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(54) Title: PROCESS FOR THE PREPARATION OF N-ACYL BETA-AMINOALDEHYDES

(57) Abstract: This invention relates to a process for the preparation of enantiomerically enriched N-acyl β -aminoaldehydes. In particular it relates to asymmetric hydrogenation of N-acyl enamides.



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PROCESS FOR THE PREPARATION OF N-ACYL BETA-AMINOALDEHYDES

This invention relates to a process for the preparation of enantiomerically enriched N-acyl β -aminoaldehydes. In particular it relates to asymmetric hydrogenation of N-acyl enamides.

Certain compounds prepared according to the present process are disclosed in International Patent Application Publication numbers WO 01/90106 and WO 03/084954 (incorporated in their entirety herein by reference).

Enantiomerically enriched N-acyl β -aminoaldehydes are useful intermediates, in particular, for the preparation of pharmaceuticals. More particularly N-[(1S)-1-(3-fluorophenyl)-3-oxopropyl]acetamide and (1S)-4,4-difluoro-N-(3-oxo-1-phenylpropyl)cyclohexanecarboxamide are key intermediates for the preparation of methyl 1-*endo*-[8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-5-carboxylate, methyl 3-*endo*-[8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-5-carboxylate, N-[(1S)-3-[3-*endo*-(5-Isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-(3-fluorophenyl)propyl]acetamide and N-[(1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-4,4-difluorocyclohexanecarboxamide. The latter compounds are useful in the treatment of a disorder in which the modulation of CCR5 receptors is implicated, in particular HIV, retroviral infections genetically related to HIV, AIDS, and inflammatory diseases.

The syntheses of both N-[(1S)-1-(3-fluorophenyl)-3-oxopropyl]acetamide and (1S)-4,4-difluoro-N-(3-oxo-1-phenylpropyl)cyclohexanecarboxamide have been described in, respectively, WO 03/084954 and WO 01/90106. In these applications, these β -aminoaldehydes are prepared by reduction of essentially enantiomerically pure β -aminoesters followed by oxidation of the resulting alcohols under conventional conditions, or, alternatively, by partial reduction of the ester to yield the β -aminoaldehydes directly.

Processes for the preparation of enantiomerically enriched β -aminoesters by asymmetric hydrogenation of the corresponding β -(acylamino)acrylates are described in Noyori *et al.*, *Tet. Asymm.*, 1991, Vol. 2, No. 7., pp543-554, Zhang *et al.*, *J. Org. Chem*, 1999, Vol. 64, pp6907-6910, and Börner *et al.*, *J. Org. Chem*, 2001, Vol. 66, pp6816-6817.

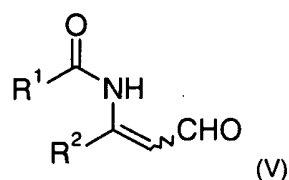
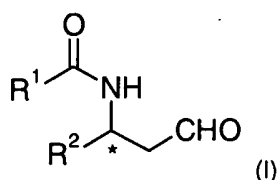
A process for the preparation of enantiomerically enriched β -aminoesters by asymmetric hydrogenation of the corresponding enamides is described in WO 03/016264.

In contrast, it has now been found that enantiomerically enriched N-acyl β -aminoaldehydes can be obtained directly by asymmetric hydrogenation of N-acyl enamides

under the reaction conditions according to the present invention that are highly suitable for large scale synthesis of the product.

Considerable economic advantages result from the yields and stereospecificity achieved. A particular advantage of the present invention is effective asymmetric
5 hydrogenation of both E and Z-enamides, which may be present in isolation or as an isomeric mixture, to yield N-acyl β -aminoaldehydes which are enriched in the same enantiomer, irrespective of the geometry of the parent enamide.

Accordingly, in the first aspect of the present invention there is provided a process for the preparation of an enantiomerically enriched compound of formula (I) comprising
10 asymmetric hydrogenation of a compound of formula (V) or a protected derivative thereof, wherein the hydrogenation is catalysed by a cationic group 8 or 9 transition metal complex comprising a chiral phosphine ligand; followed by deprotection as required;



15

wherein:

R¹ is OR^{1a}; C₁₋₆ alkyl; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₃₋₇ cycloalkyl; a 5 or 6-membered aromatic heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo,
20 halogen, CF₃, OR⁴, CN, NR³R⁴, COR⁴, CO₂R⁴ or CONR³R⁴; wherein said heterocycles contain one to three heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, halogen, CF₃, OH, CN, NR³R⁴, COR⁴, CO₂R⁴ or CONR³R⁴;

R^{1a} is C₁₋₆ alkyl substituted by 0 to 3 atoms or groups selected from phenyl, a 5 or 6-
25 membered aromatic heterocycle, halogen, C₂₋₆ alkenyl, fluorenyl, adamantyl, or trimethylsilyl; wherein said heterocycle contains one to three heteroatoms selected from N, O or S; and wherein said phenyl and heterocycle are substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, halogen, CF₃, OH, CN, NO₂, COR⁴ or CO₂R⁴;

30 R² is C₁₋₆ alkyl; phenyl; or a 5 or 6-membered aromatic heterocycle; wherein said heterocycle contains one to three heteroatoms selected from N, O or S; and wherein said phenyl and heterocycle are substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, halogen, CF₃, OH, CN, NR³R⁴, CO₂R⁴ or CONR³R⁴;

R^3 is H, C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{3-7} cycloalkyl; a 5 or 6-membered aromatic heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo, halogen, CF_3 , OR^4 , CN, COR^4 , or CO_2R^4 ; wherein said heterocycles contain one to three heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxy carbonyl, halogen, CF_3 , OH, CN, COR^4 or CO_2R^4 ;

R^4 is H or C_{1-6} alkyl;

or, when R^3 and R^4 are both attached to the same N atom, NR^3R^4 may also represent a 5 to 7 membered, saturated, partially unsaturated or aromatic, heterocycle containing from 0 to 2 additional heteroatoms selected from O, N or S; and

* denotes a chiral centre.

The term "alkyl" as a group or part of a group includes straight chain and branched groups. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. The term " C_{3-7} cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. The term halogen means fluoro, chloro, bromo or iodo.

The term "enantiomerically enriched" means that one enantiomer is present in an amount in excess of the opposite enantiomer. Enantiomeric excess is defined as the excess of one enantiomer over the other, expressed as a percentage of the whole.

In this context a chiral phosphine ligand is a chiral ligand which contains one or more chiral centres and one or more phosphorous atoms suitable for coordinating to a transition metal ion to form an organometallic complex.

In this context, a protected derivative of a compound of formulae (I) or (V) is a compound of formulae (I) or (V) wherein the carbonyl group of the aldehyde is protected. A person skilled in the art will appreciate which groups are suitable for protecting the carbonyl group of an aldehyde. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W Green and Peter G M Wuts, third edition, (John Wiley and Sons, 1999), in particular chapter 4, pages 293-368 ("Protection for the Carbonyl Group"), incorporated herein by reference, which also describes methods for the removal of such groups. Suitable protected derivatives include, but are not limited to, acyclic acetals (including but not limited to dimethyl and diisopropyl) *ibid* pp297-306, cyclic acetals (including but not limited to 1,3-dioxanes and 1,3 dioxolanes) *ibid* pp307-325 and acyclic and cyclic thioacetals *ibid* pp329-347.

In one embodiment, the asymmetric hydrogenation is effected in the presence of a solvent system.

In one embodiment of the present invention, the chiral phosphine ligand and the group 8 or 9 transition metal ion form part of a precatalyst. The term "precatalyst" refers to isolated

precatalyst which is added to the reaction vessel to effect catalysis of the hydrogenation process and which typically undergoes a change in composition in situ to generate one or more catalytically active species.

In an alternative embodiment, equivalent catalysis may be achieved by generation of
5 catalytically active species from the chiral phosphine ligand and an achiral group 8 or 9 transition metal ion containing precursor.

The group 8 or 9 transitional metal is preferably Rh, Ir or Ru, more preferably Rh or Ru, most preferably Rh.

In one embodiment of the present invention, the precatalyst is of formula
10 $[M(\text{Ligand})(\text{diene})]A$, wherein M is a group 8 or 9 transition metal ion; Ligand is the chiral phosphine ligand; diene is either cyclooctadiene (COD) or norbornadiene (NBD); and A is an anion selected from BF_4^- , PF_6^- , trifluoromethylsulfonate (TfO^-), SbF_6^- and tetra[3,5-bis(trifluoromethyl)phenyl]borate.

In a further embodiment, the diene is COD and A is BF_4^- .

15 In one embodiment of the present invention, the process for the preparation of an enantiomerically enriched compound of formula (I) comprises asymmetric hydrogenation of a protected derivative of a compound of formula (V).

In another embodiment of the present invention R^1 is C_{1-6} alkyl substituted by 0 to 3 fluorine atoms, C_{3-7} cycloalkyl substituted by 0 to 3 fluorine atoms, C_{1-6} alkoxy substituted by 0 to 3 fluorine atoms, or a 4 to 7-membered saturated heterocycle containing 1 to 3
20 heteroatoms selected from N, O or S.

In a further embodiment of the invention R^1 is C_{1-4} alkyl substituted by 0 to 3 fluorine atoms, C_{3-6} cycloalkyl substituted by 0 to 3 fluorine atoms, C_{1-4} alkoxy substituted by 0 to 3 fluorine atoms, or a 5 or 6-membered, N, O or S containing, saturated heterocycle.

25 In yet a further embodiment of the invention R^1 is C_{1-3} alkyl substituted by 0 or 3 fluorine atoms, C_{3-6} cycloalkyl substituted by 0 to 2 fluorine atoms, C_{1-3} alkoxy substituted by 0 to 3 fluorine atoms, or a 5 or 6-membered, O-containing, saturated heterocycle.

In yet a further embodiment of the invention R^1 is C_{1-2} alkyl or C_{1-2} alkoxy.

In yet a further embodiment, R^1 is 4,4-difluorocyclohexyl.

30 In yet a further embodiment, R^1 is benzyloxy or t-butyloxy.

In yet a further embodiment of the invention R^2 is phenyl substituted by 0 to 3 fluorine atoms.

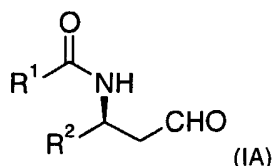
In yet a further embodiment of the invention R^2 is phenyl substituted by 0 or 1 fluorine atoms.

35 In yet a further embodiment of the invention R^2 is unsubstituted phenyl.

In yet a further embodiment of the invention R^2 is mono-fluoro-substituted (e.g. meta substituted) phenyl.

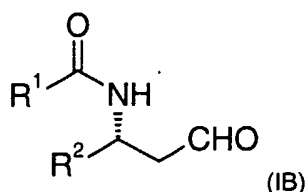
It is to be understood that the invention covers all combinations of particular embodiments of the invention as described herein.

In one embodiment, the enriched enantiomer of a compound of formula (I) is a compound of formula (IA)



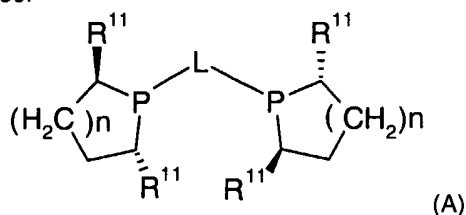
wherein R^1 and R^2 are as previously defined for a compound of formula (I).

In a further embodiment, the enriched enantiomer of a compound of formula (I) is a compound of formula (IB)



wherein R^1 and R^2 are as previously defined for a compound of formula (I).

In one embodiment of the invention, the chiral phosphine ligand is of formula (A) or the opposite enantiomer thereof



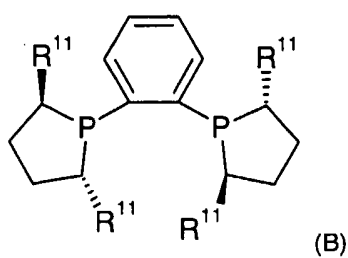
wherein:

R^{11} is C_{1-6} alkyl or phenyl;

L is ferrocene; C_{2-4} alkylene, C_{2-4} alkenylene, phenyl, naphthyl, or a 5 to 10-membered aromatic heterocycle; wherein said heterocycle contains one to three heteroatoms selected from N, O or S; and wherein said phenyl, naphthyl or heterocycle is optionally substituted by 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, halogen, CF_3 , OH, CN;

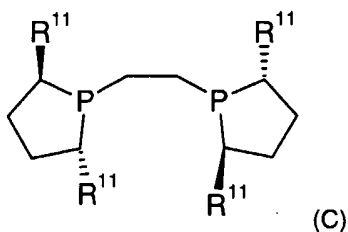
n is 0, 1 or 2.

In a further embodiment, the chiral phosphine ligand is of formula (B) or the opposite enantiomer thereof



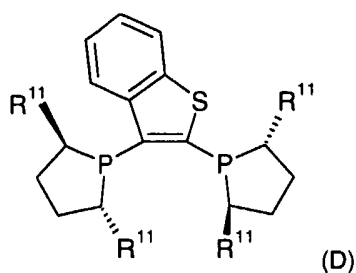
wherein R^{11} is as defined above.

In yet a further embodiment, chiral phosphine ligand is of formula (C) or the opposite enantiomer thereof



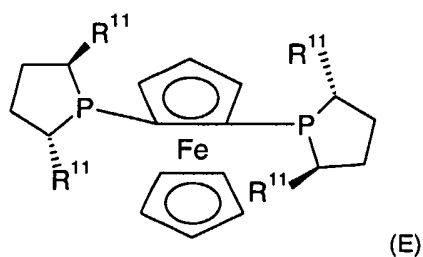
wherein R^{11} is as defined above.

In yet a further embodiment, the chiral phosphine ligand is of formula (D) or the opposite enantiomer thereof



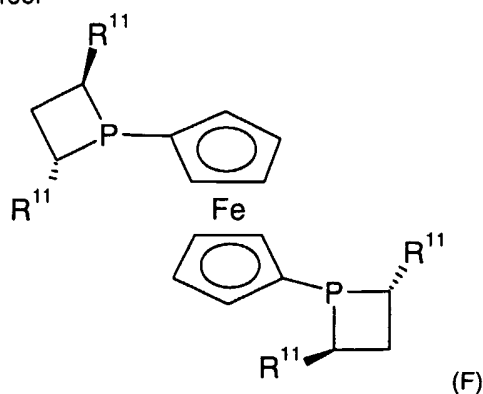
wherein R^{11} is as defined above.

In yet a further embodiment, the chiral phosphine ligand is of formula (E) or the opposite enantiomer thereof



wherein R^{11} is as defined above.

In yet a further embodiment, the chiral phosphine ligand is of formula (F) or the opposite enantiomer thereof



wherein R^{11} is as defined above.

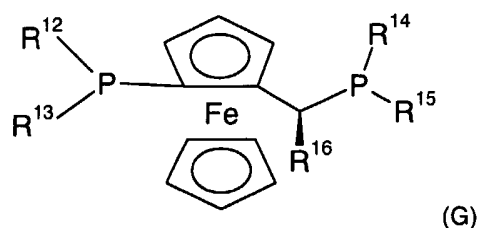
5 In yet a further embodiment, R^{11} is C_1 - C_6 alkyl.

In yet a further embodiment, R^{11} is C_1 - C_4 alkyl.

In yet a further embodiment, R^{11} is methyl, ethyl or isopropyl.

In yet a further embodiment, R^{11} is phenyl.

10 In yet a further embodiment, the chiral phosphine ligand is of formula (G) or the opposite enantiomer thereof

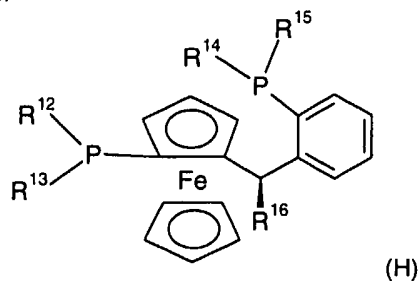


wherein:

R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from cyclohexyl, t-butyl or phenyl, wherein said phenyl is optionally substituted by $-CF_3$, methyl, or methoxy;

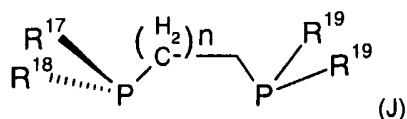
15 R^{16} is methyl, methoxy or NMe_2 .

In yet a further embodiment, the chiral phosphine ligand is of formula (H) or the opposite enantiomer thereof



wherein R^{12} , R^{13} , R^{14} , R^{15} and R^{16} are as defined above.

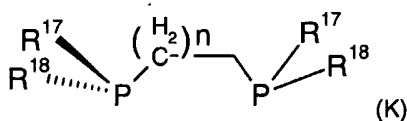
In yet a further embodiment, the chiral phosphine ligand is of formula (J) or the opposite enantiomer thereof



wherein:

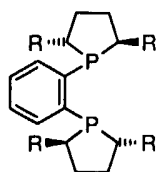
- 5 R^{17} , R^{18} and R^{19} are independently C_{1-6} alkyl or phenyl wherein said phenyl is optionally substituted by $-\text{CF}_3$, methyl, or methoxy; and R^{17} and R^{18} are different from each other ;
 n is 0,1 or 2.

In yet a further embodiment, the chiral phosphine ligand is of formula (K) or the opposite enantiomer thereof



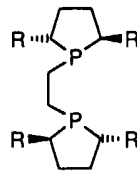
wherein:

- 10 R^{17} and R^{18} are independently C_{1-6} alkyl or phenyl wherein said phenyl is optionally substituted by $-\text{CF}_3$, methyl, or methoxy; and R^{17} and R^{18} are different from each other ;
 n is 0,1 or 2.
- 15 In yet a further embodiment, R^{17} is t-butyl.
 In yet a further embodiment, R^{18} is methyl.
 In yet a further embodiment, R^{19} is t-butyl.
 In yet a further embodiment, n is 0.
- Further examples of suitable chiral phosphine ligands are provided below.



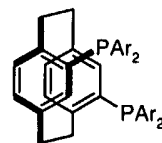
DuPHOS

R = Me (*R*)-Me-DuPHOS
 R = Et (*R*)-Et-DuPHOS
 R = *i*Pr (*S*)-*i*Pr-DuPHOS



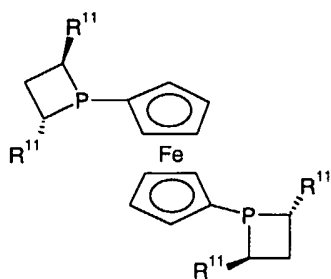
BPE

R = Me (*R*)-Me-BPE
 R = Et (*R*)-Et-BPE
 R = *i*Pr (*S*)-*i*Pr-BPE
 R = Ph (*S*)-Ph-BPE

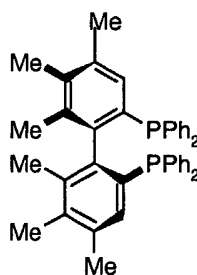
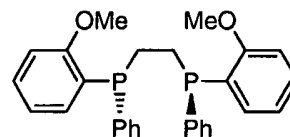


PhanePHOS

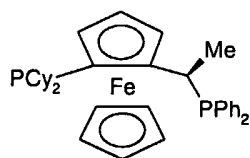
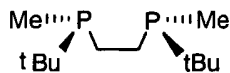
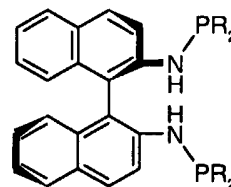
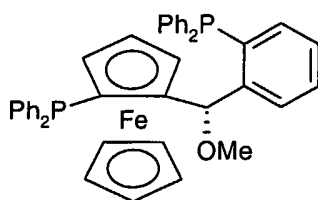
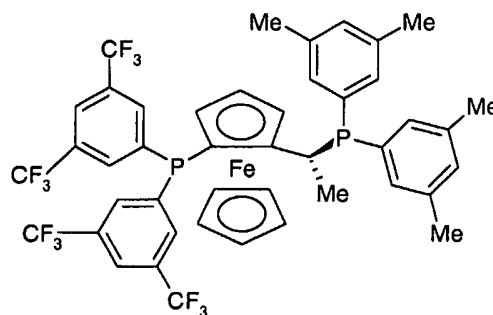
Ar = Ph (*R*)-PhanePHOS
 Ar = (3,5-Me₂)C₆H₃ (*R*)-Xyl-PhanePHOS

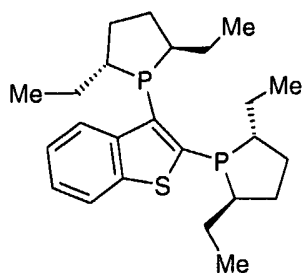


R=Me (*R*)-MeFerroTANE
 R=Et (*R*)-EtFerroTANE

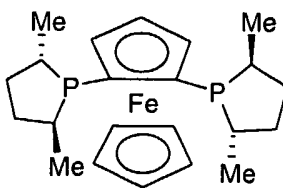
(*S*)-HexaPHEMP(*R,R*)-DiPAMP

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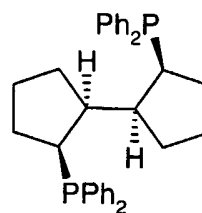
(*R*)-(*S*)-"JOSIPHOS-2"(*S,S*)-BisP*R = Ph (*R*)-DPP BINAM(*S*)-(*S*)-Ph₂PPhCHOMe-T-PPh₂(*R*)-(*S*)-(3,5-(CF₃)₂Ph)₂PF-Pxyl₂



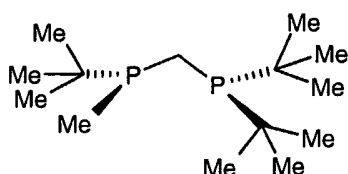
(R,R)-Et-Butiphane



(S,S)-Me-Kephos



(S,S)-Bicp



(S)-Trichickenfootphos (TCFP)

5

In one embodiment of the present invention, asymmetric hydrogenation according to the present process yields a compound of formula (IA) in a range between 70% and 100% enantiomeric excess.

10

In a further embodiment of the present invention, asymmetric hydrogenation according to the present process yields a compound of formula (IA) in a range between 90% and 100% enantiomeric excess.

In one embodiment of the present invention, asymmetric hydrogenation according to the present process yields a compound of formula (IB) in a range between 70% and 100% enantiomeric excess.

15

In a further embodiment of the present invention, asymmetric hydrogenation according to the present process yields a compound of formula (IB) in a range between 90% and 100% enantiomeric excess.

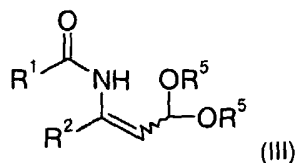
In one embodiment of the present invention, the solvent system comprises an alcohol having between 1 and 10 carbon atoms.

20

In one embodiment of the present invention, the protected derivative of the compound of formula (V) is an acetal derivative.

In a further embodiment, the acetal derivative of the compound of formula (V) is a compound of formula (III).

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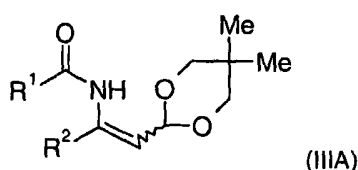


wherein R^1 and R^2 are as previously defined for a compound of formula (I) and R^5 is C_{1-6} alkyl.

In a further embodiment of the present invention wherein the acetal derivative of formula (III) is used, the solvent present during asymmetric hydrogenation according to the present process is R^5OH (IV) wherein R^5 is as previously defined for a compound of formula (III).

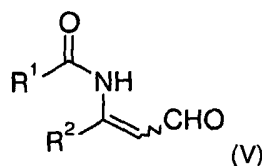
In yet a further embodiment, R^5 is methyl.

In another embodiment, the acetal derivative of the compound of formula (V) is a compound of formula (IIIA).



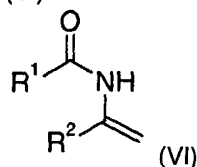
wherein R^1 and R^2 are as previously defined for a compound of formula (I).

In one embodiment, the preparation of the acetal of formula (III) comprises reaction of a compound of formula (V)



with R^5OH (IV) under conventional conditions, wherein R^1 , R^2 and R^5 are as previously defined for a compound of formula (III).

In a further embodiment, the preparation of a compound of formula (V) comprises formylation of a compound of formula (VI)

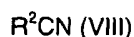


wherein R^1 and R^2 are as previously defined for a compound of formula (V), under conventional conditions.

In yet a further embodiment, the preparation of a compound of formula (VI) comprises reaction of a compound of formula (VII)



with a compound of formula (VIII)

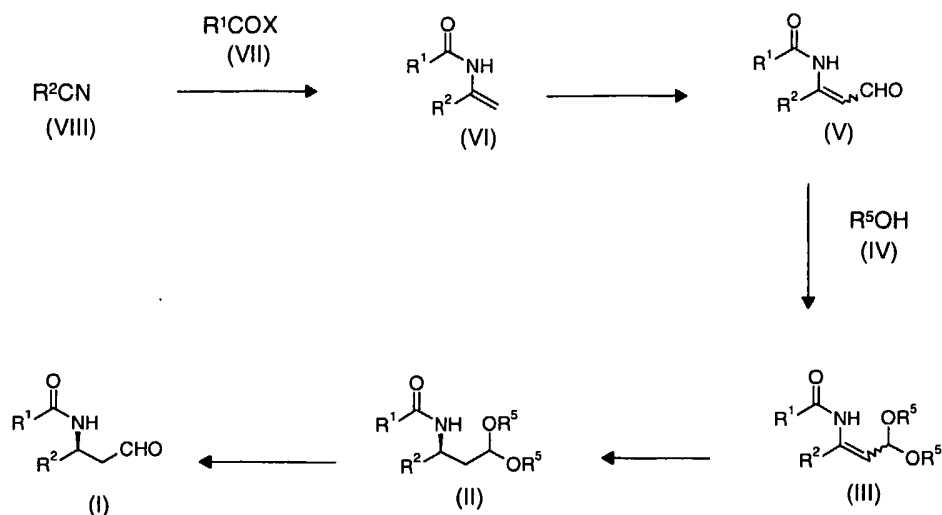


in the presence of MeMgX and optionally of CuX wherein R¹ and R² are as previously defined for a compound of formula (I) and X is halogen.

In one particular embodiment of the present invention, the compounds of formula (I) can be prepared according to Scheme 1.

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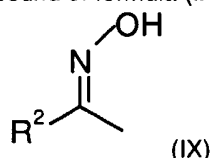
Scheme 1



wherein R¹, R² and R⁵ are as defined hereinabove.

In a further embodiment, the preparation of a compound of formula (V), wherein R¹ is methyl, comprises reaction of a compound of formula (IX)

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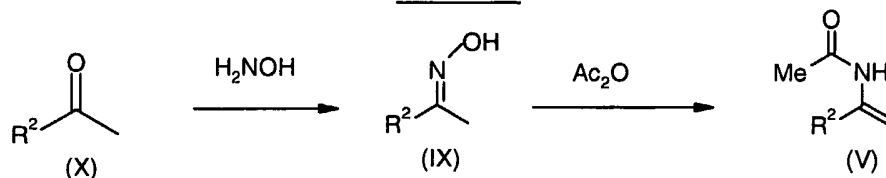


with acetic anhydride in the presence of iron metal.

In yet a further embodiment, a compound of formula (V), wherein R¹ is methyl, can be prepared according to Scheme 1a.

15

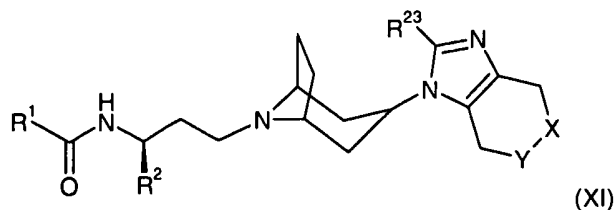
Scheme 1a



The preparations of the starting materials used in the process of the present invention are conventional and appropriate reagents and reaction conditions for their preparation as

well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the Preparations hereto.

In another aspect, the invention provides processes for the preparation of a compound of formula (XI)



or a pharmaceutically acceptable salt, solvate or derivative thereof,
wherein:

R^1 and R^2 are as previously defined for a compound of formula (I);

10 X and Y are selected from CH_2 and NR^{24} such that one of X and Y is CH_2 and the other is NR^{24} ;

R^{24} is R^{25} , COR^{25} , CO_2R^{25} , $CONR^{26}R^{27}$, SO_2R^{25} ; or $(C_{1-6} \text{ alkylene})phenyl$, wherein phenyl is substituted by 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxy carbonyl, halogen, CF_3 , OH, CN, $NR^{26}R^{27}$, COR^{27} , CO_2R^{27} or $CONR^{26}R^{27}$;

R^{23} is C_{1-4} alkyl substituted by 0 to 3 fluorine atoms;

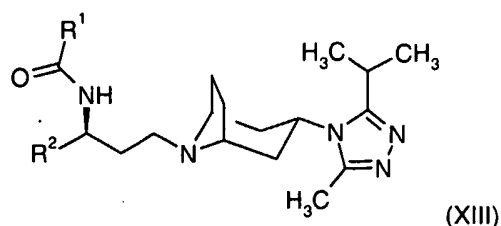
15 R^{25} is C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{3-7} cycloalkyl; a 5 or 6-membered aromatic heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo, halogen, CF_3 , OR^{27} , CN, $NR^{26}R^{27}$, COR^{27} , CO_2R^{27} or $CONR^{26}R^{27}$; wherein said heterocycles contain one to three heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by
20 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxy carbonyl, halogen, CF_3 , OH, CN, $NR^{26}R^{27}$, COR^{27} , CO_2R^{27} or $CONR^{26}R^{27}$;

R^{26} is H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{3-7} cycloalkyl; a 5 or 6-membered aromatic heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo, halogen, CF_3 , OR^{27} , CN, COR^{27} or CO_2R^{27} ; wherein said heterocycles contain one to three heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxy carbonyl, halogen, CF_3 , OH, CN, COR^{27} or CO_2R^{27} ;

R^{27} is H or C_{1-6} alkyl;

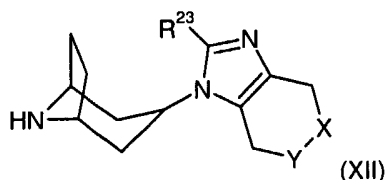
30 or, when R^{26} and R^{27} are both attached to the same N atom, $NR^{26}R^{27}$ may also represent a 5 to 7 membered, saturated, partially unsaturated or aromatic, heterocycle containing from 0 to 2 additional heteroatoms selected from O, N or S.

In another aspect, the invention provides processes for the preparation of a compound of formula (XIII)



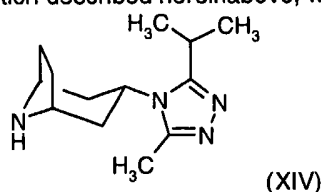
or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein R¹ and R² are as previously defined for a compound of formula (I).

In one embodiment, compounds of formula (XI) may be prepared by reductive amination of a compound of formula (IA), prepared according to the asymmetric hydrogenation process of the invention as described hereinabove, with an amine of formula (XII)



under conventional conditions, wherein R²³, X and Y are as defined for a compound of formula (XI). Reductive amination may conveniently be effected according to the conditions described in WO 03/084954 (p14, step (g)).

In a further embodiment, compounds of formula (XIII) may be prepared by reductive amination of a compound of formula (IA), prepared according to the asymmetric hydrogenation process of the invention described hereinabove, with an amine of formula (XIV)

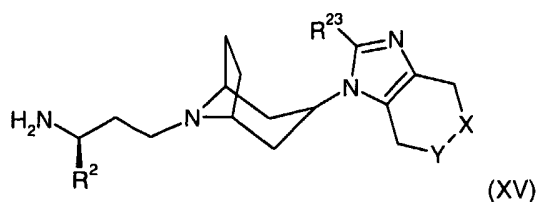


under conventional conditions.

Reductive amination may conveniently be effected according to the conditions described in WO 01/90106 (p13, lines 11 to 22).

In yet a further embodiment, compounds of formula (XI) may be prepared by

- a) preparation of a carbamate of formula (XI), wherein R¹ is OR^{1a}, prepared by reductive amination of a compound of formula (IA), prepared according to the asymmetric hydrogenation process of the invention described hereinabove, with an amine of formula (XII);
- followed by
- b) cleavage of the carbamate of formula (XI), to yield an amine of formula (XV)



wherein R^2 , R^{23} , X and Y are as defined for a compound of formula (XI);

followed by

- c) acid amine coupling of an amine of formula (XV) with an acid of formula (XVI)



wherein Z is OH, or a carboxylic acid activating group such as chloro or 1H-imidazol-1-yl;

under conventional conditions.

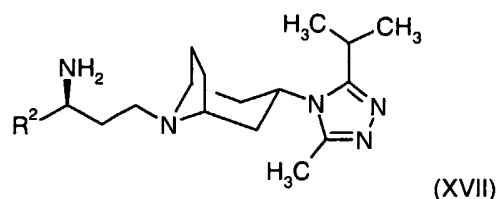
Acid amine coupling may conveniently be effected according to the conditions described in WO 03/084954 (p14 line 29 to p15 line 7).

In yet a further embodiment, compounds of formula (XIII) may be prepared by

- a) preparation of a carbamate of formula (XIII), wherein R^1 is OR^{1a} , prepared by reductive amination of a compound of formula (IA), prepared according to the asymmetric hydrogenation process of the invention described hereinabove, with an amine of formula (XIV);

followed by

- b) cleavage of the carbamate of formula (XIII), to yield an amine of formula (XVII)



wherein R^2 is as defined for a compound of formula (XIII); followed by

- c) acid amine coupling of an amine of formula (XV) with an acid of formula (XVI)



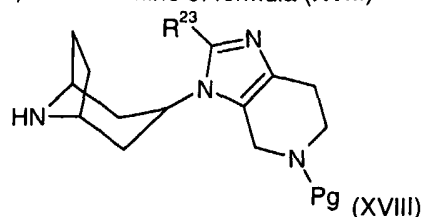
wherein Z is OH, or a carboxylic acid activating group such as chloro or 1H-imidazol-1-yl;

under conventional conditions.

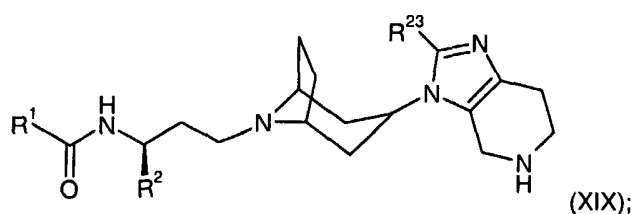
Acid amine coupling may conveniently be effected according to the conditions described in WO 01/90106 (p5 line 11 to 18 and p7 line 21 to p8 line 23).

In yet a further embodiment, compounds of formula (XI) wherein Y is NR^{24} may be prepared by

- a) reductive amination of a compound of formula (IA), prepared according to the asymmetric hydrogenation process of the invention as described hereinabove, with an amine of formula (XVIII)



- 5 under conventional conditions, wherein R^{23} is as defined for a compound of formula (XI) and Pg is an amine protecting group; followed by
- b) deprotection under conventional conditions to yield an amine of formula (XIX)

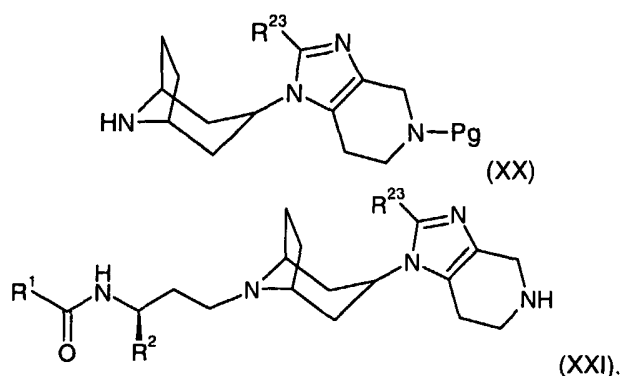


- 10 followed by

- c) conversion of the amine of formula (XIX) to a compound of formula (XI).

Conversion of an amine of formula (XIX) to a compound of formula (XI) may be conveniently carried out according to methods described in WO 03/084954 (in particular method M described therein at p 10 line 15).

- 15 A person skilled in the art will appreciate that compounds of formula (XI) wherein X is NR^{24} may be prepared by a process directly analogous to the process described above, using in step a) an amine (XX), step b) yielding an amine (XXI).



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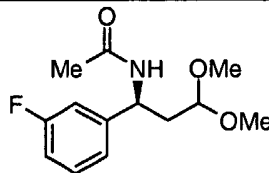
Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention.

Compounds of formulae (II), (III), (IIIA), (V) and (VI) are key intermediates and represent a particular aspect of the present invention.

The invention is illustrated by the following Examples and Preparations in which the following further abbreviations may be used:

- 5 h = hour
min = minute
MS = mass spectrum
TLC = thin layer chromatography
NMR = nuclear magnetic resonance
10 NOE = nuclear Overhauser effect
Me = methyl
^tBu = tertiary butyl
TBME = tertiary butyl methyl ether
DCM = dichloromethane
15 EtOAc = ethyl acetate
ⁿPrAc = n-propyl acetate
DMF = Dimethyl formamide

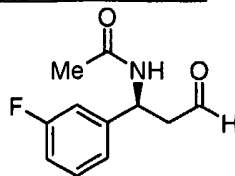
Example 1: Asymmetric hydrogenation of N-Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-
20 dimethoxy-2-propene
a) (3S)-N Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-dimethoxy-propane



- A solution of *N*-Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-dimethoxy-2-propene (49.40 g, 195.3 mmol) in methanol (240 ml) was charged to a glass liner and secured in a Parr 600ml
25 pressure vessel. The solution was charged with nitrogen to a pressure of 10 bar and then stirred rapidly whilst heating to 40 °C (internal). After 20 minutes the gas was vented and the charge/vent cycle was repeated two times and stirring was then stopped. [(*S,S*)-Et-DuPHOS Rh COD]BF₄ (10 ml of a freshly prepared 7.8 mM solution in deoxygenated methanol, 0.078 mmol, S/C 2500) was then added and the vessel was charged with hydrogen to a pressure of
30 10 bar and then vented slowly. This charge/vent cycle was repeated twice and the vessel was then charged with hydrogen to a pressure of 10 bar and stirring initiated. After 5 hours no further hydrogen was consumed and the vessel was vented. The solution was concentrated *in vacuo* to provide the title compound as an orange oil (49.8 g, quantitative), 94.5 % ee.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.28 (1H, ddd, *J* 8.0, 8.0 and 6.0 Hz), 7.04 (1H, d, *J* 8.0 Hz), 6.98-6.91 (2H, m), 6.62 (1H, d, *J* 7.2 Hz), 5.11 (1H, dd, *J* 12.8 and 7.2 Hz), 4.23 (1H, dd, *J* 6.0 and 6.0 Hz), 3.31 (6H, d, *J* 6.0 Hz), 2.08-2.04 (2H, m) and 2.00 (3H, s).

b) (3*S*)-*N*-Acetyl-3-amino-3-(3-fluoro-phenyl)-propanal



5

Hydrochloric acid (200 ml of a 2M aqueous solution, 400 mmol) was added to a solution of (3*S*)-*N*-Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-dimethoxy-propane (50.2 g, 197 mmol) in THF (50 ml). After vigorous stirring at room temperature for 17 hours, the solution was concentrated *in vacuo*. Saturated sodium bicarbonate (~400 ml) was added to the residue to neutralise the solution (pH 7) and ethyl acetate (200 ml) was then added. After partitioning the phases, the aqueous phase was saturated with sodium chloride and then extracted with ethyl acetate (2 x 200 ml). The combined organic extracts were then washed with brine (200 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (150 ml) and concentrated *in vacuo*. This was repeated once and the residue was then dissolved in a mixture of dichloromethane (100 ml) and methyl *tert*-butyl ether (100 ml) and concentrated *in vacuo*. The residue was finally dissolved in methyl *tert*-butyl ether (100 ml) and concentrated *in vacuo*. This was repeated once more to provide the title compound as a waxy solid (37.6 g, 91%), 95.3 % ee.

¹H NMR (400 MHz, CDCl₃) δ ppm 9.73 (1H, br s), 7.33-7.27 (1H, m), 7.08 (1H, d, *J* 8.0 Hz), 7.03-6.95 (2H, m), 6.39 (1H, d, *J* 6.8 Hz), 5.49 (1H, q, *J* 6.8 Hz), 3.06 (1H, ddd, *J* 17.0, 6.8 and 2.0 Hz), 2.94 (1H, ddd, *J* 17.0 Hz, 6.8 and 1.2 Hz).

Asymmetric hydrogenation of *N*-Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-dimethoxy-2-propene utilizing various precatalysts is further illustrated in Table 1.

25

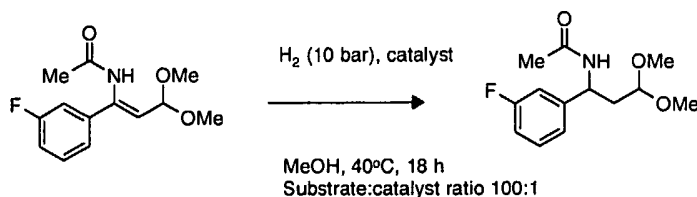
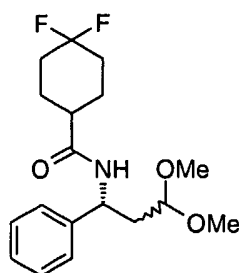


Table 1

Precatalyst	T (°C)	P (bar)	Con %	Ee %
[(R,R)-Me-DuPHOS Rh COD]BF ₄	40°C	10	>95	91.3
[(S,S)-Et-DuPHOS Rh COD]BF ₄	40°C	10	>95	98.2
[(S,S)- ⁱ Pr-DuPHOS Rh COD]BF ₄	40°C	10	>95	79.9
[(R,R)-Et-BPE Rh COD]BF ₄	40°C	10	>95	77.4
[(S,S)- ⁱ Pr-BPE Rh COD]BF ₄	40°C	10	>95	82.9
[(S,S)-BisP* Rh COD] BF ₄	40°C	10	>95	84.7
[(R)-DPP BINAM Rh COD] BF ₄	40°C	10	>95	82.5
[(S)-BINOL-(S)-PhanePHOS Rh COD]BF ₄	40°C	10	>95	79.7

- The asymmetric hydrogenation of *N*-Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-dimethoxy-2-propene utilizing the precatalysts in Table 1 was effected as follows:
- 0.01 mmol of precatalyst (or metal precursor (0.01mmol of metal) and ligand (1.1 equivalents of diphosphine per metal) as specified) was placed in a suitable tube, This tube was closed by a septum and set under an atmosphere of argon with three consecutive cycles of vacuum/argon via a canula. Absolute methanol (2ml) was then added via a canula. The resulting solution was stirred at room temperature for 20 min. At the same time, *N*-Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-dimethoxy-2-propene (1mmol) was placed in a Schlenk flask under argon. Methanol (3ml) was added and this mixture was allowed to stir at room temperature for 10min. The mixture was then transferred to the tube containing the precatalyst solution. The tube was then placed in an autoclave that had been placed under argon. The autoclave was then closed and set to the prescribed pressure of hydrogen and prescribed temperature. After 18 hours the reaction was stopped and the crude reaction mixture was filtered over silica and analysed by HPLC.

Example 2: Asymmetric hydrogenation of 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene
(3*R*)-*N*-(4,4-Difluoro-cyclohexanecarbonylamino)-3-amino-3-(3-phenyl)-1,1-dimethoxy-propane



- A solution of 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene (1.0g, 3.0 mmol) and [(*R,R*)-Me-DuPHOS Rh COD]BF₄ (19mg, 0.028 mmol) in methanol (5 ml) and acetic acid (1 drop) was charged to a pressure vessel. The vessel was then purged with nitrogen by pressurising to 10 bar and then venting. This purging procedure was then repeated a further four times. The vessel was pressurised with hydrogen (10 bar), then vented and pressurised again with hydrogen (10 bar). The mixture was then stirred at ambient temperature for 16 hours and the vessel vented. The solution was concentrated *in vacuo* to provide the title compound as an orange oil (g, quantitative), 96.4 % ee.
- ¹H NMR (300 MHz, CDCl₃) δ ppm 7.21-7.58 (5H, m), 6.59 (1H, d), 5.12 (1H, q), 4.22 (1H, t), 3.84 (6H, d), 1.63-2.24 (9H, m) and 2.08 (2H, s).

Asymmetric hydrogenation of 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene utilizing various precatalysts is further illustrated in Table 2.

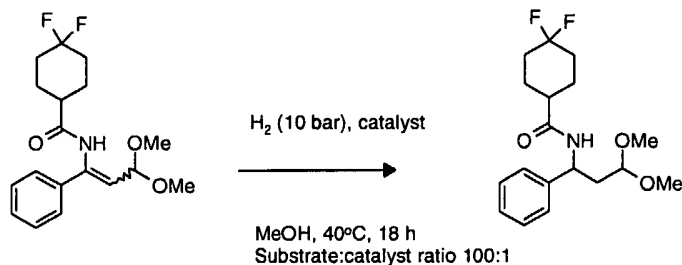


Table 2

Precatalyst	T (°C)	P (bar)	Con %	Ee %
[(<i>R,R</i>)-Me-FerroTANE Rh COD]BF ₄	40°C	10	>95	72.6
[(<i>S,S</i>)-Et-FerroTANE Rh COD]BF ₄	40°C	10	>95	72.7
[(<i>R,R</i>)-Me-DuPHOS Rh COD]BF ₄	40°C	10	>95	95.7
[(<i>S,S</i>)-Et-DuPHOS Rh COD]BF ₄	40°C	10	>95	92
[(<i>S,S</i>)- <i>i</i> -Pr-DuPHOS Rh COD]BF ₄	40°C	10	>95	92.3

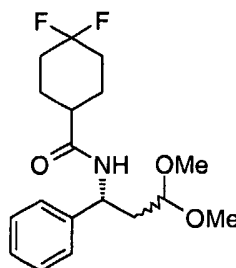
[(R,R)-Me-BPE Rh COD]BF ₄	40°C	10	>95	83.6
[(R,R)-Et-BPE Rh COD]BF ₄	40°C	10	>95	77.9
[(S,S)- ⁱ Pr-BPE Rh COD]BF ₄	40°C	10	>95	83.2
[(R,R)-Ph-BPE Rh COD]BF ₄	40°C	10	>95	94.5
[(R,R-DIPAMP) Rh (COD)]BF ₄	40°C	10	>95	78.3
[(S,S)-BisP* Rh COD] BF ₄	40°C	10	>95	78.9
[(R)-DPP BINAM Rh COD] BF ₄	40°C	10	>95	82.5
[(S)-BINOL-(S)-PhanePHOS Rh COD]BF ₄	40°C	10	>95	79.7

The asymmetric hydrogenation of 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene utilizing the precatalysts in Table 2 was effected according to the method described in relation to Table 1 using the corresponding substrate.

5

Example 3: Asymmetric hydrogenation of 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene

(3*R*)-N-(4,4-Difluoro-cyclohexanecarbonylamino)-3-amino-3-(3-phenyl)-1,1-dimethoxy-propane



10

3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene (1.0g, 3.0 mmol) and [(S)-TCFP Rh COD]BF₄ (7mg, 0.012 mmol) was charged to a pressure vessel. The vessel was purged with argon by pressurising to 10 bar and then venting. This purging procedure was repeated a further two times. Degassed methanol (3 ml) was charged to the vessel via a syringe. The vessel was then purged with nitrogen by pressurising to 10 bar and then venting. This purging procedure was repeated a further two times times. The vessel was then pressurised with hydrogen (10 bar), then vented and this purging procedure was repeated a further two times. The vessel was pressurised again with hydrogen (10 bar). The mixture was then stirred at 40°C for 5.5 hours and the vessel vented. The solution was concentrated *in vacuo* to provide the title compound as a cream solid (g, quantitative), 94.7 % ee.

20

^1H NMR (300 MHz, CD_3OD) δ ppm 7.39-7.22 (5H, m), 4.98 (1H, t, J 7.5 Hz), 4.25 (1H, t, J 6.0 Hz), 3.30 (s, 6H), 2.39-2.26 (m, 1H), 2.14-1.62 (10H, m).

Example 4: Asymmetric hydrogenation of N-[2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-phenyl-vinyl]-acetamide

Asymmetric hydrogenation of N-[2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-phenyl-vinyl]-acetamide utilizing various precatalysts is illustrated in Table 3.

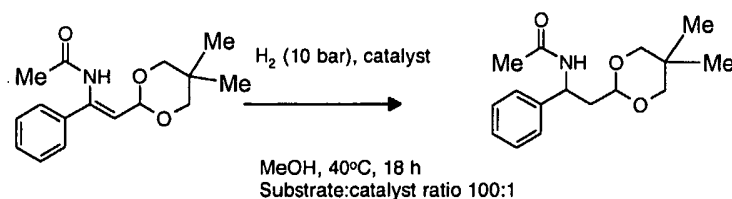


Table 3

Precatalyst	T (°C)	P (bar)	Con %	Ee %
[Rh (NBD) ₂]BF ₄ and (S)-(S)-Ph ₂ PPhCHOMe-T-PPh ₂	40°C	10	100	95
[Rh (NBD) ₂]BF ₄ and (R)-(S)-(3,5-CF ₃ Ph) ₂ PF-Pxyl ₂	40°C	10	100	83
[(S,S)-Et-Butiphane Rh COD]BF ₄	40°C	10	100	84
[(R,R)-Et-DuPHOS Rh COD]BF ₄	40°C	10	100	88

The asymmetric hydrogenation of N-[2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-phenyl-vinyl]-acetamide utilizing the precatalysts in Table 3 was effected according to the method described in relation to Table 1 using the corresponding substrate.

Example 5: Asymmetric hydrogenation of (3,3-Dimethoxy-1-phenyl-propenyl)-carbamic acid benzyl ester

Asymmetric hydrogenation of (3,3-Dimethoxy-1-phenyl-propenyl)-carbamic acid benzyl ester utilizing various precatalysts is illustrated in Table 4.

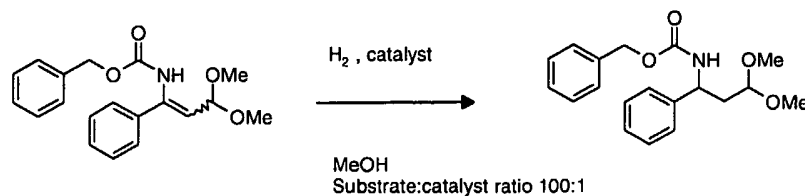


Table 4

Precatalyst	T (°C)	P (bar)	Con %	Ee %
[(R,R)-Et-DuPHOS Rh COD]BF ₄	40°C	10	>95	90
[(R,R)-Et-Butiphane Rh COD]BF ₄	rt	20	94	94
[(S,S)-Me-Kephos Rh COD]BF ₄	40°C	10	>95	83
[Rh (NBD ₂) BF ₄ and (R)-(S) -PPF-Pcy ₂	40°C	5	90	78
[(S,S)-DIPAMP Rh (COD)]BF ₄	40°C	20	97	77
[(S,S)-Bicpl [Rh (NBD) ₂] BF ₄	40°C	20	99	89

The asymmetric hydrogenation of (3,3-Dimethoxy-1-phenyl-propenyl)-carbamic acid benzyl ester utilizing the precatalysts in Table 4 was effected according to the method described in relation to Table 1 using the corresponding substrate.

Example 6: Asymmetric hydrogenation of N-(1-tert-Butyl-3,3-dimethoxy-propenyl)-acetamide
Asymmetric hydrogenation of N-(1-tert-Butyl-3,3-dimethoxy-propenyl)-acetamide utilizing various precatalysts is illustrated in Table 5.

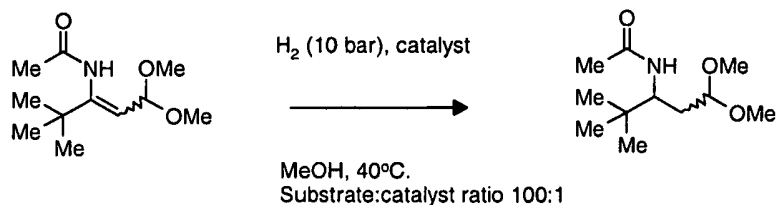
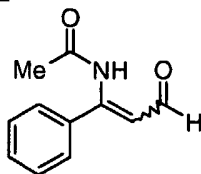


Table 5

Precatalyst	T (°C)	P (bar)	Con %	Ee %
[(R)-PhanePhos Rh COD]BF ₄	40°C	10	>95	98
[(S)-Xyl-PhanePhos Rh COD]BF ₄	40°C	10	>95	92
[(R)-HexaPHEMP Ru (OCOCF ₃) ₂]	40°C	10	>95	98
[(S,S)- ⁱ Pr-FerroTANE Ru (2-methallyl) ₂]	40°C	10	>95	81

The asymmetric hydrogenation of *N*-(1-*tert*-Butyl-3,3-dimethoxy-propenyl)-acetamide utilizing the precatalysts in Table 5 was effected according to the method described in relation to Table 1 using the corresponding substrate.

5 Example 7: Asymmetric hydrogenation of *N*-Acetyl-3-amino-3-phenyl-2-propenal
N-Acetyl-3-amino-3-phenyl-2-propenal



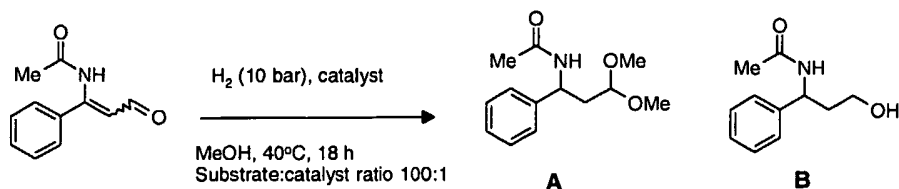
A solution of *N*-Acetyl-1-(phenyl)-vinylamine (126.6 g, 0.668 mol (~90% pure) in acetonitrile (365 ml) was added dropwise over 0.5h *via* a dropping funnel to a stirred solution of (chloromethylene)dimethylammonium chloride (111.2g g, 0.868 mol) as a suspension in acetonitrile (730 ml) at 0°C (external). After completion of the addition the reaction was allowed to warm to room temperature and stirred for 90 min. The reaction mixture was cooled to 10°C and a solution of sodium acetate (274g) in water (730 ml) was added and the reaction was stirred vigorously for 1.5 h at ambient temperature. The organics were removed and the aqueous material was extracted with dichloromethane (2x1.7l). The combined organics were dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford the crude product (207g) as a brown oil. Purification of the crude residue was accomplished by chromatography on silica (2kg) eluting with dichloromethane:ethyl acetate (6:1 -> 1.5:1), and provided the title compound as an ~4:1 mixture of *Z* and *E* stereoisomers (79g, 63%) as a light yellow solid.

¹H NMR (300 MHz, d⁶-DMSO) major *Z*-isomer δ ppm 10.06 (s, N-H), 9.36 (1H, d, CHO), 7.74-7.6 (5H, m, Ar-H), 7.03 (1H, d, C-H) and 2.09 (3H, s).

¹H NMR (300 MHz, d⁶-DMSO) minor *E*-isomer δ ppm 10.24 (s, N-H), 9.68 (1H, d, CHO), 7.74-7.6 (5H, m Ar-H), 5.97 (1H, d, C-H) and 2.18 (3H, s).

25

Asymmetric hydrogenation of *N*-Acetyl-3-amino-3-phenyl-2-propenal utilizing various precatalysts is illustrated in Table 6.



30

Table 6

Precatalyst	T (°C)	P (bar)	Con %	A %	A-ee %	B%
[Rh (NBD) ₂]BF ₄ and (S)-(S)- Ph ₂ PPhCHOMe-T-PPh ₂	40°C	10	100	80	89	17
[Rh (NBD) ₂]BF ₄ and (R)-(S)-(3,5- CF ₃ Ph) ₂ PF-PxyI ₂	40°C	10	100	100	27	
[Rh (NBD) ₂]BF ₄ and (S,S)-Bicp	40°C	10	87	87	67	
[(R,R)-Et-DuPHOS Rh COD]BF ₄	40°C	10	100	53	80	47

- 5 The asymmetric hydrogenation of *N*-Acetyl-3-amino-3-phenyl-2-propenal utilizing the precatalysts in Table 6 was effected as follows:
- 0.01 mmol of precatalyst (or metal precursor (0.01mmol of metal) and ligand (1.1 equivalents of diphosphine per metal) as specified) was placed in a suitable tube. This tube was closed by a septum and set under an atmosphere of argon with three consecutive cycles of vacuum/argon via a canula. Absolute methanol (2ml) was then added via a canula. The
- 10 resulting solution was stirred at room temperature for 20 min. At the same time, *N*-Acetyl-3-amino-3-phenyl-2-propenal (1mmol) was placed in a Schlenk flask under argon. Methanol (3ml) was added and this mixture was allowed to stir at room temperature for 10 min. The mixture was then transferred to the tube containing the precatalyst solution. The tube was then placed in an autoclave that had been placed under argon. The autoclave was then
- 15 closed and set to the prescribed pressure of hydrogen and prescribed temperature. After 18 h the reaction was stopped and the crude reaction mixture was filtered over silica and analysed by HPLC.

¹H NMR (300 MHz, d⁶-DMSO) δ ppm 8.32 (d, *NH*), 7.16-7.36 (5H, m), 4.93 (1H, q, *CH*), 4.22 (1H, q, *CH*), 3.20 (6H, s, 2 OCH₃), 1.82 (3H, s) and 1.7-2.0 (2H, m, CH₂).

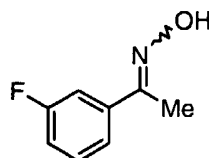
20

HPLC-Measurements:

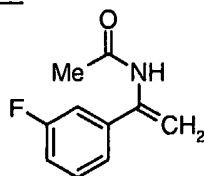
- Column: Chiracel OD-H, neutral, 250X4.6mm
- Mobile phase 94%hexane, 6% 2-propanol
- Flow 1ml/min
- 25 Detector: UV 220nm
- Injector volume: 10μl
- Temperature 40°C

A (R) 15.5 min

A (S)	17.6 min
B	28.3 min
Starting material	40.6 min

5 Preparation 11-(3-Fluoro-phenyl)-ethanone oxime

3-Fluoroacetophenone (20.0 ml, 162.1 mmol) was added dropwise to a stirred suspension of sodium acetate (14.63 g, 178.4 mmol) and hydroxylamine hydrochloride (12.39 g, 178.4 mmol) in methanol (80 ml) at room temperature. After 2 hours the reaction was cooled to 0°C and water (80 ml) was added. The resulting solution was acidified with aqueous hydrochloric acid (3M) and extracted with ethyl acetate (2 x 200 ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound (26.41 g, quantitative). *R*_f 0.28 (15% ethyl acetate-heptane); ¹H NMR (400 MHz, DMSO) δ ppm 7.41-7.30 (3H, m), 7.08 (1H, t, *J* 7.0 Hz), 2.29 (3H, s) and 2.13 (1H, s).

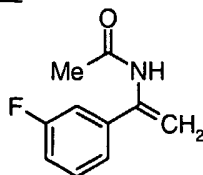
Preparation 2N-Acetyl-1-(3-fluoro-phenyl)-vinylamine

Iron (19.36 g, 344.9 mmol) was added to a stirred solution of 1-(3-fluoro-phenyl)-ethanone oxime (26.41 g, 172.4 mmol) in toluene (250 ml). Aliquots (~10 ml) of a mixture of acetic anhydride (48.4 ml, 517.4 mmol) and acetic acid (29.6 ml, 517.4 mmol) were added to the reaction mixture during which time the vessel was heated slowly to 70 °C (internal). After 5 hours at 70 °C (internal), TLC analysis showed the reaction was essentially complete. The reaction was allowed to cool before being passed through a celite pad. The solid residue was washed with additional toluene (2 x 30 ml). The resulting organics were washed with aqueous sodium hydroxide solution (2 M, 2 x 150 ml), dried (MgSO₄), filtered and concentrated under reduced pressure. The crude residue was passed through a short pad of silica using methyl *tert*-butyl ether as eluent before being further purified by flash column chromatography using firstly 50% methyl *tert*-butyl ether-heptane and then 75% methyl *tert*-butyl ether-heptane as eluant. This afforded the title compound (estimated to be 95% pure, 22.19 g, 81%). *R*_f 0.26

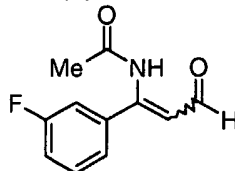
(75% methyl *tert*-butyl ether-heptane); ^1H NMR (400 MHz, DMSO) δ ppm 7.37-7.31 (1H, m), 7.21 (1H, br d, J 7.0 Hz), 7.19 (1H, br d, J 10.0 Hz), 7.05 (1H, ddd, J 8.0, 8.0 and 2.0 Hz), 6.81 (1H, br s, NH), 5.85 (1H, br s), 5.13 (1H, br s) and 2.14 (3H, br s).

5 Preparation 3

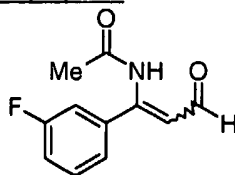
N-Acetyl-1-(3-fluoro-phenyl)-vinylamine



Methylmagnesium bromide (2.4 l of a 3M solution in ether, 7.20 mol) was added to a stirred suspension of 3-fluorobenzonitrile (793 g, 6.55 mol) and copper(I) bromide (37.6 g, 131 mmol) in THF (5.7 l) over 140 minutes. An exotherm of 24 °C was noted and the mixture was at a gentle reflux. Once the addition was complete, the mixture was heated at reflux (internal temperature: 52 °C) for 135 minutes. The reaction mixture was then cooled to 5 °C (internal temperature) and a solution of acetic anhydride (701 ml, 7.2 mol) in tetrahydrofuran (700 ml) was added over one hour, whilst maintaining the temperature below 18 °C (internal). After a further 17 hours, saturated ammonium chloride (300 ml) was added. The mixture was diluted with methyl *tert*-butyl ether (~1.4 l) and further ammonium chloride (2.55 l) was added batchwise over one hour, ensuring a free-flowing suspension at all times. The mixture was then stirred for 150 minutes at 22 °C (internal). Water (500 ml) was added and the layers were separated. The organic phase was then washed with saturated ammonium chloride (4 x 1.4 l). The combined aqueous washes were then extracted with methyl *tert*-butyl ether (2 l). The combined organic extracts were washed with brine (2 x 1 l) and concentrated *in vacuo*. Methanol (3.5 l) and potassium carbonate (181 g, 1.31 mol) were sequentially added to the residue that was then stirred at room temperature for one hour. The supernatant was decanted, concentrated *in vacuo* and subsequently partitioned between methyl *tert*-butyl ether (3.5 l) and water (2 l) by stirring for one hour and then allowed to settle for 30 minutes. The organic phase was washed with saturated ammonium chloride (2 x 1.4 l). The aqueous washes were then combined and extracted with methyl *tert*-butyl ether (3.5 l). The combined organic extracts were washed with brine (2 x 1.4 l), dried (MgSO_4), filtered and concentrated *in vacuo*. The crude product was dissolved in methyl *tert*-butyl ether (1.1 l) and filtered through a pad of silica, eluting with methyl *tert*-butyl ether (7 l) until no further product was detected in the filtrate. Concentration *in vacuo* provided the title compound that was dissolved in acetonitrile (total volume of solution: 3 l) and used in the Preparations 4 and 5. An aliquot was removed, concentrated *in vacuo* and was determined to be 75% pure on the basis of its ^1H NMR spectrum.

Preparation 4*N*-Acetyl-3-amino-(3-Fluoro-phenyl)-2-propenal

- 5 A solution of *N*-Acetyl-1-(3-fluoro-phenyl)-vinylamine (11.07 g, 61.8 mmol) in acetonitrile (25 ml) was added dropwise via a cannula to a stirred solution of (chloromethylene)dimethylammonium chloride (9.88 g, 77.2 mmol) as a suspension in acetonitrile (55 ml) at 0 °C (external). After 15 minutes the cold bath was removed and the reaction was allowed to warm to room temperature over 80 minutes, after which time TLC
- 10 showed the reaction to be essentially complete. A solution of sodium acetate (25.3 g, 308.9 mmol) in water (80 ml) was added and the reaction was stirred vigorously for 2 hours. The organics were removed and the aqueous material was extracted with ethyl acetate (100 ml). The combined organics were dried (MgSO₄), filtered and concentrated under reduced pressure to afford a yellow solid. Purification of the crude residue was accomplished by
- 15 slurring the material in a mixture of methyl *tert*-butyl ether and dichloromethane (3:1, 55 ml) for 4 hours. The resulting solid was collected by filtration and washed with additional solvent (30 ml) before being dried under vacuum to afford the title compound as an ~8:1 mixture of stereoisomers (7.56 g, 59%). *R*_f 0.17 (75% methyl *tert*-butyl ether-heptane); ¹H NMR (400 MHz, CDCl₃) δ ppm 9.36 (1H, d, *J* 8.0 Hz), 7.50-7.45 (1H, m), 7.24-7.21 (3H, m), 7.17-7.14
- 20 (1H, m), 6.91 (1H, br s) and 2.20 (3H, s). Peaks for the minor regioisomer discernible at 9.52 (1H, s) and 5.67 (1H, s).

Preparation 5*N*-Acetyl-3-amino-(3-Fluoro-phenyl)-2-propenal

25

- Oxalyl chloride (394 ml, 4.59 mol) was added over one hour to a stirred solution of DMF (370 ml, 4.80 mol) in acetonitrile (2.45 l) whilst maintaining the temperature below 10 °C (internal). Once the addition was complete, the mixture was stirred for one hour during which the temperature rose to 12 °C. The mixture was re-cooled to 5 °C and *N*-Acetyl-1-(3-fluoro-phenyl)-vinylamine in acetonitrile (2.55 l of a 2.18M solution based on input of 3-
- 30

fluorobenzonitrile, 4.17 mol based on 75% purity as determined by ^1H NMR) was added in successive batches (3 x 500 ml, 1 x 250 ml, 1 x 300 ml then 500 ml) with each addition taking 3 minutes. Once the addition was complete, acetonitrile (100 ml then 50 ml) was used to wash in any remaining substrate. A small exotherm (2-3 °C) was noted during addition of the

5 *N*-Acetyl-1-(3-fluoro-phenyl)-vinylamine. The mixture was stirred at 10 °C for 90 minutes after which a solution of sodium acetate (1.71 kg, 20.9 mol) in water (5.1 l) was added at such a rate to maintain the temperature below 10 °C (the coolant temperature was set at 0 °C during this addition). Once the addition was complete, the temperature was increased to 20 °C and the mixture stirred for 17 hours. Stirring was stopped and the layers separated. The

10 aqueous phase was extracted with ethyl acetate (3.4 l) and the combined organic extracts were washed with brine (3.4 l), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was slurried for 17 hours in a mixture of methyl *tert*-butyl ether (2.52 l) and DCM (840 ml). Filtration was followed by washing the residue with two portions of methyl *tert*-butyl ether /dichloromethane (3:1 v/v) (670 ml then 400 ml). The filtrate was then dried *in vacuo* to

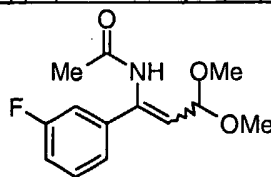
15 provide the crude product (298 g).

This crude material was combined with crude material obtained from a smaller scale reaction using the same batch of enamide (24.14 g) and the combined material (322 g) was recrystallised from acetic acid (485 ml). Filtration of the solid was followed by sequentially washing with acetic acid (250 ml) and methyl *tert*-butyl ether (2 x 250 ml) to provide the title

20 compound as a white solid and essentially a single stereoisomer (183.9 g, 14% overall based the input of 3-fluorobenzonitrile). The material had identical spectral properties to that produced in Preparation 4.

Preparation 6

25 *N*-Acetyl-3-amino-3-(3-fluoro-phenyl)-1,1-dimethoxy-2-propene



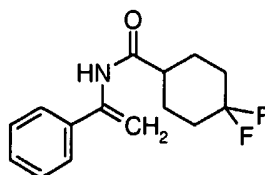
Sulfuric acid (100 μl of a solution of concentrated sulfuric acid (1 ml) in methanol (1 ml) prepared under ice-water cooling, ~ 0.9 mmol) was added to a stirred suspension of *N*-Acetyl-3-amino-(3-Fluoro-phenyl)-2-propenal (47.29 g, 228.5 mmol) and trimethylorthoacetate (38

30 ml, 297.0 mmol) cooled using an ice-water bath. After stirring at this temperature for 2 hours, saturated sodium bicarbonate (15 ml) and water (5 ml) were added to adjust the pH to 6 and the mixture was then concentrated *in vacuo*. The residue was partitioned between methyl *tert*-butyl ether (200 ml) and a mixture of water (75 ml) and saturated sodium bicarbonate (25 ml). The aqueous phase was extracted with methyl *tert*-butyl ether (100 ml) and the

combined organic extracts were washed with water (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. Drying *in vacuo* with stirring provided the title compound as an off-white solid (11.93 g, 96%) as a mixture of stereoisomers in the approximate ratio 3:1. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.91 (1H, br s), 7.38-6.91 (4H, m), 5.43 (1H, d, *J* 3.6 Hz), 5.15 (1H, d, *J* 4.4 Hz), 3.34 (6H, s) and 2.06 (3H, s). Peaks for the minor stereoisomer discernible at 6.55 (1H, d, *J* 8.0 Hz), 4.66 (1H, d, *J* 7.6 Hz), 3.28 (6H, s) and 1.94 (3H, s).

Preparation 7

1-(4,4-Difluorocyclohexanecarbonylamino)-1-phenyl-ethene

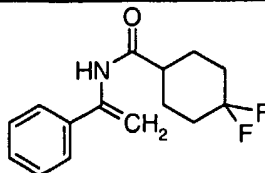


Methylmagnesium bromide (16.1 ml of a 3M solution in diethyl ether, 48.3 mmol) was added dropwise to a stirred suspension of copper(I) bromide (252 mg, 0.88 mmol) and benzonitrile (4.53 g, 43.9 mmol) in tetrahydrofuran (30 ml). The mixture was then heated at reflux for 2 hours and was then cooled to room temperature before placing in an ice-water bath. A solution of 4,4-difluorocyclohexanecarbonyl chloride (8.82 g, 48.3 mmol) in tetrahydrofuran (20 ml) was then added dropwise. The addition funnel was washed through with further tetrahydrofuran (10 ml) and the mixture was warmed to room temperature. After stirring for 72 hours the mixture was diluted with methyl *tert*-butyl ether (100 ml) and then sequentially washed with saturated ammonium chloride (2 x 100 ml) and saturated sodium bicarbonate (100 ml). The aqueous washes were extracted with methyl *tert*-butyl ether (100 ml) and the combined organic extracts were then washed with brine (100 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was partially purified by flash column chromatography (eluent: heptane/ethyl acetate 4:1 to 3:1 to 2:1) to provide two mixed fractions enriched in the title compound and a diacylated derivative in the total ratio of 4:1 (9.10 g, 71%). Potassium carbonate (68 mg, 0.49 mmol) was added to a solution of the fraction enriched in the diacylated derivative (2.02 g, 1.47 mmol based on ~30% purity as determined by integration of the ¹H NMR spectrum of the mixture) in methanol (8 ml). After stirring at room temperature for 2 hours the mixture was concentrated *in vacuo*. The residue was partitioned between water (20 ml) and dichloromethane (20 ml). The organic extract was washed with brine (20 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to provide the title compound as a light yellow solid (1.80 g, quantitative). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.48-7.28 (5H, m), 6.78 (1H, br s), 5.91 (1H, br s), 5.10 (br s) and 2.46-1.72 (9H, m).

The fraction enriched in the title compound was approximately 90% pure, as determined by ^1H NMR spectroscopy, and was used without further purification.

Preparation 8

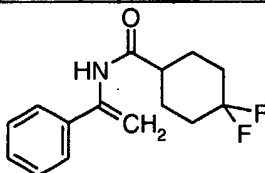
5 1-(4,4-Difluorocyclohexanecarbonylamino)-1-phenyl-ethene



- Methylmagnesium bromide (160 ml of a 1.4 M solution in Toluene:THF (3:1), 224 mmol) was charged to a dry inert reaction vessel under N_2 . Benzonitrile (23 ml, 225 mmol) was added dropwise over 25 min ($\sim 10^\circ\text{C}$ exotherm observed) and the reaction mixture stirred for 18 h.
- 10 The solution was then added dropwise over 140 min to a stirred solution of 4,4-difluorocyclohexanecarbonyl chloride (41 g, 225 mmol) in toluene (4.5 ml/g, ~ 150 ml) ($\sim 5^\circ\text{C}$ exotherm observed). The reaction mixture was stirred for 1 h and quenched with aqueous ammonium chloride (10%, 100 ml) over 5 min. The organic phase was washed with water (50 ml), concentrated *in vacuo* to 140 ml and granulated over 12 h. The resulting slurry was
- 15 cooled to 0°C for 4 h, filtered, washed with toluene (2×20 ml) and dried under vacuum at $35^\circ\text{C}/50$ mbar for 18 h to provide the title compound as a pure white solid (24 g, 40%).
- ^1H NMR (300 MHz, CDCl_3) δ ppm 9.34 (1H, s), 7.40-7.23 (5H, m), 6.10 (1H, s), 5.35 (1H, s), 2.30-2.18 (m, 1H), 2.06-1.42 (8H, m).

20 Preparation 9

1-(4,4-Difluorocyclohexanecarbonylamino)-1-phenyl-ethene

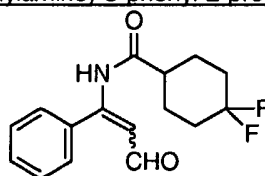


- Benzonitrile (2.0g; 19mmol) was dissolved in tetrahydrofuran (12ml) and Copper(I) bromide (55mg; 0.39mmol) added in one portion. The slurry was cooled to -5°C and
- 25 methylmagnesium bromide (3M in diethylether; 7.1ml; 21mmol) was added slowly maintaining the temperature below 10°C . Once addition was complete, the reaction was heated to reflux for 2.5h. A sample was withdrawn and partitioned between *tert*-butyl methyl ether and saturated aqueous ammonium chloride solution. Reaction completion was confirmed by TLC (1:2 ethylacetate/heptane). The reaction mixture was cooled to 0°C and lithium chloride
- 30 (0.82g; 19mmol) was added stirring the resultant slurry for 2 hrs. 4,4-difluorocyclohexanecarbonyl chloride (3.53g; 19mmol) was dissolved in tetrahydrofuran (8ml)

under N₂ at 0°C and the reaction mixture added to it dropwise over 30 min. The resulting solution was stirred at ambient temperature for 16h, then saturated aqueous sodium carbonate solution (40ml) was added causing a 10°C exotherm and the mixture to set solid. White solid was formed. Addition of water (40ml) and tetrahydrofuran (40ml) gave a mobile slurry. The slurry was stirred for 1h and the solid removed by filtration. *Tert*-butyl methyl ether (40ml) was added to the 2 phase solution and the phases were separated. The organics were washed with saturated aqueous ammonium chloride solution (2×40ml) and the combined aqueous phases re-extracted with *tert*-butyl methyl ether (40ml). The organics were washed with brine (40ml), dried over MgSO₄ and concentrated in vacuo to provide the title compound as a pale green solid (4.87g; 94.7%). Recrystallised from ⁿPrAc (3mlg⁻¹). ¹H NMR (CDCl₃) δ ppm 1.62-2.36 (m, 9H), 5.12 (br s, 1H), 5.85 (br s, 1H), 7.09 (br s, 1H), 7.39 (s, 5H).

Preparation 10

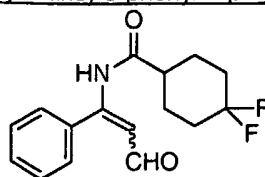
3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-2-propenal



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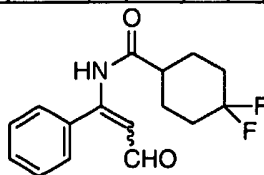
A solution of 1-(4,4-Difluorocyclohexanecarbonylamino)-1-phenyl-ethene (7.03g, 26.5 mmol) in acetonitrile (30 ml) was added in a dropwise manner to a ice-water bath cooled stirred suspension of (chloromethylene)dimethylammonium chloride (4.41 g, 34.5 mmol) in acetonitrile (30 ml). A further portion of acetonitrile (10 ml) was used to wash through the addition funnel. Once the addition was complete, the ice-water bath was removed and the mixture was stirred for 2 hours. A solution of sodium acetate (10.9 g, 133 mmol) in water (34 ml) was added and the resultant mixture was vigorously stirred for 2 hours. The phases were then partitioned and the aqueous phase was extracted with ethyl acetate (50 ml). The organic phase was concentrated *in vacuo* and the residue was then partitioned between water (50 ml) and ethyl acetate (50 ml) and further extracted with ethyl acetate (50 ml). The combined organic extracts were washed with water (50 ml), brine (50 ml), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was slurried in methyl *tert*-butyl ether (25 ml) for 17 hours, filtered and washed with further methyl *tert*-butyl ether (25 ml) to provide the title compound as a light yellow solid and a ~14:1 mixture of stereoisomers (4.87 g, 63%). ¹H NMR (400 MHz, CDCl₃) δ ppm 9.31 (1H, d, *J* 8.0 Hz), 7.55-7.45 (3H, m), 7.42-7.39 (2H, m), 7.21 (1H, d, *J* 8.0 Hz), 7.03 (1H, br s), 2.33 (1H, tt, *J* 10.8 and 4.0 Hz), 2.25-2.16 (2H, m) and 2.04-1.69 (6H, m). Signals for the minor stereoisomer were discernible at 9.51 (1H, d, *J* 2.0 Hz) and 5.69 (1H, d, *J* 2.0 Hz).

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Preparation 113-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-2-propenal

To a stirred solution of dimethylformamide (120 ml) cooled with an ice-water bath under N₂ was added POCl₃ (7.7 ml, 83 mmol) dropwise over 15 min. The reaction mixture was stirred for 30 min then a solution of 1-(4,4-Difluorocyclohexanecarbonylamino)-1-phenyl-ethene (20.0 g, 75 mmol) in dimethylformamide (80 ml) was added dropwise over 30 min. Once the addition was complete, the reaction mixture was stirred for 30 min and the ice-water bath was removed. The reaction mixture was stirred for 90 min at room temperature. The reaction mixture was then cooled with an ice-water bath and sodium acetate (37.0 g, 450 mmol) in water (80 ml) was added dropwise over 20 min. Once the addition was complete, the ice-water bath was removed and the mixture was granulated for 16 h. The slurry was filtered and washed with water (50 ml). The filtrate was stirred for 10 min and the resulting precipitate was filtered and washed with further water (50 ml). This process was repeated a further two times and the four crops were combined and dried under vacuum at 50 °C/50 mbar for 6 h to provide the title compound as an off yellow solid (19.2 g, 87%) and a 2:3 mixture of Z:E regioisomers.

¹H NMR (300 MHz, CDCl₃) δ ppm 9.39 (1H, d, *J* 8.0 Hz), 7.63-7.38 (5H, m), 7.25 (1H, d, *J* 8.0 Hz), 6.92 (1H, br s), 2.39-2.30 (m, 1H), 2.04-1.66 (8H, m). Signals for the minor stereoisomer were discernible at 11.65 (1H, br-s), 9.52 (1H, d, *J* 2.0 Hz), 5.71 (1H, d, *J* 2.0 Hz) and 2.57-2.41 (m, 1H).

Preparation 123-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-2-propenal

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A solution of 1-(4,4-Difluorocyclohexanecarbonylamino)-1-phenyl-ethene (79.1g, 298mmol) in acetonitrile (400ml) and diaza(1,3)bicyclo[5.4.0]undecane (DBU, 45.3g, 298mmol) was added to a cooled suspension (0°C) of (chloromethylene)dimethylammoniumchloride (45.8g, 358mmol) in acetonitrile (400ml) dropwise over 45 min maintaining temperature below 5°C. After stirring the reaction mixture for 2 h at ambient temperature, reaction completion was confirmed by TLC (1:1 ethylacetate/heptane, visualised under uv) confirmed complete

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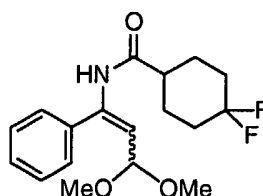
consumption of starting material. Sodium acetate (122g, 1.49mol) in water (400ml) was added and stirred for 1h. The phases were separated. The organic phase was concentrated in vacuo and the residue was partitioned between water (640ml) and ethylacetate (640ml). The phases were separated. The combined aqueous phases were re-extracted with ethyl acetate (2x640ml). The organic phase was washed with water (640ml), brine (640ml), dried over MgSO₄, and concentrated in vacuo to a beige solid. The solid was slurried in *tert*-butyl methyl ether (140ml) for 4h, collected by filtration and washed with *tert*-butyl methyl ether (40ml). The title compound was obtained as a pale yellow solid in quantitative yield.

¹H NMR (CDCl₃)

- 10 Z isomer δ: 1.62-2.45 (m,9H), 5.68 (d,1H), 7.32-7.55 (m,5H), 9.49 (d,1H), 11.64 (br s,1H(NH))
E isomer δ: 1.62-2.45 (m,9H), 7.17 (d,1H), 7.32-7.55 (m,5H), 7.61 (br s,1H(NH)), 9.17 (d,1H)

Preparation 13

3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene

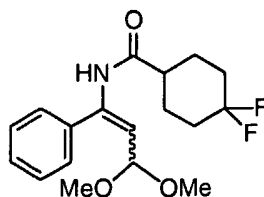


Sulfuric acid (3 drops of a solution of concentrated sulfuric acid (1 ml) in methanol (1 ml)) was added to stirred suspension of 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-2-propenal (4.79 g, 16.3 mmol) and trimethylorthoacetate (2.7 ml, 21.2 mmol) in methanol (48 ml). After 90 minutes the mixture was poured into a mixture of water (75 ml) and saturated sodium bicarbonate (25 ml). After extracting with methyl *tert*-butyl ether (150 ml), the organic extract was washed with water (50 ml) and dried (MgSO₄), filtered and concentrated *in vacuo* to provide the title compound as a light yellow solid (5.40 g, 97%) and a 2:1 mixture of regioisomers.

- 25 ¹H NMR (400 MHz, CDCl₃) δ ppm 7.99 (1H, br s), 7.43-7.26 (4H, m), 5.35 (1H, d, *J* 4.0 Hz), 5.16 (1H, d, *J* 4.0 Hz), 3.36 (6H, s) and 2.36-1.74 (9H, m). Peaks for the minor stereoisomer discernible at 6.69 (1H, d, *J* 8.0 Hz), 6.55 (1H, br s) and 4.69 (1H, d, *J* 8.0 Hz).

Preparation 14

- 30 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-1,1-dimethoxy-2-propene

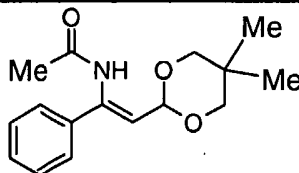


To a stirred suspension of 3-(4,4-Difluoro-cyclohexanecarbonylamino)-3-phenyl-2-propenal (22 g, 0.075 mol, Preparation 11) in MeOH (155 ml) cooled to 0 °C was added trimethylorthoacetate (15 ml, 0.120 mmol) followed by fluoroboric acid (48% aq. 138 µl, 0.00075 mmol) in MeOH (25 ml). The reaction mixture was stirred for 30 min and further fluoroboric acid (48% aq. 550 µl, 0.003 mmol) followed by further MeOH (75 ml) were added. After 60 minutes the mixture was quenched with water (100 ml) and saturated sodium bicarbonate (50 ml). After extracting with ethyl acetate (2 × 200 ml), the organic extract was washed with water (150 ml), concentrated *in vacuo* to ~1ml/g and heptane added (130 ml). The resulting slurry was filtered, washed with heptane (60 ml) and dried for 8 h under vacuum at 40 °C/50mbar to provide the title compound as a white solid (23.5 g, 92%) and a 3:1 mixture of Z:E regioisomers.

¹H NMR (300 MHz, CD₃OD) δ ppm 7.49-7.34 (5H, m), 5.82 (1H, d, *J* 6.0 Hz), 5.17 (1H, d, *J* 6.0 Hz), 3.40 (6H, s) and 2.66-2.54 (m, 1H) and 2.24-1.80 (m, 8H). Peaks for the minor stereoisomer discernible at 6.41 (1H, d, *J* 8.0 Hz), 4.66 (1H, d, *J* 8.0 Hz), 3.37 (s, 3H) and 2.49-2.39 (1H, m).

Preparation 15

N-[2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-phenyl-vinyl]-acetamide



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A 500ml flask was charged with *N*-Acetyl-3-amino-3-phenyl-2-propenal (29.1g ~114.7mmol), 2,2-dimethyl-propan-1,3-diol (14.3g, 138mmol) and methanol (100ml) and a mixture of H₂SO₄ (conc): MeOH 1:1 (45ml) was added. The mixture was diluted with toluene (300ml) and the toluene was subsequently removed under reduced pressure at 55°C. This cycle was repeated twice. The reaction was quenched by addition of aqueous sodium bicarbonate solution (200ml) and diluted with water (50ml). The mixture was extracted with TBME (2x 300ml). The combined organic extracts were washed with brine (100ml), dried (Na₂SO₄), filtered and concentrated under reduced pressure to yield the crude product (E/Z 1:2.3). The crude product was triturated with heptane: EtOAc (1:1) to yield a first crop of pure Z isomer (13.8g). A second crop yielded a mixture of E and Z isomer (E:Z 1:1.5).

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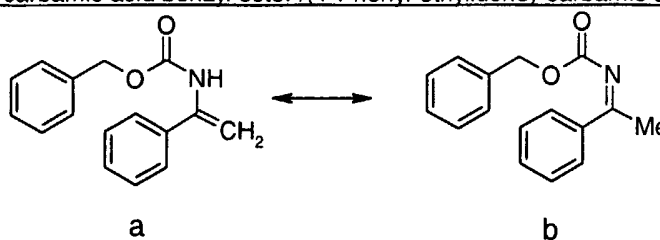
Chromatography of the filtrate on silica eluting with DCM/EtOAc (9/1 -> 2/1) gave the later eluting E-isomer (3.7g). Stereochemical was assignment based on NOE.

Z ¹H NMR (300 MHz, d6-DMSO) δ ppm 9.38 (1H, s), 7.4-7.3 (5H, m), 5.62 (1H, d), 5.18 (1H, d), 3.54 (4H, AB), 1.99 (3H, s), 1.16 (3H, s), 0.72 (3H, s).

5 E ¹H NMR (300 MHz, d6-DMSO) δ ppm 9.24 (1H, s), 7.4-7.3 (5H, m), 6.38 (1H, d), 4.58 (1H, d), 3.38 (4H, AB), 1.98 (3H, s), 1.14 (3H, s), 0.60 (3H, s).

Preparation 16

(1-Phenyl-vinyl)-carbamic acid benzyl ester / (1-Phenyl-ethylidene)-carbamic acid benzyl ester



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Methylmagnesium bromide (213ml, 0.640mol) of a 3M solution in diethyl ether, was added dropwise to a stirred suspension of copper(I) bromide (0.42g, 0.012 mol) and benzonitrile (60.4 g, 0.580 mol) in tetrahydrofuran (360 ml) keeping the temperature below 0°C. The mixture was then heated at reflux for 2.5 hours and cooled to room temperature. Lithium chloride (24.8g, 0.580mol) was added and the resultant mixture was stirred for 1h at ambient temperature before cooling the mixture to 0°C. A solution of benzylchloroformate (104.2g, 0.580mol) at 0°C in tetrahydrofuran (240 ml) was then added dropwise over 1h. The resulting greenish solution was warmed to room temperature. After stirring for 16 hours the mixture was cooled to 0°C and carefully quenched by addition of saturated aqueous NaHCO₃ solution (1.2l). The mixture was extracted with two portions of TBME (1.2l and 0.6l). The aqueous phase was filtered and then extracted with TBME (0.4l). The combined organic extracts were washed with saturated aqueous NH₄Cl solution (2 x 1.2l) and water (1.2l), dried (MgSO₄), filtered and concentrated to yield the title product (149.9g) as a yellow oil.

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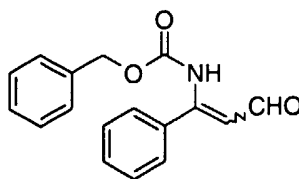
16a ¹H NMR (300 MHz, d6-DMSO) δ ppm 9.10 (1H, br s), 7.6-7.2 (10H, m), 5.35 (1H, s), 5.11 (2H, s), 4.98 (2H, s).

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16b ¹H NMR (300 MHz, d6-DMSO) δ ppm 9.10 (1H, br s), 7.82 (2H, d) 7.6-7.2 (8H, m), 5.29(2H, s), 3.,38 (3H, s).

Preparation 17

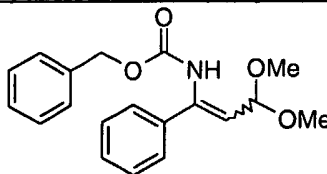
30 (3-Oxo-1-phenyl-propenyl)-carbamic acid benzyl ester



- A solution of (1-Phenyl-vinyl)-carbamic acid benzyl ester / (1-Phenyl-ethylidene)-carbamic acid benzyl ester (Preparation 16, 149.8g, 0.591mol) in acetonitrile (325 ml) was added in a dropwise manner to an ice-water bath cooled, stirred suspension of (chloromethylene)dimethylammonium chloride (98.3g, 0.768mol) in acetonitrile (650 ml) in such a manner that the temperature did not rise above 10°C. Once the addition was complete, the mixture was warmed to ambient temperature and stirred for 1.5h at room temperature. The mixture was cooled to 10°C and a solution of sodium acetate (240g) in water (650ml) was added slowly and the resultant mixture was stirred for 1.5 hours at room temperature. The phases were then partitioned and the aqueous phase was extracted with dichloromethane (2x1l). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to a dark yellow oil (203g). Chromatography on silica (1.5kg) eluting with heptane/EtOAc (1/1) gave an E/Z-mixture (1/4.6) of the title compound (102.2g).
- ¹H NMR (300 MHz, d₆-DMSO) δ ppm 10.20 (1H, br s), 9.10 (1H, s), 7.5-7.2 (10H, m), 6.65 (1H, d), 5.18 (2H, s).
- ¹H NMR (300 MHz, d₆-DMSO) δ ppm 10.20 (1H, br s), 9.74 (1H, s), 7.6-7.3 (10H, m), 5.84 (1H, d), 5.12 (2H, s).

Preparation 18

- (3,3-Dimethoxy-1-phenyl-propenyl)-carbamic acid benzyl ester



- Pyridinium 4-toluenesulphonate (550mg) was added to a clear yellow solution of (3-oxo-1-phenyl-propenyl)-carbamic acid benzyl ester (10g, 35.55mol) and trimethylorthoformate (10ml), in methanol (10 ml). The resultant mixture was stirred for 6h at room temperature. After complete conversion (as judged by TLC (heptane/ethylacetate (1/1)) the mixture was poured into saturated sodium bicarbonate solution (30ml) and extracted with TBME (2x30ml). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to provide the title compound as a light yellow oil as a mixture of isomers E/Z 2.8/1 (11.56g). Small amounts of residual trimethylorthoformate were noted in the NMR.

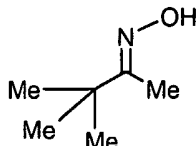
Z ^1H NMR (300 MHz, $\text{d}_6\text{-DMSO}$) δ ppm 9.04 (1H, br s), 7.5-7.2 (10H, m), 5.64 (1H, d), 5.20 (1H, d), 5.06 (2h, s), 3.24 (6H, s).

E ^1H NMR (300 MHz, $\text{d}_6\text{-DMSO}$) δ ppm 9.20 (1H, br s), 7.5-7.2 (10H, m), 6.00 (1H, d), 5.06 (2h, s), 4.54 (1H, d), 3.15 (6H, s).

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Preparation 19

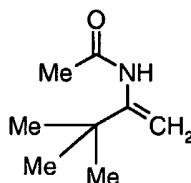
3-Dimethyl-butan-2-one oxime



Sodium acetate (27.1 g, 330 mmol) was added in 3 portions to a stirred suspension of
10 hydroxylamine hydrochloride (22.9 g, 330 mmol) in methanol (150 ml) at room temperature. Pinacolone (37.6 ml, 300 mmol) was then added dropwise over 1 hour. The reaction was stirred at room temperature for 16 hours before being poured in melting ice (150 g). This suspension was stirred for 1 hour while the remaining ice melted before the solid material was collected by filtration. The solid was washed with water (200 ml) before being dried under
15 vacuum overnight to afford the title compound (26.890 g, 78%). ^1H NMR (400 MHz, CDCl_3) δ ppm 9.58 (1H, brs), 1.88 (3H, s) and 1.14 (9H, s).

Preparation 20

N-(1-*tert*-Butyl-vinyl)-acetamide



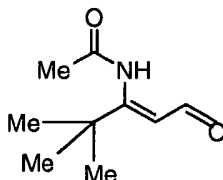
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A mixture of acetic anhydride (42 ml, 440 mmol) and acetic acid (26 ml, 440 mmol) was added to a stirred suspension of 3,3-dimethyl-butan-2-one oxime (16.893 g, 147 mmol) and powdered iron (16.38 g, 293 mmol) in toluene (180 ml) at room temperature. The reaction was slowly heated to 70°C (internal) and was kept at this temperature for 3 h before being
25 allowed to cool back to room temperature. Celite (4 g) was added to the vessel and then the reaction mixture was passed through a celite pad, eluting with additional toluene (180 ml). The liquor was concentrated under reduced pressure. The crude residue was diluted with toluene (300 ml) before being washed with 2M aqueous sodium hydroxide solution (2 x 100 ml). The organic material was dried (MgSO_4), filtered and concentrated under reduced
30 pressure to afford the title compound (14.992 g, 72%).

^1H NMR (400 MHz, CDCl_3) δ ppm 6.44 (1H, brs), 5.63 (1H, brs), 4.80 (1H, brs), 2.09 (3H, s) and 1.13 (9H, s).

Preparation 21

5 *N*-(1-*tert*-Butyl-3-oxo-propenyl)-acetamide

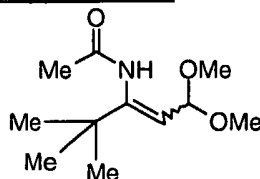


Oxalyl chloride (14.9 ml, 174 mmol) was added to a stirred solution of DMF (14.0 ml, 182 mmol) in acetonitrile (130 ml) at such a rate so as to maintain the temperature between 0°C and 5°C (internal). The reaction was stirred at 10°C (internal) for 15 minutes before being recooled to 2°C (internal). A solution of *N*-(1-*tert*-butyl-vinyl)-acetamide (22.338 g, 158 mmol) in acetonitrile (35ml + 15 ml) was added over 15 minutes. The reaction was stirred for 1 hour at 2°C (internal) before a solution of sodium acetate (65 g, 791 mmol) in water (180 ml) was added. The reaction was allowed to warm slowly to room temperature over 3 hours before the two layers were separated and then the aqueous layer was extracted with ethyl acetate (180 ml). The combined organics were washed with brine (100 ml + 50 ml), dried (MgSO_4), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography using 20% ethyl acetate – methyl *tert*-butyl ether as eluent and then by solvent slurry in methyl *tert*-butyl ether (20.6 ml) to afford the title compound (5.882 g, 22%) as a single geometric isomer.

^1H NMR (400 MHz, CDCl_3) δ ppm 9.51 (1H, d), 7.74 (1H, brs), 5.81 (1H, d), 2.22 (3H, s) and 1.21 (9H, s).

Preparation 22

25 *N*-(1-*tert*-Butyl-3,3-dimethoxy-propenyl)-acetamide



A solution of sulphuric acid (90 μ l, 19:1, methanol:concentrated sulphuric acid) was added to a stirred solution of *N*-(1-*tert*-butyl-3-oxo-propenyl)-acetamide (0.87 g, 5.1 mmol) and trimethyl orthoacetate (0.86 ml, 6.7 mmol) in methanol (4.5 ml) at 0°C (external). After stirring at this temperature for 90 minutes, saturated aqueous sodium bicarbonate solution (1 ml) was added and the reaction was allowed to warm to room temperature. The solution was poured

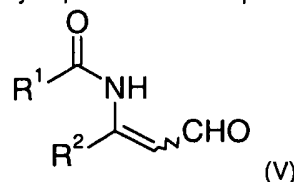
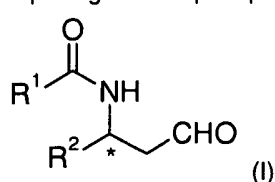
into a mixture of methyl *tert*-butyl ether (20 ml) and a 3:1 mixture of water and saturated aqueous sodium bicarbonate solution (10 ml). The aqueous layer was extracted with additional methyl *tert*-butyl ether (20 ml) before the combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound

5 (1.005 g, 91%) as a 4:1 mixture of geometric isomers.

Major isomer: ¹H NMR (400 MHz, CDCl₃) δ ppm 6.27 (1H, brs), 5.46 (1H, d), 4.94 (1H, d), 3.31 (6H, brs), 2.10 (3H, s) and 1.11 (9H, s); Discernible data for minor isomer: ¹H NMR (400 MHz, CDCl₃) δ ppm 6.23 (1H, brs), 5.59 (1H, d), 3.34 (6H, brs) and 1.99 (3H, s).

CLAIMS

1. A process for the preparation of an enantiomerically enriched compound of formula (I) comprising asymmetric hydrogenation of a compound of formula (V) or a protected derivative thereof, wherein the hydrogenation is catalysed by a cationic group 8 or 9 transition metal complex comprising a chiral phosphine ligand; followed by deprotection as required;



wherein:

- R¹ is OR^{1a}; C₁₋₆ alkyl; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₃₋₇ cycloalkyl; a 5 or 6-membered aromatic heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo, halogen, CF₃, OR⁴, CN, NR³R⁴, COR⁴, CO₂R⁴ or CONR³R⁴; wherein said heterocycles contain one to three heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, halogen, CF₃, OH, CN, NR³R⁴, COR⁴, CO₂R⁴ or CONR³R⁴;

- R^{1a} is C₁₋₆ alkyl substituted by 0 to 3 atoms or groups selected from phenyl, a 5 or 6-membered aromatic heterocycle, halogen, C₂₋₆ alkenyl, fluorenyl, adamantyl, or trimethylsilyl; wherein said heterocycle contains one to three heteroatoms selected from N, O or S; and wherein said phenyl and heterocycle are substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, halogen, CF₃, OH, CN, NO₂, COR⁴ or CO₂R⁴;

- R² is C₁₋₆ alkyl; phenyl; or a 5 or 6-membered aromatic heterocycle; wherein said heterocycle contains one to three heteroatoms selected from N, O or S; and wherein said phenyl and heterocycle are substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, halogen, CF₃, OH, CN, NR³R⁴, CO₂R⁴ or CONR³R⁴;

- R³ is H, C₁₋₆ alkyl; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₃₋₇ cycloalkyl; a 5 or 6-membered aromatic heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo, halogen, CF₃, OR⁴, CN, COR⁴, or CO₂R⁴; wherein said heterocycles contain one to three heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, halogen, CF₃, OH, CN, COR⁴ or CO₂R⁴;

R⁴ is H or C₁₋₆ alkyl;

or, when R^3 and R^4 are both attached to the same N atom, NR^3R^4 may also represent a 5 to 7 membered, saturated, partially unsaturated or aromatic, heterocycle containing from 0 to 2 additional heteroatoms selected from O, N or S; and

* denotes a chiral centre.

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2. A process as claimed in claim 1 wherein the asymmetric hydrogenation is effected in the presence of a solvent system.

3. A process as claimed in claim 1 or 2 wherein the group 8 or 9 transitional metal is Rh, Ir or Ru.

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4. A process as claimed in any of claims 1 to 3 wherein the group 8 or 9 transitional metal is Rh or Ru.

5. A process as claimed in any of claims 1 to 4 wherein the group 8 or 9 transitional metal is Rh.

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6. A process as claimed in any of claims 1 to 5 wherein the chiral phosphine ligand forms part of a precatalyst of formula $[M(\text{Ligand})(\text{diene})]A$, wherein M is a group 8 or 9 transition metal ion; Ligand is the chiral phosphine ligand; diene is either cyclooctadiene (COD) or norbornadiene (NBD); and A is an anion selected from BF_4^- , PF_6^- , trifluoromethylsulfonate (TfO^-), SbF_6^- and tetra[3,5-bis(trifluoromethyl)phenyl]borate.

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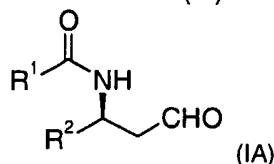
7. A process as claimed in claim 6 wherein the diene is COD and A is BF_4^- .

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8. A process as claimed in any of claims 1 to 7 comprising asymmetric hydrogenation of a protected derivative of a compound of formula (V).

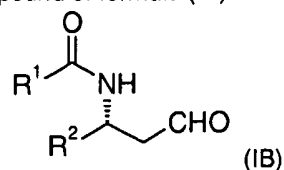
9. A process as claimed in any of claims 1 to 8 wherein the enriched enantiomer of a compound of formula (I) is a compound of formula (IA)

30



wherein R^1 and R^2 are as defined in claim 1.

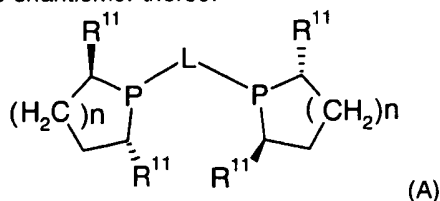
10. A process as claimed in any of claims 1 to 8 wherein the enriched enantiomer of a compound of formula (I) is a compound of formula (IB)



wherein R¹ and R² are as defined in claim 1.

5

11. A process as claimed in any of claims 1 to 10 wherein the chiral phosphine ligand is of formula (A) or the opposite enantiomer thereof



wherein:

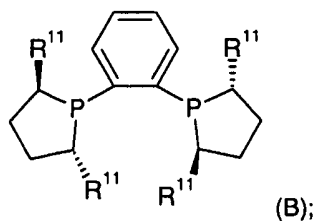
10 R¹¹ is C₁₋₆ alkyl or phenyl;

L is ferrocene; C₂₋₄ alkylene, C₂₋₄ alkenylene, phenyl, naphthyl, or a 5 to 10-membered aromatic heterocycle; wherein said heterocycle contains one to three heteroatoms selected from N, O or S; and wherein said phenyl, naphthyl or heterocycle is optionally substituted by 0 to 3 atoms or groups selected from C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy

15 alkoxy, halogen, CF₃, OH, CN;

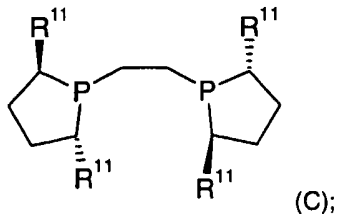
n is 0, 1 or 2.

12. A process as claimed in any of claims 1 to 10 wherein the chiral phosphine ligand is of formula (B) or the opposite enantiomer thereof

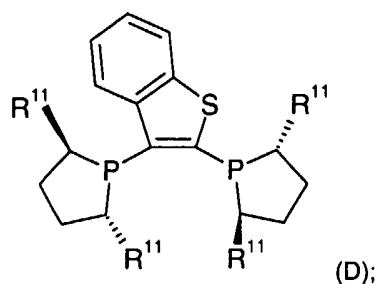


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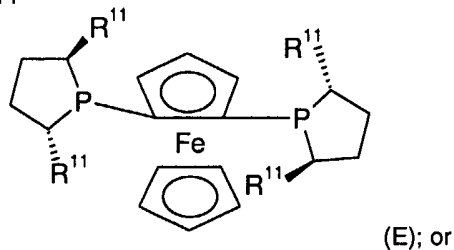
formula (C) or the opposite enantiomer thereof



formula (D) or the opposite enantiomer thereof;

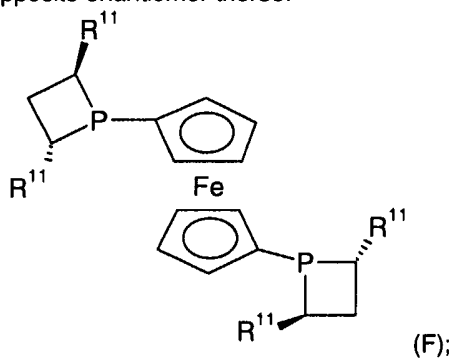


formula (E) or the opposite enantiomer thereof



5

formula (F) or the opposite enantiomer thereof



wherein R¹¹ is as defined in claim 11.

10

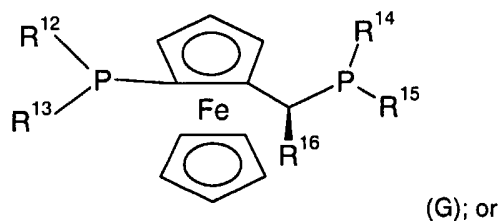
13. A process as claimed in claim 11 or 12, wherein R¹¹ is C₁-C₆ alkyl.

14. A process as claimed in any of claims 11 to 13, wherein R¹¹ is C₁-C₄ alkyl.

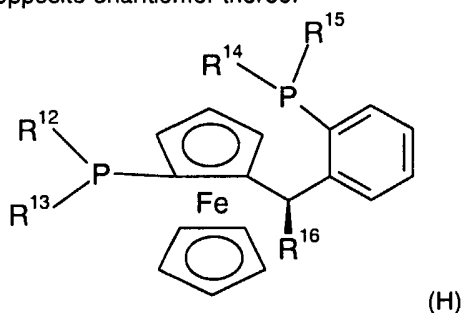
15. A process as claimed in any of claims 11 to 14, wherein R¹¹ is methyl, ethyl or isopropyl.

16. A process as claimed in claim 11 or 12 wherein R¹¹ is phenyl.

17. A process as claimed in any of claims 1 to 10 wherein the chiral phosphine ligand is of formula (G) or the opposite enantiomer thereof



5 formula (H) or the opposite enantiomer thereof

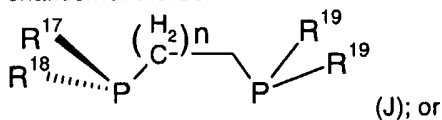


wherein:

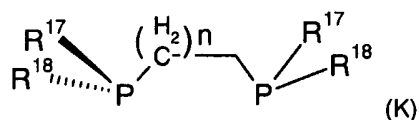
R^{12} , R^{13} , R^{14} and R^{15} are each independently selected from cyclohexyl, t-butyl or phenyl, wherein said phenyl is optionally substituted by $-\text{CF}_3$, methyl, or methoxy;

10 R^{16} is methyl, methoxy or NMe_2 .

18. A process as claimed in any of claims 1 to 10 wherein the chiral phosphine ligand is of formula (J) or the opposite enantiomer thereof



15 formula (K) or the opposite enantiomer thereof

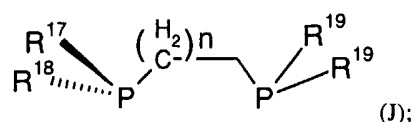


wherein:

R^{17} , R^{18} and R^{19} are independently C_{1-6} alkyl or phenyl wherein said phenyl is optionally substituted by $-\text{CF}_3$, methyl, or methoxy; and R^{17} and R^{18} are different from each other ;

20 n is 0, 1 or 2.

19. A process as claimed in any of claims 1 to 10 and 18, wherein the chiral phosphine ligand is of formula (J) or the opposite enantiomer thereof



wherein R^{17} , R^{18} , R^{19} and n are as defined in claim 18.

20. A process as claimed in claim 19, wherein R^{17} is t-butyl, R^{18} is methyl, R^{19} is t-butyl and n is 0.

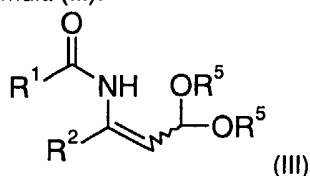
21. A process as claimed in claim 9 wherein asymmetric hydrogenation yields a compound of formula (IA) in at least 70% enantiomeric excess.

22. A process as claimed in claim 10 wherein asymmetric hydrogenation yields a compound of formula (IB) in at least 70% enantiomeric excess.

23. A process as claimed in any of claims 1 to 22 wherein the solvent system comprises an alcohol having between 1 and 10 carbon atoms.

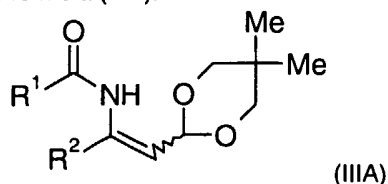
24. A process as claimed in any of claims 1 to 23 wherein the protected derivative of the compound of formula (V) is an acetal derivative.

25. A process as claimed in claim 24 wherein the acetal derivative of the compound of formula (V) is a compound of formula (III).



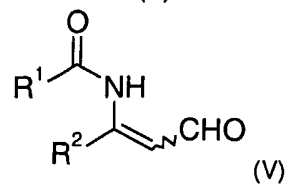
wherein R^1 and R^2 are as defined in claim 1 and R^5 is C_{1-6} alkyl.

26. A process as claimed in claim 24 wherein the acetal derivative of the compound of formula (V) is a compound of formula (IIIA).



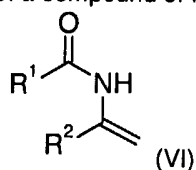
wherein R^1 and R^2 are as defined in claim 1.

27. A process as claimed in claim 25 wherein the preparation of the acetal of formula (III) comprises reaction of a compound of formula (V)



5 with R⁵OH (IV) under conventional conditions, wherein R¹, R² and R⁵ are as defined in claim 25.

28. A process as claimed in any of claims 1 to 27 wherein the preparation of a compound of formula (V) comprises formylation of a compound of formula (VI)



10 wherein R¹ and R² are as defined in claim 1, under conventional conditions.

29. A process as claimed in any of claims 1 to 28 wherein the preparation of a compound of formula (VI) comprises reaction of a compound of formula (VII)

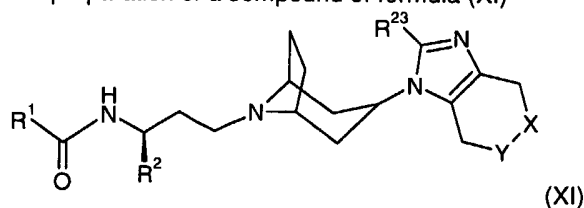


15 with a compound of formula (VIII)

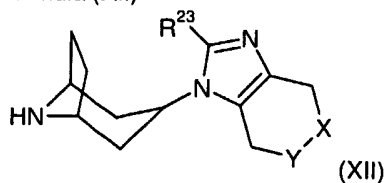


in the presence of MeMgX and optionally of CuX,
wherein R¹ and R² are as defined in claim 1 and X is halogen.

20 30. A process for the preparation of a compound of formula (XI)



or a pharmaceutically acceptable salt, solvate or derivative thereof, comprising reductive amination of a compound of formula (IA) prepared according to any of claims 1 to 9, 11 to 21 or 23 to 29, with an amine of formula (XII)



wherein:

R^1 and R^2 are as defined in claim 1;

X and Y are selected from CH_2 and NR^{24} such that one of X and Y is CH_2 and the other is NR^{24} ;

5 R^{24} is R^{25} , COR^{25} , CO_2R^{25} , $CONR^{26}R^{27}$, SO_2R^{25} , or $(C_{1-6} \text{ alkylene})\text{phenyl}$, wherein phenyl is substituted by 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, halogen, CF_3 , OH, CN, $NR^{26}R^{27}$, COR^{27} , CO_2R^{27} or $CONR^{26}R^{27}$;

R^{23} is C_{1-4} alkyl substituted by 0 to 3 fluorine atoms;

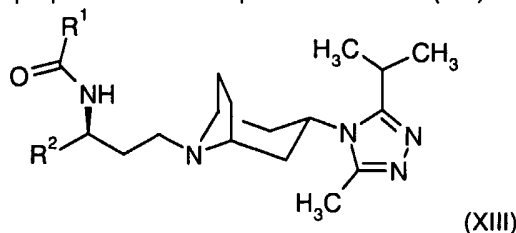
R^{25} is C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{3-7} cycloalkyl; a 5 or 6-membered aromatic
10 heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo, halogen, CF_3 , OR^{27} , CN, $NR^{26}R^{27}$, COR^{27} , CO_2R^{27} or $CONR^{26}R^{27}$; wherein said heterocycles contain one to three heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, halogen, CF_3 , OH, CN, $NR^{26}R^{27}$, COR^{27} , CO_2R^{27} or $CONR^{26}R^{27}$;
15

R^{26} is H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{3-7} cycloalkyl; a 5 or 6-membered aromatic heterocycle; or a 4 to 7-membered saturated heterocycle; wherein said alkyl, alkenyl, alkynyl and cycloalkyl are substituted by 0 to 3 atoms or groups selected from oxo, halogen, CF_3 , OR^{27} , CN, COR^{27} or CO_2R^{27} ; wherein said heterocycles contain one to three
20 heteroatoms selected from N, O or S; and wherein said heterocycles are substituted by 0 to 3 atoms or groups selected from C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, halogen, CF_3 , OH, CN, COR^{27} or CO_2R^{27} ;

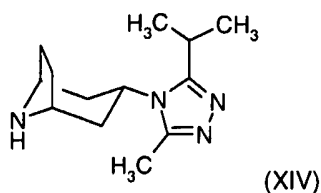
R^{27} is H or C_{1-6} alkyl;

or, when R^{26} and R^{27} are both attached to the same N atom, $NR^{26}R^{27}$ may also
25 represent a 5 to 7 membered, saturated, partially unsaturated or aromatic, heterocycle containing from 0 to 2 additional heteroatoms selected from O, N or S.

31. A process for the preparation of a compound of formula (XIII)



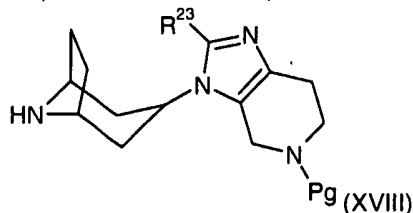
30 or a pharmaceutically acceptable salt, solvate or derivative thereof, comprising reductive amination of a compound of formula (IA) prepared according to any of claims 1 to 9, 11 to 21 or 23 to 29, with an amine of formula (XIV)



wherein R^1 and R^2 are as defined in claim 1.

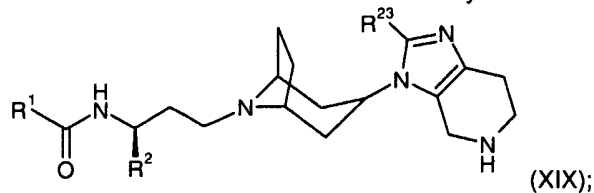
32. A process for the preparation of a compound of formula (XI) wherein Y is NR^{24} comprising

- a) reductive amination of a compound of formula (I), prepared according to any of claims 1 to 9, 11 to 21 or 23 to 29, with an amine of formula (XVIII)



under conventional conditions, wherein R^{23} is as defined in claim 30 and Pg is an amine protecting group; followed by

- b) deprotection under conventional conditions to yield an amine of formula (XIX)



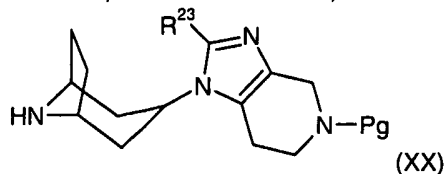
followed by

- c) conversion of the amine of formula (XIX) to a compound of formula (XI).

15

33. A process for the preparation of a compound of formula (XI) wherein X is NR^{24} comprising

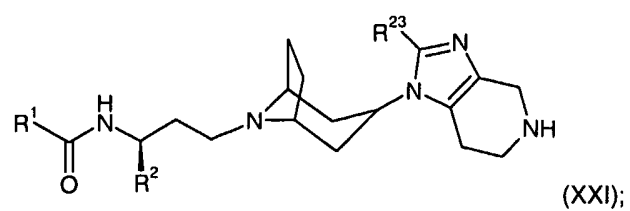
- a) reductive amination of a compound of formula (I), prepared according to any one of claims 1 to 9, 11 to 21 or 23 to 29, with an amine of formula (XX)



under conventional conditions, wherein R^{23} is as defined in claim 30 and Pg is an amine protecting group; followed by

- b) deprotection under conventional conditions to yield an amine of formula (XXI)

20



followed by

c) conversion of the amine of formula (XXI) to a compound of formula (XI).

5 34. A compound of formula (II), (III), (IIIA), (V) and (VI).