES BY ASYMMETRIC HYDROGENATION

(57) Abstract: The present invention relates to a process for the efficient preparation of enantiomerically enriched beta amino acid derivatives which are useful in the asymmetric synthesis of biologically active molecules. The process comprises an enantioselective hydrogenation of a prochiral beta amino acrylic acid derivative substrate in the presence of a transition metal precursor complexed with a chiral ferrocenyl diphosphine ligand with in situ protection of the primary amine product. The invention also relates to a novel process for the preparation of chiral beta-amino acid amide as inhibitors of the dipeptidyl peptidase-IV of structural formula III and the useful intermediates obtained therein. The products resulting from the instant process are inhibitors of dipeptidyl peptidase-IV and thereby useful for the treatment of Type 2 diabetes.
TITLE OF THE INVENTION
PROCESS TO CHIRAL BETA AMINO ACID DERIVATIVES BY ASYMMETRIC HYDROGENATION

FIELD OF THE INVENTION

The present invention relates to a process for the efficient preparation of enantiomerically enriched beta amino acid derivatives which are useful in the asymmetric synthesis of biologically active molecules. The process comprises an enantioselective hydrogenation of a prochiral beta-amino acrylic acid derivative substrate in the presence of a transition metal precursor complexed with a chiral ferrocenyl diphosphine ligand with in situ protection of the primary amine product.

BACKGROUND OF THE INVENTION

The present invention provides an efficient process for the preparation of an enantiomerically enriched beta amino acid derivative of structural formula I:

\[
\begin{align*}
&\text{O} \\
&\text{R}^8 \text{NH} \text{O} \\
&\text{R}^1 \text{Z}
\end{align*}
\]

(1)

having the \((R)\)- or \((S)\)-configuration at the stereogenic center marked with an \(*\); wherein R\(^8\) is C\(_{1-4}\) alkyl, aryl, arylmethyl, C\(_{1-4}\) allyloxy, allyloxy, and 9-fluorenylmethoxy; Z is OR\(^2\) or NR\(^2\)R\(^3\); R\(^1\) is C\(_{1-8}\) alkyl, aryl, heteroaryl, aryl-C\(_{1-2}\) alkyl, or heteroaryl-C\(_{1-2}\) alkyl; R\(^2\) and R\(^3\) are each independently hydrogen, C\(_{1-8}\) alkyl, aryl, or aryl-C\(_{1-2}\) alkyl; or R\(^2\) and R\(^3\) together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system optionally containing an additional heteroatom selected from O, S, and NC\(_{1-4}\) alkyl, said heterocyclic ring system being optionally fused with a 5- to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC\(_{1-4}\) alkyl, said fused ring system being unsubstituted or substituted with one to two substituents independently selected from hydroxy, amino, fluoro, C\(_{1-4}\) alkyl, C\(_{1-4}\) alkoxy, and trifluoromethyl.

The process of the present invention relates to a method for the preparation of chiral beta amino acid derivatives of structural formula I in an efficient enantioselective fashion via transition metal-catalyzed asymmetric hydrogenation of a prochiral enamine of structural formula II:
wherein the amino group is initially unprotected, in the presence of a chiral ferrocenyl diphosphine ligand, with \textit{in situ} protection of the primary amine product.


The catalytic asymmetric hydrogenation of unprotected enamine amides and esters using a transition metal precursor complexed with a chiral ferrocenyl diphosphine ligand has been described to be a powerful method for the synthesis of unprotected \(\beta\)-amino acid derivatives [see Y. Hsiao, et al., "Highly Efficient Synthesis of \(\beta\)-amino acid Derivatives via Asymmetric Hydrogenation of Unprotected Enamines," \textit{J. Am. Chem. Soc.}, 126: 9918-9919 (2004)]. A limitation of this method is the potential for product inhibition and the incompatibility of the primary amine products with other functionalities present in the substrates, such as ester and keto groups. The present invention is concerned with a modification of the procedure disclosed in WO 2004/007793 (published 7 October 2004) which results in an improvement of the performance of the asymmetric hydrogenation reaction by eliminating product inhibition and providing products with compatible functionalities. This is achieved by \textit{in situ} protection of the primary amine product of the hydrogenation reaction as an acylated derivative. The modified asymmetric hydrogenation reaction is milder and more efficient and proceeds with excellent reactivity and enantioselectivity.

Another aspect of the present invention provides a process for the preparation of chiral beta-amino acid amides of structural formula III which are inhibitors of dipeptidyl peptidase-IV:

\[
\begin{align*}
\text{Ar} & \quad \text{NH}_2 & \quad \text{O} \\
\quad & \quad \text{N} & \quad \text{O} \\
\quad & & \quad \text{NH} \\
\quad & & \quad \text{Ar} \\
\text{R}^9 & \quad \text{*} & \quad \text{**}
\end{align*}
\]

having the (\(R\))-configuration at the stereogenic centers marked with an * and **; wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and R⁹ is C₁-₄ alkyl unsubstituted or substituted with one to five fluorines.

The present invention also provides structurally novel compounds that are useful intermediates in the disclosed process for the preparation of compounds of structural formula III.

The compounds of structural formula III, and pharmaceutically acceptable salts thereof, along with their use as inhibitors of dipeptidyl peptidase-IV for the treatment of Type 2 diabetes, were disclosed in WO 04/037169 (published 6 May 2004), the contents of which are incorporated by reference herein in their entirety.

WO 04/037169 also described a process for preparing compounds of formula III. However, a large number of synthetic transformations was required with a low overall chemical and optical yield. With the present invention, there are produced more efficiently compounds of structural formula III with an optical purity in excess of 95% in considerably fewer chemical steps with an overall chemical yield of about 30% starting from cheap readily available precursors. Moreover, no chromatographic purification step is necessary throughout the synthetic sequence.

SUMMARY OF THE INVENTION

The present invention is concerned with a process for the preparation of enantiomerically enriched beta amino acid derivatives of structural formula I. The process utilizes an asymmetric hydrogenation of a prochiral beta amino acrylic acid derivative, wherein the primary amino group is unprotected, in the presence of a transition metal precursor complexed with a chiral ferrocenyl diphosphine ligand with in situ protection of the primary amine product as an acylated derivative. The process of the present invention is applicable to the preparation of beta amino acid derivatives on a pilot plant or industrial scale. The beta amino acid derivatives are useful to prepare a wide variety of biologically active molecules.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an efficient process for the preparation of an enantiomerically enriched beta amino acid derivative of structural formula I:

\[
\begin{align*}
\text{O} & \\
\text{R}^6 & \\
\text{NH} & \\
\text{O} & \\
\text{R}^1 & \\
\text{**} & \\
\text{Z} & \\
\end{align*}
\]

having the (R)- or (S)-configuration at the stereogenic center marked with an **; in an enantiomeric excess of at least 70% over the opposite enantiomer, wherein
Ra is C₁₋₄ alkyl, aryl, arylmethyl, C₁₋₄ alkoxy, allyloxy, and 9-fluorenylmethyloxy;
Z is OR² or NR²R³;
R¹ is C₁₋₈ alkyl, aryl, heteroaryl, aryl-C₁₋₂ alkyl, or heteroaryl-C₁₋₂ alkyl;
R² and R³ are each independently hydrogen, C₁₋₈ alkyl, aryl, or aryl-C₁₋₂ alkyl; or R² and R³ together
with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system
optionally containing an additional heteroatom selected from O, S, NH, and NC₁₋₄ alkyl, said
heterocyclic ring being unsubstituted or substituted with one to three substituents independently selected
from oxo, hydroxy, halogen, C₁₋₄ alkoxy, and C₁₋₄ alkyl wherein alkyl and alkoxy are unsubstituted or
substituted with one to five fluorines; and said heterocyclic ring system being optionally fused with a 5-
to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic
heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC₀₋₄ alkyl, said
fused ring system being unsubstituted or substituted with one to two substituents selected from hydroxy,
amino, fluorine, C₁₋₄ alkyl, C₁₋₄ alkoxy, and trifluoromethyl.

The process of the present invention comprises the step of hydrogenation of a prochiral
enamine of structural formula II:

\[
\begin{align*}
\text{NH}_2 \\
\text{O} \\
\text{Z} \\
\end{align*}
\]

in a suitable organic solvent in the presence of an Ra carbonylating reagent and a transition metal
precursor complexed to a chiral ferrocenyl diphosphine ligand of structural formula IV:

\[
\begin{align*}
\text{PR}^5 \text{R}^6 \\
\text{PR}^7 \text{R}^7 \\
\text{Fe} \\
\end{align*}
\]

wherein R⁴ is C₁₋₄ alkyl or aryl;
R⁵ and R⁶ are each independently C₁₋₆ alkyl, C₅₋₁₂ cycloalkyl, or aryl; and
R⁷ is C₁₋₄ alkyl or aryl; and wherein said Ra carbonylating reagent is added prior to, during, or after said
hydrogenation.

The process of the present invention contemplates that the catalytic complex of the
transition metal precursor and the chiral ferrocenyl diphosphine ligand may be either (a) generated in situ
by the sequential or contemporaneous addition of the transition metal species and the chiral ferrocenyl
diphosphine ligand to the reaction mixture or (b) pre-formed with or without isolation and then added to the reaction mixture. A pre-formed catalytic complex is represented by the formula:

\[
\begin{array}{c}
\text{R} \\
\text{R} \\
\text{P} \\
\text{P} \\
\text{Rh} \\
\text{L} \\
\text{L} \\
\text{R} \\
\text{R} \\
\end{array}
\]

where \( X \) represents a non-coordinating anion, such as trifluoromethanesulfonate, tetrafluoroborate, and hexafluorophosphate, and \( L \) is a neutral ligand such as an olefin (or chelating di-olefin such as 1,5-cyclooctadiene or norbornadiene) or a solvent molecule (such as MeOH and TFE). In the case where olefin is arene, the complex is represented by the formula:

\[
\begin{array}{c}
\text{R} \\
\text{R} \\
\text{P} \\
\text{P} \\
\text{Rh} \\
\text{L} \\
\text{R} \\
\text{R} \\
\end{array}
\]

The pre-formed catalytic complex in the case where \( X \) represents halogen is represented by the formula:

\[
\begin{array}{c}
\text{R} \\
\text{R} \\
\text{P} \\
\text{P} \\
\text{Rh} \\
\text{X} \\
\text{R} \\
\text{R} \\
\end{array}
\]

The ligands of structural formula IV are known in the art as Josiphos ligands and are commercially available from Solvias AG, Basel, Switzerland.
In one embodiment of the ligands of formula IV useful in the process of the present invention, the carbon stereogenic center marked with an *** has the \((R)\)-configuration as depicted in formula V:

![Diagram V]

In another embodiment of the ligands of formula IV useful in the process of the present invention, \(R^4\) is \(C_{1-2}\) alkyl, \(R^5\) and \(R^6\) are \(C_{1-4}\) alkyl, and \(R^7\) is aryl. In a class of this embodiment, \(R^4\) is methyl, \(R^5\) and \(R^6\) are \(t\)-butyl, and \(R^7\) is unsubstituted phenyl. The latter ligand is known in the art as \(t\)-butyl Josiphos. Commercially available forms of the \(t\)-butyl Josiphos ligand are the \(S,R\) and \(R,S\) enantiomeric forms. \(R,S-t\)-butyl Josiphos is \(((R)-1-[(S)-(diphenylphosphino)ferrocenyl)]ethyl-di-tert-butylphosphine of formula VI below:

![Diagram VI]

The ferrocenyl diphosphine ligands of formula IV have two centers of asymmetry, and the process of the present invention is intended to encompass the use of single enantiomers, individual diastereomers, and mixtures of diastereomers thereof. The present invention is meant to comprehend the use of all such isomeric forms of the ligands of structural formula IV for the asymmetric hydrogenation of a compound of formula II. The facial enantioselectivity of the hydrogenation reaction will depend on the particular stereoisomer of the ligand that is employed in the reaction. It is possible to control the configuration at the newly formed stereogenic center in a compound of formula I marked with an * by the judicious choice of the chirality of the ferrocenyl diphosphine ligand of formula IV.

In one embodiment of the substrate for the process of the present invention, \(R^1\) is benzyl wherein the phenyl group of benzyl is unsubstituted or substituted one to three substituents selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy. In another embodiment of the process of the present invention, \(Z\) is \(NR^2R^3\). In a class of this embodiment, \(NR^2R^3\) is a heterocycle of the structural formula VII:
wherein $R^8$ is hydrogen or C$_{1-4}$ alkyl which is unsubstituted or substituted with one to five fluorines. In another class of this embodiment of the process of the present invention, $NR^2R^3$ is a heterocycle of the structural formula VIII:

(VIII)

wherein $R^9$ is C$_{1-4}$ alkyl unsubstituted or substituted with one to five fluorines.

In another embodiment of the substrate for the process of the present invention, $R^1$ is 6-methoxy-pyridin-3-yl and $Z$ is C$_{1-4}$ alkoxy. In a class of this embodiment, $Z$ is methoxy or ethoxy.

The asymmetric hydrogenation reaction of the present invention is carried out in a suitable organic solvent. Suitable organic solvents include lower alkanols, such as methanol, ethanol, isopropyl alcohol, hexafluoroisopropyl alcohol, phenol, 2,2,2-trifluoroethanol (TFE), and mixtures thereof; tetrahydrofuran; methyl t-butyl ether; and mixtures thereof.

Asymmetric hydrogenation of an amine ester or amide intermediate of structural formula II is carried out in the presence of an $R^8$ carbonylating reagent. The $R^8$ carbonylating reagent is added either before the initiation of the hydrogenation reaction, during the hydrogenation reaction, or after the completion of the hydrogenation reaction. In a preferred embodiment, the $R^8$ carbonylating reagent is added prior to the initiation of the hydrogenation reaction.

The reaction temperature for the reaction may be in the range of about 10 °C to about 90 °C. A preferred temperature range for the reaction is about 20 °C to about 65 °C.

The hydrogenation reaction can be performed at a hydrogen pressure range of about 20 psig to about 1500 psig. A preferred hydrogen pressure range is about 40 psig to about 200 psig.

The transition metal precursors are $[\text{M(monoolefin)}_2\text{Cl}_2]$, $[\text{M(diolefin)}\text{Cl}_2]$, $[\text{M(monoolefin)}_2\text{acetylacetonate}]$, $[\text{M(diolefin)}\text{acetylacetonate}]$, $[\text{M(monoolefin)}_4\text{X}]$, or $[\text{M(diolefin)}_2\text{X}]$ wherein X is a non-coordinating anion selected from the group consisting of methanesulfonate, trifluoromethanesulfonate (Tf), tetrafluoroborate (BF$_4$), hexafluorophosphate (PF$_6$), and hexafluoroantimonate (SbF$_6$), and M is rhodium (Rh) or iridium (Ir). Transition metal precursors where M is ruthenium (Ru) are $[\text{M(arene)}\text{Cl}_2]_2$, $[\text{M(diolefin)}\text{Cl}_2]_n$, or $[\text{M(diolefin)}(\eta^3-2\text{-methyl-1-propenyl})_2]$. In one embodiment the transition metal precursor is $[\text{Rh(cod)}\text{Cl}_2]$, $[\text{Rh(norbornadiene)}\text{Cl}_2]$. 

- 7 -
[Rh(cod)₂]X, or [Rh(norbornadiene)₂]X. In a class of this embodiment, the transition metal precursor is [Rh(cod)Cl]₂.

The ratio of transition metal precursor to substrate is about 0.01 to about 10 mol %. A preferred ratio of the transition metal precursor to substrate is about 0.05 mol % to about 0.8 mol %.

The Ra carbonylating reagent is an activated form of a carboxylic acid or carboxylic acid of formula RaCO₂H. Embodiments of Ra carbonylating reagent include symmetrical carboxylic acid anhydrides, symmetrical carboxylic acid anhydrides, reactive esters, mixed carboxylic acid carboxylic acid anhydrides (mixed carbonates), and mixed carbonates with activated “alcohol” components. Exemplifications of mixed carbonates include alkylcarboxylic acid p-nitrophenyl esters. Exemplifications of carbonates with activated “alcohol” components include N-hydroxysuccinimide and 1-hydroxybenzotriazole esters of carboxylic acids, such as N-(9-fluorenylmethoxycarbonyloxy)succinimide (Ra = 9-fluorenylmethoxy). Examples of reactive esters are phenyl trifluoroacetate (Ra = trifluoromethyl) and p-nitrophenyl acetate (Ra = methyl). Use of an activated form of a carboxylic acid affords an amide derivative of a compound of formula I, and use of an activated form of a carboxylic acid affords a urethane derivative of a compound of formula I. In a preferred embodiment the Ra carbonylating reagent is a symmetrical carboxylic acid anhydride, such as di-tert-butyl dicarbonate (also referred to as Boc anhydride or Boc₂O; Ra = tert-butyloxy), dibenzyl dicarbonate (Ra = benzyloxy), and diallyl dicarbonate (Ra = allyloxy). In a class of this embodiment the Ra carbonylating reagent is di-tert-butyl dicarbonate to provide a tert-butylcarbamate derivative of a compound of formula I.

The beta amino acrylic acid derivative substrates of formula II for the asymmetric hydrogenation contain an olefinic double bond, and unless specified otherwise, are meant to include both E and Z geometric isomers or mixtures thereof as starting materials. The squiggly bond in the substrate of structural formula II signifies either the Z or E geometric isomer or a mixture thereof.

In one embodiment of the present invention, the geometric configuration of the double bond in the beta amino acrylic acid derivative substrate for the asymmetric hydrogenation reaction is the Z-configuration as depicted in formula IX:

\[
\begin{align*}
\text{R'} & \quad \text{NH}_2 \\
\text{Z} & \quad \text{O} \\
\end{align*}
\]

The beta amino acrylate esters of formula II for the asymmetric hydrogenation reaction of the present invention can be prepared from a beta-keto ester of structural formula X in high yield by reaction with a source of ammonia in a suitable organic solvent such as methanol, ethanol, isopropyl alcohol, tetrahydrofuran, and aqueous mixtures thereof.
Sources of ammonia include ammonium acetate, ammonium hydroxide, and ammonium formate. In one embodiment the source of ammonia is ammonium acetate. The beta-keto esters can be prepared as described by D.W. Brooks et al., Angew. Chem. Int. Ed. Engl., 18: 72 (1979).

The beta amino acrylamides \((Z = NR_2R_3)\) can also be prepared from the corresponding esters via amide exchange as described in Org. Syn. Collect., Vol. 3, p. 108.

Throughout the instant application, the following terms have the indicated meanings:

The term “% enantiomeric excess” (abbreviated “ee”) shall mean the % major enantiomer less the % minor enantiomer. Thus, an 80% enantiomeric excess corresponds to formation of 90% of one enantiomer and 10% of the other. The term “enantiomeric excess” is synonymous with the term “optical purity.”

The term “enantiomerically enriched” shall mean that a compound of structural formula I is obtained by the process of the present invention with an enantiomeric excess of the desired \((R)\)-enantiomer greater than 70% over the \((S)\)-enantiomer. In one embodiment a compound of formula I having the \((R)\)-configuration is obtained with an ee greater than 80%. In a class of this embodiment the \((R)\)-enantiomer is obtained with an ee greater than 90%. In a subclass of this class the \((R)\)-enantiomer is obtained with an ee greater than 95%.

The term “% diastereomeric excess” (abbreviated “de”) shall mean the % major diastereomer less the % minor diastereomer. Thus, an 80% diastereomeric excess corresponds to formation of 90% of one diastereomer and 10% of the other.

The term “diastereomeric ratio” (abbreviated “dr”) shall mean the % major diastereomer divided by the % minor diastereomer. Thus, a diastereomeric ratio of 19 corresponds to formation of 95% of one diastereomer and 5% of the other.

The term “enantioselective” shall mean a reaction in which one enantiomer is produced (or destroyed) more rapidly than the other, resulting in the predominance of the favored enantiomer in the mixture of products.

The term “diastereoselective” shall mean a reaction in which one diastereomer is produced (or destroyed) more rapidly than the other, resulting in the predominance of the favored diastereomer in the mixture of products.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine, and iodine.

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl. Unless otherwise indicated, the alkyl
groups are unsubstituted or substituted with one to three groups independently selected from the group consisting of halogen, hydroxy, carboxy, aminocarbonyl, amino, C\textsubscript{1-4} alkoxy, and C\textsubscript{1-4} alkylthio.

The abbreviation “cod” means “1,5-cyclooctadiene.”

The term “aryl” includes phenyl and naphthyl. “Aryl” is unsubstituted or substituted with one to three substituents independently selected from fluoro, hydroxy, nitro, trifluoromethyl, amino, C\textsubscript{1-4} alkyl, and C\textsubscript{1-4} alkoxy.

Another embodiment of the present invention concerns a process for the preparation of a compound of structural formula III:

![Formula III](image)

having the (R)-configuration at the stereogenic centers marked with an * and **; wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and R\textsuperscript{9} is C\textsubscript{1-4} alkyl unsubstituted or substituted with one to five fluorines;

comprising the steps of:

(a) producing a compound of structural formula XI:

![Formula XI](image)

by treating a compound of structural formula XII:

![Formula XII](image)

with a compound of structural formula XIII:
in a suitable organic solvent;

(b) producing a compound of structural formula XIV:

\[
\text{(XIV)}
\]

5 by treating said compound of structural formula XI:

\[
\text{(XI)}
\]

with a source of ammonia in a suitable organic solvent;

(c) producing a mixture of compounds of structural formulae XV and XVI:

\[
\text{(XV)}
\]
\[
\text{(XVI)}
\]

10 wherein Boc represents a tert-butyloxycarbonyl protecting group;

by hydrogenation of said compound of structural formula XIV:

\[
\text{(XIV)}
\]

in a suitable organic solvent in the presence of a tert-butylcarbonylating reagent and a transition metal complexed to a chiral ferrocenyl diphosphine ligand of structural formula V:
wherein the stereogenic center marked with a *** has the (R)-configuration;
R⁴ is C₁-₄ alkyl or aryl;
R⁵ and R⁶ are each independently C₁-₆ alkyl, C₅-₁₂ cycloalkyl, or aryl; and
R⁷ is C₁-₄ alkyl or aryl; and wherein said tert-butylcarbonylating reagent is added prior to, during, or
after said hydrogenation;
(d) producing a compound of structural formula XV:

![Chemical Structure XV](image)

by treating said mixture of compounds of structural formulae XV and XVI:

![Chemical Structures XV and XVI](image)

with base in an organic solvent followed by crystallization of said compound of structural formula XV;
and
(e) cleavage of said tert-butyloxy carbonyl protecting group in said compound of structural formula XV:

![Chemical Structure XV](image)

to afford said compound of structural formula III.
Compounds of structural formula III can be converted into their pharmaceutically acceptable acid addition salts by treatment with an appropriate pharmaceutically acceptable acid. When the Boc-cleavage Step (e) is carried out with hydrogen chloride in an organic solvent, compounds of formula III are obtained in the form of their HCl addition salts.

In one embodiment of the process of the present invention, R⁹ is 2,2,2-trifluoroethyl (CH₂CF₃) and Ar is phenyl substituted with one to three substituents independently selected from the group consisting of fluorine, bromine, and trifluoromethyl. In a class of this embodiment Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl. In subclass of this class, Ar is 2,4,5-trifluorophenyl.

In one embodiment of this aspect of the present invention, the \( \text{R,}\text{R-diastereomer of structural formula XV} \) is present in a diastereomeric excess of at least 90% (diastereomeric ratio of 19) over the \( \text{R,}\text{S-diastereomer of structural formula XVI} \). In a class of this embodiment the \( \text{R,}\text{R-diastereomer of structural formula XV} \) is present in a diastereomeric excess of at least 95% (diastereomeric ratio of 39) over the \( \text{R,S-diastereomer} \). In a subclass of this class the \( \text{R,}\text{R-diastereomer of structural formula XV} \) is present in a diastereomeric excess of at least 98% (diastereomeric ratio of 99) over the \( \text{R,}\text{S-diastereomer} \).

Another aspect of the present invention comprises structurally novel compounds of structural formula XI which are useful intermediates in the preparation of compounds of structural formula III:

\[
\begin{align*}
\text{Ar} & \quad \text{O} \\
\text{O} & \quad \text{N} \\
\text{R}^9 & \quad \text{O} \\
\text{NH} & \quad \text{XI}
\end{align*}
\]

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and \( R^9 \) is \( \text{C}_{1-4} \) alkyl unsubstituted or substituted with one to five fluorines.

In one embodiment of this aspect of the present invention, Ar is 2,4,5-trifluorophenyl and \( R^9 \) is 2,2,2-trifluoroethyl.

Another aspect of the present invention comprises structurally novel compounds of structural formula XIV which are useful intermediates in the preparation of compounds of structural formula III:

\[
\begin{align*}
\text{Ar} & \quad \text{NH}_2 \\
\text{O} & \quad \text{N} \\
\text{R}^9 & \quad \text{O} \\
\text{NH} & \quad \text{XIV}
\end{align*}
\]
wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and R⁹ is C₁-₄ alkyl unsubstituted or substituted with one to five fluorines.

In one embodiment of this aspect of the present invention, Ar is 2,4,5-trifluorophenyl and R⁹ is 2,2,2-trifluoroethyl.

In another embodiment of the process of the present invention, the final product of the reaction sequence of structural formula III is isolated from the reaction mixture. In a further embodiment, the final product is converted into a pharmaceutically acceptable salt thereof.

The first step in the instant process for the preparation of the compounds of formula III entails the preparation of a Meldrum’s acid adduct of structural formula XII:

![Structural formula XII](image)

This is accomplished by treating an appropriately substituted phenylacetic acid with a carboxyl group activating agent to generate an active carboxylic acid species, such as an acyl halide; an active ester, such as an aryl ester; a mixed carboxylic acid anhydride; an acyl imidazole; a mixed carboxylic acid carbonic acid anhydride; and a phosphoric or phosphinic acid mixed anhydride. The activated phenylacetic acid is allowed to react with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum’s acid) in the presence of base.

Formation of the active carboxylic acid species is carried out using methods that are well-known in the practice of organic chemistry. For example, 1,1’-carbonyldiimidazole or 1,1’-thiocarbonyldiimidazole may be used to generate an acyl imidazole; trimethylacetyl (pivaloyl) chloride or isovaleryl chloride to generate a pivalic or isovaleric acid mixed anhydride; oxalyl chloride (in the presence of a catalytic amount of DMF) or phosphorus pentachloride to generate an acid chloride; isobutyl chloroformate to generate an isobutylcarboxylic acid mixed anhydride; and diethylchlorophosphite to generate a diethylphosphoric acid mixed anhydride. Examples of active aryl esters include p-nitrophenyl esters, 2,4-dinitrophenyl esters, and pentafluorophenyl esters. Meldrum’s acid may be initially present in the reaction mixture during the formation of the activated acid species or added subsequently after generation of the activated acid species. The reaction is carried out in a suitable organic solvent, such as THF, dimethoxymethane, DME, DMF, DMAc, NMP, DMSO, IPAc, EtoAc, MTBE, toluene, and MeCN. If formation of the activated acid species liberates acid, then the reaction is carried out in the presence of base, such as triethylamine, N,N-diisopropylethylamine, diisopropylamine, 2,4,6-collidine, imidazole, pyridine, lutidine, N,N-dimethylaniline, DMAP, DABCO, and DBU. In one embodiment the Meldrum’s acid adduct is prepared using the combination of pivaloyl chloride, N,N-diisopropylethylamine, and DMAP.
The subsequent step in the process of the present invention entails reaction of a Meldrum's acid adduct of structural formula XII with a substituted 1,4-diazepan-2-one (lactam) intermediate of structural formula XIII:

\[
\begin{array}{c}
\text{R}^9 \\
\text{HN} \\
\text{O} \\
\text{NH}
\end{array}
\]

(XIII)

or an acid salt thereof to elaborate a beta-ketoamide of structural formula XI. When an acid addition salt of the lactam intermediate is used, a base or an acid can be added to the reaction mixture. Embodiments of bases that can be used in this reaction include triethylamine, N,N-diisopropylethylamine, diisopropylamine, 2,4,6-collidine, imidazole, pyridine, lutidine, DMAP, DABCO, and DBU. Embodiments of acids that can be used in this reaction include trifluoroacetic acid, trichloroacetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, camphorsulfonic acid, acetic acid, and pivalic acid. A preferred acid is trifluoroacetic acid. The reaction is carried out in a suitable reaction solvent, such as THF, dimethoxymethane, DME, EtOAc, IPA, MeCN, DMF, DMAc, NMP, DMSO, MTBE, and toluene.

In one embodiment of the present process the formation of a beta ketoamide of structural formula XI is carried out in acidic reaction media to achieve high conversion and high yield. Otherwise, the accuracy of the base charge in the formation of the Meldrum's acid adduct is critical in order to ensure that the ketoamide formation step proceeds in high yield and conversion. Introducing an acid into the reaction system is advantageous, in that it neutralizes the excess base used in formation of the Meldrum's acid adduct if a through-process is applied and results in high conversion allowing for lowering the reaction temperature and suppressing formation of impurities.

In one embodiment, the Meldrum's acid adduct is not isolated from the reaction mixture but is reacted with the lactam intermediate of formula XIII, preferably in the form of an acid salt, such as the hydrochloride salt. The reaction is carried out optionally in the presence of acid in a suitable organic solvent.

The enamine amides of formula XIV are substrates for the asymmetric hydrogenation reaction and are prepared by reaction of a beta-ketoamide of structural formula XI with a source of ammonia in a suitable organic solvent such as methanol, ethanol, isopropyl alcohol, tetrahydrofuran, and aqueous mixtures thereof.
Sources of ammonia include ammonium acetate, ammonium hydroxide, and ammonium formate. In one embodiment the source of ammonia is ammonium acetate.

In one embodiment, the beta-ketoamide is not isolated from the reaction mixture but is converted into the enamine amide with a source of ammonia in a suitable organic solvent.

The enamine amide intermediates of structural formula XI contain an olefinic double bond, and unless specified otherwise, are meant to include both $E$ and $Z$ geometric isomers or mixtures thereof as starting materials.

Asymmetric hydrogenation of an enamine amide intermediate of structural formula XIV is carried out in a suitable organic solvent in the presence of a tert-butyloxyxycarbonylating reagent and a transition metal catalyst complexed to a chiral ferrocenyl diphosphine ligand of structural formula V:

\[
\begin{align*}
\begin{array}{c}
\text{Fe} \quad \begin{array}{ccc}
\text{R}^4 & \text{PR}^5\text{R}^6 & \text{P(R}^7\text{)}_2 \\
\circ & \circ & \circ
\end{array}
\end{array}
\end{align*}
\]

wherein the stereogenic center marked with an *** has the (R)-configuration; $\text{R}^4$ is $\text{C}_{1-4}$ alkyl or aryl; $\text{R}^5$ and $\text{R}^6$ are each independently $\text{C}_{1-6}$ alkyl, $\text{C}_{5-12}$ cycloalkyl, or aryl; and $\text{R}^7$ is $\text{C}_{1-4}$ alkyl or aryl.

The tert-butyloxyxycarbonylating reagent is added either prior to the initiation or during the asymmetric hydrogenation reaction. Alternatively, the tert-butyloxy- carbonylating reagent is added after the completion of the asymmetric hydrogenation reaction. In a preferred embodiment the tert-butyloxyxycarbonylating reagent is added prior to the initiation of the hydrogenation.

In one embodiment of the ligands of formula V useful in the process of the present invention, $\text{R}^4$ is $\text{C}_{1-2}$ alkyl, $\text{R}^5$ and $\text{R}^6$ are $\text{C}_{1-4}$ alkyl, and $\text{R}^7$ is aryl. In a class of this embodiment, $\text{R}^4$ is methyl, $\text{R}^5$ and $\text{R}^6$ are $t$-butyl, and $\text{R}^7$ is phenyl.

The asymmetric hydrogenation reaction of the present invention is carried out in a suitable organic solvent. Suitable organic solvents include lower alkanols, such as methanol, ethanol, isopropyl alcohol, and trifluoroethanol; tetrahydrofuran; methyl $t$-butyl ether; and aqueous mixtures thereof.
The reaction temperature for the reaction may be in the range of about 0 °C to about 90 °C. A preferred temperature range for the reaction is about 20 °C to about 50 °C. The reaction is typically carried out at ambient room temperature.

The hydrogenation reaction can be performed at a hydrogen pressure range of about 20 psig to about 1000 psig. A preferred hydrogen pressure range is about 80 psig to about 200 psig.

The transition metal catalytic species may be [M(cod)Cl]₂, [M(norbornadiene)Cl]₂, [M(cod)₂]X, or [M(norbornadiene)₂]X wherein X is methanesulfonate, trifluoromethanesulfonate, tetrafluoroborate, hexafluorophosphate, or hexafluoroantimonate and M is rhodium (Rh), iridium (Ir), or ruthenium (Ru). A preferred catalyst when M is Rh is [Rh(cod)Cl]₂.

The ratio of substrate to catalyst is about 0.01 to about 10 mol %. In one embodiment the substrate to catalyst ratio is about 0.05 mol % to about 1.0 mol %. In a class of this embodiment the substrate to catalyst ratio is about 0.1 mol % to about 0.5 mol %. The reaction is typically carried out at a substrate to catalyst ratio of about 0.2 mol %.

The asymmetric hydrogenation proceeds with high enantioselectivity at the stereogenic carbon center marked with an * and with high chemical yield. Typical assay yields are 98% with 98.5 ee's.

The asymmetric hydrogenation is performed either in the presence of a tert-butyloxycarbonylating reagent, such as di-tert-butyl dicarbonate, or the tert-butyloxycarbonylating reagent is added after the hydrogenation reaction is complete, to afford protection of the chiral amine product as its tert-butyl carbamate derivative. The reaction affords a mixture of \( R,R \) and \( R,S \) diastereomers of structural formulae XV and XVI. Racemization in the presence of base affords the desired \( R,R \)-diastereomer in high optical purity and chemical yield. The racemization can be effected with an alkali metal alkoxide, such as sodium methoxide and potassium \( t \)-butoxide; an alkali metal hydroxide, such as lithium hydroxide, potassium hydroxide, and sodium hydroxide; an alkali metal carbonate, such as sodium carbonate, potassium carbonate, cesium carbonate, and lithium carbonate; or an organic amine base, such as DBU, DBN, and tetramethylguanidine; in an alcoholic or aqueous alcoholic solvent, such as methanol, ethanol, \( n \)-propanol, and isopropanol, or a nonalcoholic solvent, such as acetonitrile. In one embodiment, the racemization is carried out using sodium hydroxide in ethanol.
The final step in the process consists of cleavage of the Boc protecting group to afford a compound of structural formula III. This is accomplished, for example, by treatment of a compound of structural formula XV with HCl in an alcohol solvent, such as anhydrous isopropanol.

The 1,4-diazepan-2-one intermediates substituted at C-3 with R⁹ are prepared according to the procedures depicted in Scheme I.

**Abbreviations:** DABCO is 1,4-diazabicyclo[2.2.2]octane; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; DEA is diethylamine; DMAc is N,N-dimethylacetamide; DMAP is 4-(dimethylamino)pyridine; DME is 1,2-dimethoxyethane; DMF is N,N-dimethylformamide; DMSO is dimethylsulfoxide; EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; EtOAc is ethyl acetate; EtOH is ethanol; HOBr is 1-hydroxybenzotriazole hydrate; HPLC is high-performance liquid chromatography; IPA is isopropanol; IPAc is isopropyl acetate; tPr₂NEt is N,N-diisopropylethylamine; MeCN is acetonitrile; MeOH is methanol; MTBE is methyl t-butyl ether; NMP is N-methylpyrrolidinone; and THF is tetrahydrofuran.

**Scheme 1**

Amino acid ester 1-2 is prepared by treatment of diphenylmethylene glycine imine (1-1) with potassium t-butoxide in a solvent such as DMF followed by addition of an alkyl bromide or alkyl iodide. Basic hydrolysis of ethyl ester 1-2 followed by Michael addition to acrylonitrile generates nitrile 1-3. Reduction of nitrile 1-3 in the presence of base and Raney nickel affords amino acid 1-4.

Cyclization to the lactam 1-5 is effected with EDC in the presence of HOBr and collidine.
Representative experimental procedures utilizing the novel process are detailed below. For purposes of illustration, the following Example is directed to the preparation of compound 2-11, but doing so is not intended to limit the process of the present invention to the specific conditions for making this particular compound.

The starting materials are either commercially available or known in the chemical scientific or patent literature. Purification procedures include e.g., distillation, crystallization and normal or reverse phase liquid chromatography.

Step A: Ethyl 2-amino-4,4,4-trifluorobutanoate hydrochloride salt (2-2)

To a 100-L jacketed vessel equipped with overhead stirrer, nitrogen inlet, vacuum inlet, and thermocouple was charged 35 L of DMF and cooled to -20 °C. The vessel was purged by nitrogen gas. Potassium t-butoxide (3.11 kg, 27.8 mol) was added with vigorous stirring. The mixture was aged for 5 min to allow dissolution of the solid. The glycine imine 2-1 (7.00 kg, 26.2 mol) was added. Air was removed from the reaction vessel using three vacuum/nitrogen fill cycles. 2,2,2-Trifluoroethyl iodide was charged into a 5-L round bottom flask. The iodide was transferred into the stirring enolate solution in portions using residual vacuum. The mixture was aged at 0 °C for 5 h and then slowly warmed to room temperature over 1 h and held overnight. Half of the reaction mixture was transferred into a 100-L extractor containing 18 L of 5% ammonium chloride solution and 35 L of IPAc at 10 °C. The mixture was vigorously stirred, the layers allowed to settle, and the lower aqueous layer separated. The organic layer was washed three times with 18 L of 2% sodium chloride solution. The process was repeated with the second half of the reaction mixture. The combined organic layers were concentrated in a 100-L round bottom flask attached to a batch concentrator at 20-25 °C, 28-29 in Hg. Concentrated hydrochloric acid (2.7 L, 32.7 mol) was added. The batch was heated to 50 °C and aged for 30 min. The batch was then concentrated at 55-60 °C, 21-23 in Hg to 35 L total volume. The batch was then solvent switched into IPAc with constant feed distillation at 55-60 °C. A total of 50 L of IPAc was flushed through. The slurry was allowed to slowly cool to room temperature. The solid was isolated by filtration. The cake was washed with IPAC, 7 L displacement wash, 7 L slurry wash, and 5 L displacement wash. The cake was dried on the filter under nitrogen. The trifluoroethyl amino ester 2-2 was obtained as an off-white solid.

Step B: 2-[(2-Cyanoethyl)amino]-4,4,4-trifluorobutanoic acid (2-3)
To 100-L cylindrical vessel equipped with coiling coils, thermocouple, nitrogen inlet, and vacuum inlet was charged water (35.7 L) and potassium hydroxide (4.38 kg, 67.7 mol) resulting in an exotherm to 36 °C. The mixture was cooled to 12 °C (cooling coils set at -20 °C), and trifluoroethyl amino ester HCl 2-2 (7.14 kg, 32.2 mol) was charged over 30 min while maintaining the temperature under 15 °C. The coiling coils were set to 20 °C, and after the ice on the coils melted, the coils and sides of the vessel were rinsed with water (2.0 L). Air was removed from the vessel by vacuum/nitrogen cycling. The reaction was aged for 1 h at 15-20 °C. The reaction solution was transferred through a 20 μm and then a 5 μm in-line filter to a 100-L, 4-neck round bottom flask equipped with overhead stirring, thermocouple, nitrogen inlet, and vacuum inlet. Potassium monophosphate (1.17M solution, 3.80 L) was charged in portions to pH 9.84. Air was removed from the vessel by vacuum/nitrogen cycling, and then acrylonitrile (3.18 L, 48.3 mol) was charged in one portion at room temperature with a nitrogen sweep. Air was again removed from the vessel by vacuum/nitrogen cycling, and the reaction was aged at room temperature overnight. With cooling from a cool water bath, concentrated hydrochloric acid (0.18 L) was charged dropwise via addition funnel over 15 min to the reaction solution to induce seeding. The resulting slurry was aged for 40 min to develop a seed bed. The remaining concentrated hydrochloric acid (3.17 L) was charged via addition funnel over 1.75 h maintaining the temperature below 30 °C. The resulting white slurry was aged for 1 h. The solids were isolated via filtration using a 23.5 inch diameter filter pot. The cake was washed twice with 13.0 L water followed by a displacement wash with 14.2 L MeCN. The cake was dried on the filter under nitrogen. The Michael adduct 2-3 was obtained as a white, free flowing solid.

Step C: 2-[(3-Aminopropyl)amino]-4,4,4-trifluorobutanoic acid (2-4)

To a slurry of 2.7 Kg (12.85 mol) of nitrile 2-3 in 11.5 L of MeOH were charged 4.17 Kg (19.31 mol) of 25 wt% NaOMe solution in MeOH. All solids dissolved after 20 min of stirring. Raney
nickel-2800 slurry in water (23 wt%, 625 g) was charged to the solution and the vessel charged with hydrogen at 90 psig at 25 ºC, in a stirred autoclave. After 18 h, the catalyst was filtered over Celite and washed with 6.5 L of MeOH.

Step D: 3-(2,2,2-Trifluoroethyl)-1,4-diazepan-2-one (2-5)

To 59.0 Kg of the methanolic solution from Step C containing 5.27 Kg of diaminoacid 2-4 (24.6 mol) were charged 3.8 Kg of concentrated hydrochloric acid (37 wt%, 38.7 mol). The temperature rose to 33 ºC. An ice bath was used to cool the resulting slurry to 20 ºC. After combining the filtrate and washings from the previous step, the concentration of diaminoacid 2-4 in solution was around 90 mg/g (about 10L/Kg of 2-4). HOBT (665 g, 4.92 mol, 20 mol%) and collidine (596 g, 4.92 mol, 20 mol%) were then added. The slurry was aged at 20 ºC for 10 min and EDC (4.99 Kg, 26.0 mol) was charged over 30 min. A slight exotherm of 6 ºC was registered. After aging overnight, the crude reaction mixture was filtered through a 10-15 micron pore size filter to remove the solids in suspension. A total of 18.7 Kg of solution was obtained after the filtration. The solution was concentrated at reduced pressure to 11 Kg total weight. 5-6 N HCl in IPA was added to this solution until pH of 3 was obtained (5.3 L). The temperature was kept below 39 ºC with an ice bath. The slurry was aged overnight at 20 ºC. The solids were filtered and washed with 9 Kg of IPA and dried in the filter pot.

Step E: 2,2-Dimethyl-5-[(2,4,5-trifluorophenyl)acetyl]-1,3-dioxan-4,6-dione (2-6)

Trifluorophenylacetic acid (3.5 Kg, 18.4 mol), Meldrum’s acid (2.92 Kg, 20.25 mol), and DMAP (225 g, 1.84 mol) were charged into a 72 L three-neck flask. MeCN (14 L) was added in one portion at room temperature to dissolve the solids. iPr2NEt (7.06 L, 40.5 mol) was added in one portion at room temperature. Pivaloyl chloride (2.5 L, 20.25 mol) was then added dropwise over 1 to 2 h while
the reaction temperature was maintained below 55 °C. The reaction was then aged at 50 °C for 2-3 h. The reaction was cooled to 20 °C and 7 L of 17.7 wt% aqueous phosphoric acid was charged to homogeneous solution over 1 h. The product crystallized out of solution and slurry was aged 1 h. Then an additional 21 L of 17.7 wt% phosphoric acid was charged and final pH of aqueous layer was 2.5. The slurry was filtered at ambient temperature and the mother liquors recycled to remove all solids from the flask. The cake was washed with 15 L of 2:3 MeCN/H2O and the wet cake stirred and then filtered. The cake was washed an additional two times with 15 L of 2:3 MeCN/H2O and filtered. The wet cake was then dried in vacuum oven at 40 °C for up to 5 d to afford Meldrum's adduct 2-6.

\[^1^H\text{-NMR}\ (400 \text{ MHz}, \text{CDCl}_3): \delta \ 15.50 \ (s, \text{1H}), \ 7.14 \ (m, \text{1H}), \ 6.96 \ (m, \text{1H}), \ 4.45 \ (s, \text{2H}), \ 1.76 \ (s, \text{6H}) \text{ ppm;}\]

\[^{13}C\text{-NMR}\ (100 \text{ MHz}, \text{CDCl}_3): \delta \ 192.76, \ 170.66, \ 160.42, \ 156.47 \ (\text{ddd,} \ J_{\text{CF}} = 245.7, \ 9.6, \ 2.4 \text{ Hz}), \ 149.79 \ (\text{ddd,} \ J_{\text{CF}} = 251.4, \ 14.5, \ 12.0 \text{ Hz}), \ 146.90 \ (\text{ddd,} \ J_{\text{CF}} = 244.9, \ 12.0, \ 3.2 \text{ Hz}), \ 119.40 \ (\text{dd,} \ J_{\text{CF}} = 19.3, \ 5.6 \text{ Hz}), \ 117,41, \ 105.63, \ 91.99, \ 34.59, \ 27.06 \text{ ppm.}\]

**Step F:**

4-[3-Oxo-4-(2,4,5-trifluorophenyl)butanoyl]-3-(2,2,2-trifluoroethyl)-1,4-diazepan-2-one (2-7)

\[\begin{align*}
\text{2-6} & \quad + \quad \text{HCl} \\
\text{2-5} & \quad \text{iPr}_2\text{NEt, CH}_3\text{CN} \\
\text{2-7} &
\end{align*}\]

Meldrum's adduct 2-6 (5.62 kg, 17.8 mol) and 18 L of MeCN was charged to 100-L cylindrical vessel equipped with bubbler. 2.7 L (15.48 mol) of $i\text{Pr}_2\text{NEt}$ was then charged to slurry. Diazapinone HCl 2-5 (3.6 kg, 15.48 mol) was then charged to the homogeneous solution in one portion followed by 18 L of MeCN to rinse solids from side of flask. The slurry was heated to 40 °C and aged for at least 12 h. The reaction was then cooled to ambient temperature and 25 L of MTBE was charged to reaction followed by 14 L of water. The aqueous layer was discarded. The organics were washed with 25 L of 7 wt% NaHCO$_3$ and aqueous layer was discarded. The organics were washed with 25 L of 20 wt% NaCl and aqueous layer was discarded. The organics were then solvent switched into isopropanol for the subsequent step.
Step G: 4-[(2Z)-3-Amino-4-(2,4,5-trifluorophenyl)but-2-enoyl]-3-(2,2,2-trifluoroethyl)-1,4-diazepan-2-one (2-8)

5.3 kg (12.92 mol) of ketoamide 2-7 in MTBE layers were charged into a clean 72-L round-bottomed flask. During this charge, the MTBE was distilled away, maintaining an internal volume of about 26.5 L (5 L/kg). After completion of the charge and a rinse with about 0.5 L isopropanol, the solution was solvent-switched at the same constant volume to isopropanol, followed by azeotropic drying with IPA until Karl Fisher test was less than 5000 (about 75 L total volume solvent removed, 60 L IPA charged). To the heterogeneous mixture of ketoamide 2-7 in IPA was added 3.98 kg (51.67 mol) of ammonium acetate. The reaction was heated to 45 °C and aged 3 h. The reaction mixture was then cooled to room temperature, then quenched over 15 min with aqueous ammonium hydroxide (14.8M, 1.73 kg, 25.84 mol) while keeping the internal temperature below 30 °C. Enamine amide 2-8 was further crystallized by the slow addition of 26.5 L (5 L/kg) of water over 2 h. The crystallization mixture was aged at room temperature overnight. The batch was then filtered, slurry washed once with 10.6 L of 50/50 IPA/water (2 L/kg), displacement washed once with 10.6 L of 50/50 IPA/water (2 L/kg), then dried under active nitrogen overnight.

Step H: 4-[(3R)-3-(tert-Butyloxy carbonylamino)-4-(2,4,5-trifluorophenyl)butanoyl]-3-(2,2,2-trifluoroethyl)-1,4-diazepin-2-one (2-9 and 2-10)
To a 10-gallon autoclave was charged as a slurry mixture using 21.6 L of methanol, 4.4 kg (10.8 mol) of enamine amide 2-8, 2.47 kg (11.3 mol) of di-tert-butyl dicarbonate, and [Rh(cod)Cl]₂ (5.33 g, 10.8 mmol). The substrate mixture was degassed with 5 pump-purge cycles. Under an inert atmosphere, the (R,S)-tert-butyl Josiphos (12.3 g, 22.6 mol) was suspended in 0.4 L of degassed methanol in an inert transfer device. A rinse of 0.1 L was charged to the second container in the device. The ligand was transferred under inert conditions to the substrate/metal slurry in the autoclave. The entire mixture was purged twice. The autoclave was subjected to 100 psig of hydrogen gas at 20 °C for 18 h. The vessel was drained and the vessel was rinsed with 5-6 volumes of methanol. Chiral HPLC assay indicated that the stereogenic center to which the tert-butoxycarbonylamino group is attached was 98% optically pure and the ratio of 2-9 to 2-10 was about 1:1. The slurry was used directly in the next step.

**Step I:**

(3R)-4-[(3R)-3-(tert-Butyloxy carbonylamino)-4-(2,4,5-trifluorophenyl)butanoyl]-3-(2,2,2-trifluoroethyl)-1,4-diazepin-2-one (2-9)
Into a 100 L Buchi vessel was charged the slurry of 5.44 kg hydrogenation product mixture in about 24 L MeOH. The mixture was concentrated to about 20 L and then solvent-switched to EtOH with about 20 L of EtOH. The whole process took approximately two h and the resulting slurry was diluted with EtOH to about 35 L. After diluting the batch with EtOH to a total volume of about 55 L, NMR indicated that 5.9 wt% of MeOH was present in the final solvent system.

The ethanolic slurry was slowly heated to 70 °C and total dissolution occurred at about 68 °C. The resulting clear yellowish solution was slowly cooled at a rate of 5 °C/30 min and seeded. The cooling rate was kept constant at 5 °C/30 min (significant crystallization was observed at 60 °C) until the batch reached 40 °C. To the vigorously agitated slurry at 40 °C there was slowly charged 1N ethanolic NaOH prepared by mixing 2.7 L of EtOH, 81 g of water, and 1630 mL of ethanolic sodium ethoxide (purchased as 21 wt% solution and titrated to be 2.76 M). The slurry was further cooled to room temperature and agitated at this temperature for one h. To ensure complete epimerization, the slurry was chilled to 0 °C within two h and agitated at 0 °C overnight.

While maintaining the temperature at about 0 °C, the basic slurry was neutralized with 1N ethanolic HCl (prechilled to 0 °C) prepared by diluting 395 mL aqueous HCl (purchased as 37 wt% solution and titrated to be 11.39 M) with EtOH to 4.5 L. The addition rate was carefully controlled and the whole neutralization process, accompanied by frequent pH checking, took about 30 min. The pH of the slurry was tested to be about 5 after addition of about 95% amount of prepared HCl solution.

Another 40 L of EtOH was used to rinse off the splash on the wall of reaction vessel.

The neutral slurry was gradually heated to 70 °C and total dissolution of 2-9 and 2-10 was observed at 68 °C. The cloudy solution was slowly cooled at a rate of 5 °C/30 min and seeded with
about 10 g of 2-9 at 65 °C. The cooling rate was kept at 5 °C/30 min (significant crystallization occurred at about 60 °C) until the batch reached 20 °C. The thick slurry was brought to 0 °C and stirred at this temperature overnight.

The slurry was filtered and washed with 15 L EtOH (displacement wash), 2x15 L EtOH and 2x15 L water followed by 15 L EtOH. The wet cake was then allowed to stand under high vacuum suction (with N₂ bag) overnight, spread into four glass trays and further dried in oven (about 400 Torr, 40 °C, with N₂ flow) for 72 h. Among four trays of product dried in oven, one tray still contained about 4% water as tested by Karl Fisher and the rest of three trays all contained less than 0.8 wt% water. The tray containing wet product was further dried in oven (about 400 Torr, 40 °C, with N₂ flow) for 24 h and Karl Fisher-tested again (less than 0.5 wt% water). The product in four trays was combined. HPLC assay of final product indicated 99.5% pure 2-9.

Chiral HPLC conditions:
Column: Chiralpak AD-H (size: 4.6 x 250 nm) 5 µm packing
Eluent: 0 -15 min: 80% Heptane (with 0.1% DEA)/20% EtOH (with 0.1%DEA)
Flow rate: 1.0 mL/min
Temperature: 40 °C
Detector: UV detector @ 254 nm
Injection: 5 µL

Retention times:
(S,R) isomer: 6.72 min

(R,R) isomer: 7.65 min

(S,S) isomer: 8.20 min
(R,S) isomer: 9.17 min

Step 1: (3R)-4-[[3R]-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(2,2,2-trifluoroethyl)-1,4-diazepin-2-one, hydrochloride salt (2-11)

Into a 100 L cylindrical vessel equipped with reflux condenser, thermocouple and nitrogen inlet was charged 14 L IPA. Compound 2-9 (3.78 kg) isolated from epimerization Step I was portionwise introduced into the vessel and another 12.5 L of IPA was used to rinse off residual 2-9 on the funnel. Upon the completion of addition of starting material, HCl in IPA (2.24 L, purchased as 5 M solution in IPA and titrated to be 4.95 M) was charged to the slurry with sufficient stirring and the batch was heated to 75 °C. Although the temperature rose quickly from room temperature to about 70 °C, the internal temperature of the reaction was in the range of 70-75 °C for over two h and the thick white slurry turned into a slightly turbid yellow solution during this period due to presence of insoluble NaCl.
The reaction mixture was cooled to 10 to 20 °C. Evaporation gave 2-11 which exhibited a proton NMR spectrum identical to that reported in WO 04/037169.

Reversed phase HPLC conditions:

Column:
YMC ODS-AQ (size: 4.6 x 250 mm)
ODS-AQ-303-5 5 μm packing and 120A pore

Eluent:
0-10 min: 10% MeCN / 90% aqueous 0.1% H₃PO₄
10-20 min: 30% MeCN / 70% aqueous 0.1% H₃PO₄

Flow rate: 1.5 mL/min constant

Temperature: Ambient

Detector: UV detector @ 210 nm

Injection: 5 μL

Retention times:
Compound 2-11: 6.87 min;
R,S-isomer of 2-11: 7.08 min;
Compounds 2-9 and 2-10: 11.2 min.

EXAMPLE 2

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} \\
3-1 & \quad \text{NH} \\
\text{O} & \quad \text{NH} \\
\text{O} & \quad \text{Boc} \\
\text{t-BuO} & \\
3-2
\end{align*}
\]

0.2 mol% (R,S)-t-Butyl Josiphos
0.1 mol% [Rh(cod)Cl]₂
MeOH, 500 psig H₂, 40 °C
2 eq. (Boc)₂O

3-[N-(tert-Butyloxycarbonyl)amino]-N-phenylbutanamide (3-2)

Into a 30-mL autoclave were charged 1.0 g methyl enamine anilide (3-1) (5.67 mmol) under a nitrogen atmosphere. Di-t-butyldicarbonate (2.476 g, 11.34 mmol) was added. In a separate vial, [Rh(cod)Cl]₂ (18.19 mg, 0.0738 mmol of Rh) and (R,S)-t-butyl Josiphos (48.024 mg, 0.0886 mmol) were added followed by addition of 65 mL degassed MeOH. The catalyst solution was aged for 30 min under rigorous stirring. 10 mL of the catalyst solution was then added to the autoclave containing the enamine substrate. The autoclave was then sealed, placed into a preheated Omnical Reactmax Z6
calorimeter (40 °C) and connected to the hydrogen supply lines. The lines were initially purged with nitrogen followed by a leak test. The nitrogen pressure was released to ambient pressure. About 30 min after placing the autoclave into the instrument, the heat flow baseline was established and the vessels were pressurized simultaneously to the calorimetric reference cell to 459 psig with H₂. The head space was extended by 500 mL to insure constant pressure. Over the course of the reaction the pressure dropped about 2 psig. Assay yield was determined by HPLC to be 91.2% and optical purity to be 97% ee (HPLC conditions same as for Example 1).

A small sample of 3-2 was obtained by chromatographic methods for characterization purposes; mp 167-167.8 °C.

$^1$H-NMR (400 MHz, CDCl₃): δ 7.97 (broad, 1H), 7.54 (d, $J = 8$ Hz, 2H), 7.32 (t, 2H), 7.10 (t, 1H), 5.02 (broad, 1H), 4.07 (m, 1H), 2.60 (d, $J = 5.9$ Hz, 2H), 1.44 (s, 9H), 1.30 (d, $J = 7$ Hz, 3H); $^{13}$C-NMR (101 MHz, CDCl₃): δ 169.1, 155.7, 137.8, 128.8, 124.2, 119.9, 79.7, 44.5, 28.3, 20.9.

**EXAMPLES 3-12**
<table>
<thead>
<tr>
<th>Ex.</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Z</th>
<th>% yield</th>
<th>% ee</th>
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<tr>
<td>3</td>
<td>Me</td>
<td>NHPh</td>
<td>63&lt;sup&gt;c&lt;/sup&gt;</td>
<td>97</td>
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<tr>
<td>5</td>
<td>Me</td>
<td>NHPh</td>
<td>84</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>NHPh</td>
<td>97</td>
<td>97</td>
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<td>Ph</td>
<td>OMe</td>
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<sup>a</sup> Reaction conditions: 0.5 M in methanol, 1.1 equiv. of Boc<sub>2</sub>O, 0.2 mol % [Rh(cod)Cl]<sub>2</sub>, 0.41 mol% (R,S)-t-Bu Josphios, 20 °C, 90-100 psi H<sub>2</sub>, 18 h. <sup>b</sup> HPLC assay yield. <sup>e</sup> Boc<sub>2</sub>O added after hydrogenation was complete. <sup>d</sup> Performed at 40 psig H<sub>2</sub> on 5 mmol scale. <sup>g</sup> GC assay yield. <sup>f</sup> With 0.8 mol/% catalyst. <sup>g</sup> With 3.0 mol/% catalyst.
WHAT IS CLAIMED IS:

1. A process for preparing a compound of structural formula III:

   ![Structural Formula III](image)

   having the (R)-configuration at the stereogenic centers marked with an * and **; wherein
   Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected
   from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
   \( R^9 \) is \( C_{1-4} \) alkyl unsubstituted or substituted with one to five fluorines;
   comprising the steps of:

   (a) producing a compound of structural formula XV:

   ![Structural Formula XV](image)

   wherein Boc represents a \( \text{tert-} \)butyloxycarbonyl protecting group;
   by treating a mixture of compounds of structural formulae XV and XVI:

   ![Structural Formula XV and XVI](image)

   with base in an organic solvent followed by crystallization of said compound of structural formula XV;
   and

   (b) cleavage of said \( \text{tert-} \)butyloxycarbonyl protecting group in said compound of structural formula XV:
to afford said compound of structural formula III.

2. The process of Claim 1 additionally comprising the step of producing said mixture of compounds of structural formulae XV and XVI:

\[
\text{XV}
\]

\[
\text{XVI}
\]

by hydrogenation of a compound of structural formula XIV:

\[
\text{XIV}
\]

in a suitable organic solvent in the presence of a tert-butylcarbonylating reagent and a transition metal catalyst complexed to a chiral ferrocenyldiphosphine ligand of structural formula V:

\[
\text{V}
\]

wherein the stereogenic center marked with a *** has the (R)-configuration; R\(^4\) is C\(_1-4\) alkyl or aryl; R\(^5\) and R\(^6\) are each independently C\(_1-6\) alkyl, C\(_5-12\) cycloalkyl, or aryl; and R\(^7\) is C\(_1-4\) alkyl or aryl; and wherein said tert-butylcarbonylating reagent is added prior to, during, or after said hydrogenation.

3. The process of Claim 2 additionally comprising the step of producing a compound of structural formula XIV:
by treating a compound of structural formula XI:

with a source of ammonia in a suitable organic solvent.

4. The process of Claim 3 additionally comprising the step of producing a compound of structural formula XI:

by treating a compound of structural formula XII:

with a compound of structural formula XIII:

in a suitable organic solvent.
5. The process of Claim 1 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R^9 is 2,2,2-trifluoroethyl.

6. The process of Claim 2 wherein said transition metal catalyst is [M(cod)Cl]_2, [M(norbornadiene)Cl]_2, [M(cod)]_2X, or [M(norbornadiene)2]X wherein X is methanesulfonate, trifluoromethanesulfonate, tetrafluoroborate, hexafluorophosphate, or hexafluoroantimonate and M is rhodium, iridium, or ruthenium.

7. The process of Claim 6 wherein said transition metal catalyst is [Rh(cod)Cl]_2.

8. The process of Claim 2 wherein R^4 is methyl, R^5 and R^6 are i-butyl, and R^7 is phenyl.

9. The process of Claim 5 wherein said transition metal catalyst is [Rh(cod)Cl]_2 and said chiral ferrocenyl diphosphine ligand is R,S-i-butyl Josiphos.

10. The process of Claim 3 wherein said source of ammonia is ammonium acetate.

11. A process for preparing a compound of structural formula III:

   ![Chemical Structure](image)

   having the (R)-configuration at the stereogenic centers marked with an * and **; wherein
   Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
   R^9 is C_1-4 alkyl unsubstituted or substituted with one to five fluorines;
   comprising the steps of:
   (a) producing a compound of structural formula XI:

   ![Chemical Structure](image)
by treating a compound of structural formula XII:

(XII)

with a compound of structural formula XIII:

(XIII)

5 in a suitable organic solvent;
(b) producing a compound of structural formula XIV:

(XIV)

by treating said compound of structural formula XI:

(XI)

10 with a source of ammonia in a suitable organic solvent;
(c) producing a mixture of compounds of structural formulae XV and XVI:

(XV)  (XVI)
wherein Boc represents a tert-butyloxycarbonyl protecting group;
by hydrogenation of said compound of structural formula XIV:

\[
\text{Ar} \begin{array}{c}
\text{NH}_2 \\
\text{O} \\
\text{R}^9 \\
\text{NH}
\end{array}
\begin{array}{c}
\text{N} \\
\text{O}
\end{array} \\
\text{(XIV)}
\]

in a suitable organic solvent in the presence of a tert-butylcarbynylating reagent and a transition metal
complexed to a chiral ferrocenyldiphosphine ligand of structural formula V:

\[
\begin{array}{c}
\text{Fe} \\
\text{PR}^5 \text{R}^6 \\
\text{P(R}^7\text{)}_2
\end{array}
\]

\[
\text{(V)}
\]

wherein the stereogenic center marked with a *** has the (R)-configuration;
R\(^4\) is C\(_{1-4}\) alkyl or aryl;
R\(^5\) and R\(^6\) are each independently C\(_{1-6}\) alkyl, C\(_{5-12}\) cycloalkyl, or aryl; and
R\(^7\) is C\(_{1-4}\) alkyl or aryl; and wherein said tert-butylcarbynylating reagent is added prior to, during, or
after said hydrogenation;
(d) producing a compound of structural formula XV:

\[
\text{Ar} \begin{array}{c}
\text{NH} \\
\text{O} \\
\text{R}^9 \\
\text{NH}
\end{array}
\begin{array}{c}
\text{N} \\
\text{O}
\end{array} \\
\text{(XV)}
\]

by treating said mixture of compounds of structural formulae XV and XVI:
with base in an organic solvent followed by crystallization of said compound of structural formula XV; and

(e) cleavage of said tert-butyloxy carbonyl protecting group in said compound of structural formula XV:

\[
\begin{align*}
\text{Boc} & \quad \text{NH} \\
\text{Ar} & \quad \text{O} \\
& \quad \text{N} \\
& \quad \text{R}^9 \\
\end{align*}
\]

\[(XV)\]

5 to afford said compound of structural formula III.

12. A compound of structural formula XI:

\[
\begin{align*}
\text{Ar} & \quad \text{O} \\
& \quad \text{N} \\
& \quad \text{R}^9 \\
\end{align*}
\]

\[(XI)\]

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and R\(^9\) is C\(_{1-4}\) alkyl unsubstituted or substituted with one to five fluorines.

13. The compound of Claim 12 wherein Ar is 2,4,5-trifluorophenyl and R\(^9\) is 2,2,2-trifluoroethyl.

14. A compound of structural formula XIV:

\[
\begin{align*}
\text{Ar} & \quad \text{NH}_2 \\
& \quad \text{O} \\
& \quad \text{N} \\
& \quad \text{R}^9 \\
\end{align*}
\]

\[(XIV)\]

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy; and R\(^9\) is C\(_{1-4}\) alkyl unsubstituted or substituted with one to five fluorines.

15. The compound of Claim 14 wherein Ar is 2,4,5-trifluorophenyl and R\(^9\) is 2,2,2-trifluoroethyl.
16. The process of Claim 1 wherein said compound of structural formula III is obtained in the form of a hydrogen chloride addition salt.

17. The process of Claim 1 wherein said compound of structural formula III is converted into a pharmaceutically acceptable salt thereof.

18. A process for preparing a compound of structural formula I:

![Structural formula I](image)

having the (R)- or (S)-configuration at the stereogenic center marked with an *;
in an enantiomeric excess of at least 70% over the opposite enantiomer, wherein
R\(^a\) is C\(_1\)-C\(_4\) alkyl, aryl, arylmethyl, C\(_1\)-C\(_4\) alkoxy, allyloxy, and 9-fluorenylmethyloxy;
Z is OR\(^2\) or NR\(^2\)R\(^3\);
R\(^1\) is C\(_1\)-C\(_8\) alkyl, aryl, heteroaryl, aryl-C\(_1\)-C\(_2\) alkyl, or heteroaryl-C\(_1\)-C\(_2\) alkyl;
R\(^2\) and R\(^3\) are each independently hydrogen, C\(_1\)-C\(_8\) alkyl, aryl, or aryl-C\(_1\)-C\(_2\) alkyl; or R\(^2\) and R\(^3\) together
with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclic ring system optionally containing an additional heteroatom selected from O, S, NH, and NC\(_1\)-C\(_4\) alkyl, said
heterocyclic ring being unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, C\(_1\)-C\(_4\) alkoxy, and C\(_1\)-C\(_4\) alkyl wherein alkyl and alkoxy are unsubstituted or
substituted with one to five fluorines; and said heterocyclic ring system being optionally fused with a 5-
to 6-membered saturated or aromatic carbocyclic ring system or a 5- to 6-membered saturated or aromatic
heterocyclic ring system containing one to two heteroatoms selected from O, S, and NC\(_0\)-C\(_4\) alkyl, said
fused ring system being unsubstituted or substituted with one to two substituents selected from hydroxy,
amino, fluorine, C\(_1\)-C\(_4\) alkyl, C\(_1\)-C\(_4\) alkoxy, and trifluoromethyl;

comprising the step of hydrogenating a prochiral enamine of structural formula II:

![Structural formula II](image)

in a suitable organic solvent in the presence of an R\(^a\) carboxylating reagent and a transition metal
precursor complexed to a chiral ferrocenyl diphosphine ligand of structural formula IV:
wherein $R^4$ is C$_{1-4}$ alkyl or aryl;
$R^5$ and $R^6$ are each independently C$_{1-6}$ alkyl, C$_{5-12}$ cycloalkyl, or aryl; and
$R^7$ is C$_{1-4}$ alkyl or aryl; and

5 wherein said $R^4$ carbonylating reagent is added prior to, during, or after said hydrogenation.

19. The process of Claim 18 wherein said ferrocenyl diphosphine ligand is of structural formula V:

\[
\begin{align*}
\text{Fe} & \quad \text{P} \quad \text{PR}^5 \text{R}^6 \\
\text{Fe} & \quad \text{P} \quad \text{PR}^7_2
\end{align*}
\]

(V)

wherein the stereogenic center marked with an *** has the (R)-configuration.

20. The process of Claim 19 wherein $R^4$ is methyl, $R^5$ and $R^6$ are $t$-butyl, and $R^7$ is unsubstituted phenyl.

21. The process of Claim 18 wherein $R^1$ is benzyl wherein the phenyl group of benzyl is unsubstituted or substituted one to three substituents selected from the group consisting of fluorine, trifluoromethyl, and trifluoromethoxy.

22. The process of Claim 18 wherein $Z$ is NR$^2$R$^3$.

23. The process of Claim 22 wherein NR$^2$R$^3$ is a heterocycle of the structural formula VII:
wherein $R^8$ is hydrogen or C$_{1-4}$ alkyl which is unsubstituted or substituted with one to five fluorines.

24. The process of Claim 22 wherein NR$^2$R$^3$ is a heterocycle of the structural formula VIII:

\[
\begin{align*}
\text{VIII} & \\
\text{wherein } R^9 \text{ is C}_{1-4} \text{ alkyl unsubstituted or substituted with one to five fluorines.}
\end{align*}
\]

25. The process of Claim 18 wherein said R$^a$ carbonylating reagent is added prior to said hydrogenation.

26. The process of Claim 18 wherein said R$^a$ carbonylating reagent is a symmetrical carbonic acid anhydride.

27. The process of Claim 26 wherein said symmetrical carbonic acid anhydride is di-tert-butyl dicarbonate.

28. The process of Claim 25 wherein said R$^a$ carbonylating reagent is di-tert-butyl dicarbonate.