**Title:** PROCESS FOR THE PREPARATION OF SUBSTITUTED KETO-ENAMINES

The present invention discloses a process for the preparation of a substantially pure compound having formula (4). The process comprises the step of reacting an enolate having formula (A) with a Grignard reagent. The enolate salt is formed in situ from the reaction of a protected ester wherein M is an alkali metal. R₆ and R₇ are each hydrogen or are independently selected from (i) wherein R₆ and R₇ are independently selected from hydrogen, lower alkyl and phenyl and R₆, R₇ and R₈ are independently selected from hydrogen, lower alkyl, trifluoromethyl, alkoxy, halo and phenyl; and (ii) wherein the naphthyl ring is unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, trifluoromethyl, alkoxy and halo. Alternatively, R₆ is as defined above and R₇ is R₁₂OC(O)⁻ wherein R₁₂ is benzyl; or R₆ and R₇ taken together with the nitrogen atom to which they are bonded form (B) or (C), wherein R₆, R₇, R₈ and R₉ are independently selected from hydrogen, lower alkyl, alkoxy, halogen and trifluoromethyl.
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PROCESS FOR THE PREPARATION OF SUBSTITUTED KETO-ENAMINES

Technical Field

The present invention relates to a process for the preparation of an enamine intermediate which is useful for the preparation of substituted 2,5-diamino-3-hydroxyhexanes.

Background of the Invention

Compounds which are inhibitors of human immunodeficiency virus (HIV) protease are useful for inhibiting HIV protease in vitro and in vivo and are useful for inhibiting an HIV infection. Certain HIV protease inhibitors comprise a moiety which is a substituted 2,5-diamino-3-hydroxyhexane. HIV protease inhibitors of particular interest are compounds having formula 1:

![Chemical Structure](image)

wherein A is R₂NHCH(R₁)C(O)- and B is R₂a or wherein A is R₂a and B is R₂NHCH(R₁)C(O)- wherein R₁ is lower alkyl and R₂ and R₂a are independently...
selected from -C(O)-R₃-R₄ wherein at each occurrence R₃ is independently selected from O, S and -N(R₅)- wherein R₅ is hydrogen or lower alkyl and at each occurrence R₄ is independently selected from heterocyclic or (heterocyclic)alkyl; or a pharmaceutically acceptable salt, prodrug or ester thereof. Compounds of formula 1 are disclosed in U.S. Patent No. 5,354,866, issued October 11, 1994, U.S. Patent No. 5,541,206, issued July 30, 1996, and U.S. Patent No. 5,491,253, issued February 13, 1996.

A preferred HIV protease inhibitor having formula 1 is a compound of formula 2a:

![Chemical Structure 2a]

or a pharmaceutically acceptable salt, prodrug or ester thereof.

Another preferred HIV protease inhibitor of formula 1 is a compound of formula 2b:

![Chemical Structure 2b]

The compound having formula 2b is disclosed in U.S. Patent No. 5,421,206, issued July 30, 1996.

An intermediate which is especially useful for preparing compounds having formula 1 and 2 is a substantially pure compound having the formula 3:

-2-
wherein $R_6$, $R_7$ and $R_8$ are independently selected from hydrogen and N-protecting groups, such as, for example, t-butyloxycarbonyl (Boc), benzyl and the like; or an acid addition salt thereof. The preparation of compounds having formula 3 has been disclosed in U.S. Patent 5,491,253, issued February 13, 1996 (the '253 patent).

The procedure disclosed in the '253 patent starts with a protected L-phenylalanine benzyl ester. The ester is reacted with an $\alpha$-carbanion of acetonitrile in an inert solvent to provide a ketonitrile, shown below.

Reaction of the ketonitrile with a benzyl Grignard, usually more than about 3 equivalents, provides the enamine product. The enamine can be readily transformed into compound 3.

An object of the present invention is to provide a simple method for the preparation of enamines which can be converted into diaminols having formula 3.

An object of the present invention is to provide a method for the preparation of enamines which provides the enamines in high yield.
Summary of the Invention

The present invention discloses a process for the preparation of a substantially pure compound having formula 4:

4

The process comprises the step of reacting an enolate having the formula:

with a Grignard reagent. The enolate salt is formed in situ from a protected ester with a metal amide, MNH₂, where M is a metal cation. R₆ and R₇ are each hydrogen or are independently selected from

wherein Rₐ and R₇ are independently selected from hydrogen, lower alkyl and phenyl and R₉, R₁₀ and R₆ are independently selected from hydrogen, lower alkyl, trifluoromethyl, alkoxy, halo and phenyl; and
wherein the naphthyl ring is unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, trifluoromethyl, alkoxy and halo. Alternatively, R₆ is as defined above and R₇ is R₁₂OC(O)- wherein R₁₂ is benzyl; or R₆ and R₇ taken together with the nitrogen atom to which they are bonded form

wherein Rᵢ, Rᵢᵢ, Rᵢᵢᵢ and Rᵢᵢᵢᵢ are independently selected from hydrogen, lower alkyl, alkoxy, halogen and trifluoromethyl with the proviso that R₆ and R₇ cannot both be hydrogen.

R₁₄ is a hydrocarbyl group capable of forming a Grignard reagent. The preferred R₁₄ groups are selected from the group consisting of alkyl, substituted alkyl, alkyaryl, such as, benzyl, and substituted benzyl, aryl, such as, phenyl, substituted phenyl, naphthyl and substituted naphthyl. R₁₅ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkaryl, such as, benzyl, and substituted benzyl, aryl, such as, phenyl, substituted phenyl, naphthyl and substituted naphthyl. The process of the invention also includes the preparation of acid addition salts of compound 4.

**Detailed Description of the Invention**

All patents, patent applications, and literature references cited in the specification are hereby incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.
The present invention relates to a process for the preparation of a compound having formula 4.

![Diagram of molecule 4]

In the process of the invention R₆ and R₇ are hydrogen or are independently selected from

![Diagram of substituted group]

wherein Rₐ and Rₐ are independently selected from hydrogen, lower alkyl and phenyl and Pₐ, Rₐ and Rₐ are independently selected from hydrogen, lower alkyl, trifluoromethyl, alkoxy, halo, and phenyl; and

![Diagram of naphthyl ring]

wherein the naphthyl ring is unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, trifluoromethyl, alkoxy, and halo; or

R₆ is as defined above and R₇ is R₇aOC(O)⁻ wherein R₇a is lower alkyl or benzyl; or

R₆ and R₇ taken together with the nitrogen atom to which they are bonded are

-6-
wherein \( R_f, R_g, R_h \) and \( R_i \) are independently selected from hydrogen, lower alkyl, alkoxy, halogen, and trifluoromethyl; with the proviso that \( R_6 \) and \( R_7 \) cannot both be hydrogen.

\( R_{14} \) is a hydrocarbyl group capable of forming a Grignard reagent. The preferred \( R_{14} \) groups are selected from the group consisting of alkyl, substituted alkyl, alkaryl, such as, benzyl, and substituted benzyl, aryl, such as, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

\( R_{15} \) is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkaryl, such as, benzyl, and substituted benzyl, aryl, such as, phenyl, substituted phenyl, naphthyl and substituted naphthyl. The process of the invention also includes the preparation of acid addition salts of compound 4.

Examples of suitable substituents for substitution on the alkyl, phenyl, benzyl, and naphthyl groups include but are not limited to lower alkyl, aryl, cycloalkyl, alkoxy, alkoxyalkoxy, thioalkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, and the like. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl. The alkyl groups can be optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur, and phosphorous.

The Grignard reagents which can be used in practicing the present invention are having the formula \( R_{14} \text{MgX} \) where \( R_{14} \) is as defined above and \( X \) is a halogen atom. The halogen atoms which are useful in practicing this invention include chlorine, bromine, and iodine.

Examples of metal cations which are useful in practicing the present invention include, but are not limited to, Group I alkali metals such as, for example, sodium, lithium, potassium, and the like. The preferred metals are sodium, and potassium.
A preferred form of compound 4 is the compound 4a:

![Chemical Structure](image)

where R₆ and R₇ are independently selected from benzyl and substituted benzyl, wherein the phenyl ring of the benzyl group is substituted with one, two or three substituents independently selected from lower alkyl, trifluoromethyl, alkoxy, halo and phenyl and R₈ is hydrogen, benzyl substituted benzyl, or -C(O)R₉ wherein R₉ is lower alkyl, alkoxy, or phenyl, wherein the phenyl ring is unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, trifluoromethyl, alkoxy and halo.

A more preferred form of compound 4a is a compound where R₆ and R₇ are benzyl and R₈ is hydrogen or t-butyloxy carbonyl.

The general process of the invention is illustrated in Scheme I. Protection of the amino group in an L-amino acid and esterification provides compound III. Reaction of III with from about 1.05 to about 1.5 equivalents, preferably from about 1.1 to about 1.3 equivalents, of an α-carbanion of acetonitrile in a suitable solvent provides the enolate-nitrile intermediate I. The reaction is then concentrated and ammonia is removed. Reaction of enolate-nitrile I with about 1.0 to about 3.5 equivalents of Grignard reagent (i.e., R₄MgX) provides enamine 4. The preferred amount of Grignard reagent is from about 1.25 to about 3.0 equivalents and most preferred is from about 1.5 to about 2.5 equivalents based on the number of equivalents of protected L-amino acid.
A preferred embodiment for preparing the enamine of the invention having formula 4a is illustrated in Scheme II. The amino group in L-phenylalanine is protected as the dibenzyl amine, and the acid group is simultaneously esterified, i.e., R, R6 and R7 are benzyl, to provide compound 5. Reaction of 5 with the $\alpha$-carbonion of acetonitrile (about 2.2 equivalents) in an inert solvent, such as, methyl tert-butyl ether (MTBE), provides nitrile-enolate, 6a. Preferably the acetonitrile
anion is prepared from sodium or potassium amide (NaNH₂ or KNH₂). Most preferred is sodium amide. Reaction of the nitrile-enolate, 6a with about 1.5 equivalents of benzyl Grignard (for example, benzyl magnesium chloride) provides enamine, 4a.

The amount of acetonitrile carbanion required is from about 1.0 to about 2.0 equivalents, preferably, from about 1.1 to about 1.5 equivalents. The amount of Grignard reagent required is from about 1.0 to about 3.5 equivalents. The preferred amount of Grignard reagent is from about 1.25 to about 3.0 equivalents and most preferred is from about 1.5 to about 2.5 equivalents, based on the number of equivalents of protected L-amino acid.

Suitable inert solvents for use in the process of the invention include dialkyl ether solvents, such as, for example, methyl ether, ethyl ether, propyl ether, n-butyl ether, methyl n-butyl ether, methyl tert-butyl ether (MTBE), pentyl ether, hexyl ether, dimethoxymethane and the like; a mixture of a solvent such as, for example, tetrahydrofuran (THF), dioxane and the like with an alkyl or cycloalkyl solvent such as, for example, pentane, cyclopentane, hexane, cyclohexane, heptane, and the like. The preferred solvents are the alkyl ethers. A preferred solvent is MTBE.
SCHEME II

\[
\text{L-Phenylalanine} \xrightarrow{\text{PhCH}_2\text{Cl}/\text{K}_2\text{CO}_3} \xrightarrow{\text{H}_2\text{O}} \text{R}_6^+\text{N}^+\text{R}_7^- \xrightarrow{\text{R}_6^+\text{R}_7^+} \text{R}_6^-\text{R}_7^- \xrightarrow{\text{NaNH}_2, \text{CH}_3\text{CN}/\text{MTBE}} \text{R}_6^+\text{R}_7^- \xrightarrow{\text{PhCH}_2\text{MgX}, \text{THF}} \text{R}_6^-\text{R}_7^- \xrightarrow{\text{R}_6^+\text{R}_7^+} \]

Several processes for the conversion of compounds having formula \textbf{4a} to the hydroxy-diamine, compounds having formula \textbf{3}, are disclosed in U.S. Patent No. 5,354,866, U.S. Patent No. 5,541,206, and U.S. Patent No. 5,491,253. The processes for the preparation of compounds having formula \textbf{4a} disclosed in these patents disclose the purification and isolation of the cyano-ketone \textbf{6} prior to conversion to the enamine, \textbf{4a}. This process is illustrated in Scheme III. The
elimination of the additional step of isolating of the nitrile increases the yield by about 20% and reduces the amount of reagents needed to conduct the reaction, particularly the amount of Grignard reagent required, by about 50%.

**SCHEME III**

\[ \text{L-Phenylalanine} \xrightarrow{\text{PhCH}_2\text{Cl/K}_2\text{CO}_3} \text{H}_2\text{O} \xrightarrow{} \text{CO}_2\text{R} \]

\[ R_6 = R_7 = R = \text{Benzyl} \]

\[ \text{5} \xrightarrow{\text{NaNH}_2} \xrightarrow{\text{CH}_3\text{CN/MTBE}} \]

\[ \text{CN} \]

\[ R_6 = R_7 = \text{Benzyl} \]

\[ \text{6} \xrightarrow{\text{PhCH}_2\text{MgX}} \xrightarrow{\text{THF}} \]

\[ \text{NH}_2 \]

\[ R_6 = R_7 = \text{Benzyl} \]

\[ \text{4a} \]

The term "alkyl", as used herein, refers to straight or branched chain alkyl radicals containing from 1 to 12 carbon atoms. The term "lower alkyl" refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms.
including, but not limited to, methyl, ethyl, \textit{n}-propyl, \textit{iso}-propyl, \textit{n}-butyl, \textit{iso}-butyl, sec-butyl, t-butyl \textit{n}-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, \textit{n}-hexyl, and the like. The alkyl groups can be optionally interrupted by one or more heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur, and phosphorous.

The term "aryl", as used herein, refers to an unsubstituted carbocyclic aromatic radical, including, for example, phenyl and 1- or 2-naphthyl.

The term "cycloalkyl", as used herein, refers to a saturated monocyclic hydrocarbon radicals having from three to eight carbon atoms in the ring and optionally substituted with between one and three additional radicals selected from among alkaryl, alkoxy, loweralkyl, halo, alkylamino, hydroxy-substituted alkyl, hydroxy, alkoxy, halogen, and amino, dialkylamino and the like. Cycloalkyl radicals include, groups such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 1-fluorocyclopropyl, 2-fluorocyclopropyl, 2-amino-cyclopropyl and the like.

The term "alkoxy" as used herein, refers to groups having the formula \(-\text{OR}_{10}\) wherein \(R_{10}\) is a lower alkyl group.

The term "thioalkoxy" as used herein, refers to groups having the formula \(-\text{SR}_{11}\) wherein \(R_{11}\) is a lower alkyl group.

The term "alkoxyalkoxy" as used herein, refers to groups having the formula \(-\text{OR}_{16}\text{-OR}_{10}\) wherein \(R_{16}\) is a lower alkylene group \(R_{10}\) is a lower alkyl group.

The term "alkaryl" refers to a loweralkyl radical having appended thereto an aromatic hydrocarbon group, as for example benzyl and phenylethyl.

The term "alkylamino" as used herein, refers to groups having the formula \(-\text{NHR}_{17}\) wherein \(R_{17}\) is a lower alkyl group.

The term "dialkylamino" as used herein, refers to groups having the formula \(-\text{N(R}_{17})_{2}\) wherein each \(R_{17}\) is independently a lower alkyl group.

The term "arylamino" as used herein, refers to groups having the formula \(-\text{NHR}_{18}\) wherein \(R_{18}\) is an aryl group.

The term "diarylamo" as used herein, refers to groups having the formula \(-\text{N(R}_{18})_{2}\) wherein each \(R_{18}\) is independently an aryl group.
The term "alkylaryl amino" as used herein refers to groups having the formula -(R_17R_18)_2 wherein one R_17 is an alkyl group and the other R_18 is an aryl group.

The term "halo", as used herein, refers to F, Cl, Br or I.

The term "acid addition salts", as used herein, are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, perchloric acid, and the like, or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, malonic acid, and the like, or by using other methods used in the art such as ion exchange.

The term "haloalkyl", as used herein, refers to a lower alkyl group in which one or more hydrogen atoms has been replaced with a halogen including, but not limited to, trifluoromethyl, trichloromethyl, difluoromethyl, dichloromethyl, fluoromethyl, chloromethyl, chloroethyl, 2,2-dichloroethyl and the like.

The term "halophenyl", as used herein, refers to a phenyl group in which one, two, three, four or five hydrogen atoms have been replaced with a halogen including, but not limited to, chlorophenyl, bromophenyl, fluorophenyl, iodosphenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,3,5-trichlorophenyl, 2,4,6-trichlorophenyl, 2-chloro-4-fluorophenyl, 2-chloro-6-fluorophenyl, 2,4-dichloro-5-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,5-trichlorophenyl, 2,4,6-trichlorophenyl, 2,3,4-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2,3,4,5-tetrafluorophenyl, 2,3,5,6-tetrafluorophenyl, pentafluorophenyl and the like.

The term "N-protecting group" or "N-protected", as used herein, refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in T.H. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley & Sons, New York (1991) N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl,
trichloroacetyl, phthalyl, o-nitrophenoxycetetyl, \(\alpha\)-chlorobutyryl, benzoyl, 
4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups 
such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming 
groups such as benzyloxy carbonyl, p-chlorobenzyloxy carbonyl, p-methoxy-
benzylloxy carbonyl, p-nitrobenzylloxy carbonyl, 2-nitrobenzylloxy carbonyl, 
p-bromobenzyloxy carbonyl, 3,4-dimethoxybenzylloxy carbonyl, 3,5-dimethoxy-
benzylloxy carbonyl, 2,4-dimethoxybenzylloxy carbonyl, 4-methoxybenzylloxy-
carbonyl, 2-nitro-4,5-dimethoxybenzylloxy carbonyl, 3,4,5-trimethoxybenzylloxy-
carbonyl, 1-(p-biphenyl)-1-methylethoxy carbonyl, \(\alpha,\alpha\)-dimethyl-3,5-dimethoxy-
benzylloxy carbonyl, benzhydryloxy carbonyl, t-butyloxy carbonyl, diisopropyl-
methoxy carbonyl, isopropylloxy carbonyl, ethoxy carbonyl, methoxycarbonyl, 
allyloxy carbonyl, 2,2,2-trichloro ethoxy carbonyl, phenoxy carbonyl, 4-nitro-phen-
oxycarbonyl, fluorenlyl-9-methoxycarbonyl, cyclopentylloxy carbonyl, adamantyl-
oxycarbonyl, cyclohexyloxy carbonyl, phenylthiocarbonyl and the like; alkyl groups 
such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups 
such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, 
benzoyl, pivaloyl, t-butyacetyl, phenylsulfonyl, benzyl, t-butyloxy carbonyl (Boc) 
and benzyloxy carbonyl (Cbz).

As used herein, the terms "S" and "R" configuration are as defined by the 
IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure 

The reagents required for the synthesis of the compounds of the invention 
are readily available from a number of commercial sources such as Aldrich 
Chemical Co. (Milwaukee, WI, USA); Sigma Chemical Co. (St. Louis, MO, USA); 
and Fluka Chemical Corp. (Ronkonkoma, NY, USA); Alfa Aesar (Ward Hill, MA 
01835-9953); Eastman Chemical Company (Rochester, New York 14652-3512); 
Lancaster Synthesis Inc. (Windham, NH 03087-9977); Spectrum Chemical 
Manufacturing Corp. (Janssen Chemical) (New Brunswick, NJ 08901); Pfaltz and 
Bauer (Waterbury, CT. 06708). Compounds which are not commercially available 
can be prepared by employing known methods from the chemical literature.
The following examples illustrate the process of the invention, without limitation.

**Example 1**

**(L)-N,N-Dibenzylphenylalanine benzyl ester**

A solution containing L-phenylalanine (161 kg, 975 moles), potassium carbonate (445 kg, 3220 moles), water (675 L), ethanol (340 L), and benzyl chloride (415 kg, 3275 moles) was heated to 90±15°C for 10-24 hours. The reaction mixture was cooled to 60°C and the lower aqueous layer was removed. Heptane (850 L) and water (385 L) were added to the organic layer, stirred, and the layers separated. The organic layer was washed once with a water/methanol mixture (150 L/150 L). The organic layer was removed to provide the title product as an oil. This was carried on in the next step without purification.

Results are illustrated below.

1H NMR (300 MHz, CDCl3) δ 7.5-7.0 (m, 20H), 5.3 (d, 1H, J = 13.5 Hz), 5.2 (d, 1H, J = 13.5 Hz), 4.0 (d, 2H, J = 15 Hz), 3.8 (t, 2H, J = 8.4 Hz), 3.6 (d, 2H, J = 15 Hz), 3.2 (dd, 1H, J = 8.4, 14.4 Hz).

13C NMR (300 MHz, CDCl3) δ 172.0, 139.2, 138.0, 135.9, 129.4, 128.6, 128.5, 128.4, 128.2, 128.1, 126.9, 126.2, 66.0, 62.3, 54.3, 35.6.

IR (neat) 3090, 3050, 3030, 1730, 1495, 1450, 1160 cm⁻¹.

[α]D -79° (c = 0.9, DMF).

**Example 2**

**(2S)-5-amino-2-(N,N-dibenzyl)amino-3-oxo-1,6-diphenylhex-4-ene**

A solution comprising (L)-N,N-dibenzyl-phenylalanine benzyl ester (0.24 mole) in 85 mL methyl tert-butyl ether (MTBE) and 13.9 mL, 270 mmole, of acetonitrile was slowly added to a slurry of 90% sodium amide (22.9 g, 0.53 mole) in 185 mL MTBE, keeping the temperature below 0°C. This was stirred for 90 minutes at -5 to 0°C.

The volatile materials were removed, and the reaction volume reduced by about 25%, by vacuum distillation. Benzyl magnesium chloride solution (360 mL; 1M in tetrahydrofuran (THF)) was added to the slurry. The solution was stirred for 6 hours. The excess benzyl magnesium chloride was quenched with a solution of
120 g of citric acid in 630 mL water. The aqueous layer was separated and the
organic layer concentrated. The resulting product was crystallized from ethanol to
provide 90 g (80%) of (2S)-5-amino-2-(N,N-dibenzyl)amino-3-oxo-1,6-
diphenylhex-4-ene (enamine).

Results are illustrated below.

$^1$H NMR (CDCl$\textsubscript{3}$) 9.80 (br s, 1H), 7.45-7.05 (m, 20H), 5.10 (s, 1H), 4.90 (br s,
1H), 3.75 (d, J=15Hz, 2H), 3.65 (d, J=15Hz, 2H), 3.55-3.45 (m, 3H), 3.15 (dd, J=7.2,
13.2Hz, 1H), 2.97 (dd, J=7.2, 13.2Hz, 1H).

$^{13}$C NMR (CDCl$\textsubscript{3}$) 198.2, 162.8, 140.2, 140.1, 135.7, 129.5, 129.3, 128.9,
128.7, 128.1, 128.0, 127.3, 126.7, 125.6, 96.9, 66.5, 54.3, 42.3, 32.4.

IR (film) 3620, 3480, 3030, 1615, 1595, 1520, 1495, 1455 cm$^{-1}$.

MS (Cl) m/e (rel. int.) 461 ((M+H)$^+$, 100), 196 (10).

HPLC ee 100% (Chiracel OD column, 10% iPrOH/Hexanes).

Example 3

(2S)-5-Amino-2-(N,N-dibenzyl)amino-3-oxo-1-phenylhex-4-ene

The title compound was prepared from (L)-N,N-dibenzyl-phenylalanine
benzyl ester, 46.0 mmole, and 2.6 mL, 50 mmole, of acetonitrile. Following the
procedure described in Example 2 the ester and nitrile mixture was added to
4.4 g, 101 mmole of sodium amide in MTBE. Methyl Grignard (CH$_3$MgCl 150
mmole) was substituted for benzyl magnesium chloride. The resulting enamine
was crystallized from heptane. The yield of enamine was 17 g (43 mmole, 93%).

Results are illustrated below.

$^1$H NMR (CDCl$\textsubscript{3}$): 9.87 (br s, 1H, NH), 7.32-7.08 (m, 15H), 5.03 (s, 1H), 5.00
(br s, 1H), 3.87 (d, J=13.5Hz, 2H), 3.67 (d, J=13.5Hz, 2H), 3.52 (t, J=7.1Hz, 1H),
3.12 (dd, J=13, 7.1Hz, 1H), 3.01 (dd, J=13, 7.1Hz, 1H), 1.94 (s, 3H).

$^{13}$C NMR (CDCl$\textsubscript{3}$): 197.6, 161.1, 140.2, 140.1, 129.5, 128.7, 128.1, 128.0,
126.7, 125.6, 96.7, 66.3, 54.3, 33.1, 22.6.

IR (KBr): 3340, 3260, 3190, 3020, 1620, 1600, 1525, 745, 700 cm$^{-1}$.

HPLC; ee 100% (Chiracel OD column, 10% iPrOH/Hexanes).
Example 4

(4S)-1-Amino-4-(N,N-dibenzyl)amino-1,5-diphenyl-3-oxo-pent-1-ene

The title compound was prepared from (L)-N,N-dibenzy1-phenylalanine benzyl ester, 150 mmole, and 8.6 mL, 165 mmole, of acetonitrile. Following the procedure described in Example 2 the ester and nitrile mixture was added to 14.4 g, 330 mmole of sodium amide in MTBE. Phenyl Grignard (PhMgCl 300 mmole) was substituted for benzyl magnesium chloride. The resulting enamine was purified by column chromatography using silica gel, 240/400 mesh and 2:1 heptane/ethyl acetate as the mobile phase. The yield of enamine was 53 g (119 mmole, 79%).

Results are illustrated below.

$^1$H NMR (CDCl$_3$) 10.0 (br s, 1H, NH), 7.3 (m, 20H), 5.5 (s, 1H), 5.4 (brs, 1H, NH), 3.95 (d, J = 15Hz, 2H), 3.8 (d, J = 15Hz, 2H), 3.7 (dd, J = 7, 8Hz, 1), 3.3 (dd, J = 8, 15Hz, 1H), 3.1 (d, J = 7, 15Hz).

$^{13}$C NMR (CDCl$_3$) 198.7, 160.9, 140.1, 137.2, 131.0, 129.5, 128.9, 128.7, 128.1, 128.0, 126.7, 126.2, 125.7, 95.8, 66.9, 54.4, 32.8.

IR (film) 3450, 3350, 3070, 3030, 1600, 1560, 1520, 1490, 1450 cm$^{-1}$.

MS (Cl) m/e (rel. int.) 447 (M$^+$, 100), 300 (55).

HPLC ee 97% (Chiracel OD column, 10% i-PrOH/Hexanes).

Example 5

4-Amino-1-(N,N-dibenzyl)amino-2-oxo-5-phenyl-pent-3-ene

The title compound was prepared from N,N-dibenzy1-glycine benzyl ester, 54 mmole, and 3.3 mL, 64 mmole of acetonitrile. Following the procedure described in Example 2 the ester and nitrile mixture was added to 5.5 g, 127 mmole of sodium amide in MTBE. After solvent removal, benzyl magnesium chloride (PhCH$_2$MgCl 145 mmole) was added following the procedure in Example 2. The resulting enamine was purified by chromatography, following the procedure described in Example 4. The yield of enamine was 22.3 g (50 mmole, 78%).

Results are illustrated below.
1H NMR (CDCl3); 9.8 (brs, 1H, NH), 7.3 (m, 15H), 5.6 (s, 1H), 5.0 (brs, 1H, NH), 3.6 (s, 4H), 3.5 (s, 2H), 3.1 (s, 2H).
13C NMR (CDCl3); 198.4, 163.5, 139.2, 135.6, 128.8, 128.7, 128.6, 128.2, 127.3, 126.9, 93.5, 76.6, 62.3, 58.4, 42.2.
IR (Kbr); 3300, 3150, 2810, 1600, 1530, 1580, 1420 cm⁻¹.
MS (Cl); m/e (rel. Int.) 371 ((M+H)⁺, 100), 210 (15).
Elemental Analysis: Calculated for C25H26N2O: C, 81.1; H, 7.1; N, 7.6; O, 4.3%. Found: C, 81.3; H, 7.1; N, 7.3; O, 4.1%.

**Example 6**

(+)-4-Amino-1-(N,N-dibenzyl)amino-1,5-diphenyl-2-oxo-pent-3-ene

The title compound was prepared from N,N-dibenzyl-glycine benzyl ester, 113 mmole, and 6.5 mL, 125 mmole of acetonitrile. Following the procedure described in Example 2 the ester and nitrile mixture was added to 9.8 g, 225 mmole of sodium amide in MTBE. After solvent removal, benzyl magnesium chloride (PhCH₂MgCl 250 mmole) was added following the procedure in Example 2. The resulting enamine was purified by chromatography, following the procedure described in Example 4. The yield of enamine was 41 g (102 mmole, 90%).

Results are illustrated below.

1H NMR (CDCl3); 9.8 (brs, 1H, NH), 7.4 (m, 20H), 5.6 (s, 1H), 5.2 (brs, 1H, NH), 4.5 (s, 1H), 3.9 (d, 2H, J = 15Hz), 3.7 (d, 2H, J = 15Hz), 3.5 (s, 2H).
13C NMR (CDCl3); 198.2, 163.9, 140.9, 139.3, 137.5, 135.6, 129.6, 129.1, 128.8, 128.7, 128.3, 128.0, 127.9, 127.3, 127.2, 126.8, 95.02., 71.9, 53.9, 42.1.
IR (film); 3450, 3360, 2970, 2950, 2920, 1610, 1520, 1495, 1450 cm⁻¹.
MS (Cl); m/e (rel. int.) 447 (M⁺, 100), 340 (15), 222(45).

**Comparative Example**

(2S)-5-Amino-2-(N,N-dibenzyl)amino-3-oxo-1,6-diphenylhex-4-ene

a. 4-S-N,N-Dibenzylamino-3-oxo-5-phenyl-pentanitrile.

A solution containing the product of Example 1 (i.e., benzyl ester) (approx. 0.45 moles) in 520 mL tetrahydrofuran and 420 mL acetonitrile was cooled to
-40°C under nitrogen. A second solution containing sodium amide (48.7g, 1.25 moles) in 850 mL tetrahydrofuran was cooled to -40°C. To the sodium amide solution was slowly added 75 mL acetonitrile and the resulting solution was stirred at -40°C for more than 15 minutes. The sodium amide/acetonitrile solution was then slowly added to the benzyl ester solution at -40°C. The combined solution was stirred at -40°C for one hour and then quenched with 1150 mL of a 25% (w/v) citric acid solution. The resulting slurry was warmed to ambient temperature and the organic layer was separated. The organic layer was then washed with 350 mL of a 25% (w/v) sodium chloride solution, then diluted with 900 mL heptane. The organic layer was then washed three times with 900 mL of a 5% (w/v) sodium chloride solution, two times with 900 mL of a 10% methanolic water solution, one time with 900 mL of a 15% methanolic water solution, and then one time with 900 mL of a 20% methanolic water solution. The organic layer was stripped and the resulting material dissolved into 700 mL of hot ethanol. Upon cooling to room temperature, the desired product precipitated. Filtration provided the title product in 59% yield from the L-phenylalanine.

Results are illustrated below.

\[ \text{H NMR (CDCl}_3\text{): } \delta 7.3 \text{ (m, 15H)}, 3.9 \text{ (d, 1H, } J = 19.5 \text{ Hz)}, 3.8 \text{ (d, 2H, } J = 13.5 \text{ Hz)}, 3.6 \text{ (d, 2H, } J = 13.5 \text{ Hz)}, 3.5 \text{ (dd, 1H, } J = 4.0, 10.5 \text{ Hz)}, 3.2 \text{ (dd, 1H, } J = 10.5, 13.5 \text{ Hz)}, 3.0 \text{ (dd, 1H, } J = 4.0, 13.5 \text{ Hz)}, 3.0 \text{ (d, 1H, } J = 19.5 \text{ Hz)} \]

\[ \text{C NMR (300 MHz, CDCl}_3\text{): } \delta 197.0, 138.4, 138.0, 129.5, 129.0, 128.8, 128.6, 127.8, 126.4, 68.6, 54.8, 30.0, 28.4. \]  

\[ [\alpha]_D -95^\circ (c = 0.5, \text{ DMF}) \]

IR (CHCl\textsubscript{3}): 3090, 3050, 3030, 2250, 1735, 1600, 1490, 1450, 1370, 1300, 1215 cm\textsuperscript{-1}.

b. 2-Amino-5-S-N,N-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene

To a -5°C solution of the nitrile product from Comparative Example 2a (90 Kg, 244 moles) in tetrahydrofuran (288 L), was added benzyl magnesium chloride (378 Kg, 2M in THF, 708 moles). The solution was warmed to ambient temperature and stirred until analysis showed no nitrile starting material. The solution was then cooled to 5°C and slowly transferred to a solution of 15% citric acid (465 kg). Additional tetrahydrofuran (85 L) was used to rinse out the original container and the rinse was added to the citric acid quench container. The organic
layer was separated and washed with 10% sodium chloride (235 kg). The solvent was stripped to provide a solid. The crude solid was dissolved in ethanol (289 L) and stripped again. The product was again dissolved in warm (80°C) ethanol (581 L) and cooled to room temperature and stirred for 12 hours. The resulting product was filtered and dried in a vacuum oven at 30°C to provide the title compound, m.p. 101-102°C, 95 kg, 85 % yield, based on N,N-dibenzyl-phenylalanine benzyl ester.

Results are illustrated below.

$^1$H NMR (300 MHz, CDCl$_3$): d 9.8 (br s, 1H), 7.2 (m, 20H), 5.1 (s, 1H), 4.9 (br s, 1H), 3.8 (d, 2H, J = 14.7 Hz), 3.6 (d, 2H, J = 14.7Hz), 3.5 (m, 3H), 3.2 (dd, 1H, J = 7.5, 14.4 Hz), 3.0 (dd, 1H, J = 6.6, 14.4 Hz).

$^{13}$C NMR (CDCl$_3$): d 198.0, 162.8, 140.2, 140.1, 136.0, 129.5, 129.3, 128.9, 128.7, 128.1, 128.0, 127.3, 126.7, 125.6, 96.9, 66.5, 54.3, 42.3, 32.4.

IR (CDCl$_3$): 3630, 3500, 3110, 3060, 3030, 2230, 1620, 1595, 1520, 1495, 1450 cm$^{-1}$.

[$\alpha$]$_D$ -147° (c = 0.5, DMF).

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed embodiments. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.
CLAIMS

What is claimed is:

1. A process for the preparation of a substantially pure compound having formula 4:

![Chemical Structure 1]

said process comprising the step of reacting an enolate having the formula:

![Chemical Structure 2]

with a Grignard reagent having the formula \(R_{14}\)MgX;

wherein

- \(R_{14}\) is a hydrocarbyl group capable of forming a Grignard reagent selected from the group consisting of alkyl, alkaryl, and aryl;
- \(R_{15}\) is selected from the group consisting of hydrogen, alkyl, alkaryl, and aryl;
- \(M\) is an alkali metal ion; and
- \(X\) is a halogen atom selected from the group consisting of chlorine, bromine and iodine;

wherein \(R_6\) and \(R_7\) are independently selected from the group consisting of hydrogen, the group:
wherein $R_a$ and $R_b$ are independently selected from hydrogen, lower alkyl and phenyl and $R_c$, $R_d$ and $R_e$ are independently selected from hydrogen, lower alkyl, trifluoromethyl, alkoxy, halo and phenyl; and the group:

![Naphthyl Ring](image)

wherein the naphthyl ring is unsubstituted or substituted with one, two or three substitutents independently selected from lower alkyl, trifluoromethyl, alkoxy and halo; or

$R_6$ is as defined above and $R_7$ is $R_{12}OC(O)$- wherein $R_{12}$ is benzyl; or

$R_6$ and $R_7$ taken together with the nitrogen atom to which they are bonded are

![Aromatic Ring](image)

or

![Aromatic Ring](image)

wherein $R_f$, $R_g$, $R_h$, and $R_i$ are independently selected from hydrogen, lower alkyl, alkoxy, halogen and trifluoromethyl with the proviso that $R_6$ and $R_7$ cannot both be hydrogen.

2. The process according to Claim 1, wherein $R_{14}$ and $R_{15}$ are independently alkyl, benzyl or phenyl.
3. The process according to Claim 2, wherein $R_6$ and $R_7$ are each benzyl.

4. The process according to Claim 2, wherein $R_{14}$ and $R_{15}$ are independently methyl, benzyl or phenyl.

5. The process according to Claim 4, wherein $R_6$ and $R_7$ are each benzyl.

6. The process according to Claim 4, wherein $R_{14}$ and $R_{15}$ are independently benzyl or phenyl.

7. The process according to Claim 6, wherein $R_6$ and $R_7$ are each benzyl.

8. The process according to Claim 6, wherein $R_{14}$ and $R_{15}$ are each benzyl.

9. The process according to Claim 8, wherein $R_6$ and $R_7$ are each benzyl.

10. The process according to Claim 4, wherein $R_{14}$ is methyl and $R_{15}$ is benzyl.

11. The process according to Claim 10, wherein $R_6$ and $R_7$ are each benzyl.

12. The process according to Claim 6, wherein $R_{14}$ is phenyl and $R_{15}$ is benzyl.
13. The process according to Claim 12, wherein R₆ and R₇ are each benzyl.

14. The process according to Claim 4, wherein R₁₄ is phenyl and R₁₅ is methyl.

15. The process according to Claim 14, wherein R₆ and R₇ are each benzyl.

16. The process according to Claim 1, wherein R₁₄ is benzyl and R₁₅ is phenyl.

17. The process according to Claim 1, wherein R₆ and R₇ are each benzyl.

18. The process according to Claim 1, wherein the metal ion is selected from the group consisting of sodium, potassium and lithium.

19. The process according to Claim 18, wherein the metal ion is sodium.
**INTERNATIONAL SEARCH REPORT**

### A. CLASSIFICATION OF SUBJECT MATTER

| IPC 6 | C07C221/00 | C07C225/16 |

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):

| IPC 6 | C07C |

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

Electronic database consulted during the international search (name of database and, where practical, search terms used):

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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  - "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search: 10 September 1998

Date of mailing of the international search report: 17/09/1998

Name and mailing address of the ISA

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

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Pauwels, G
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