Abstract:
The invention relates to the preparation of gamma amino acids of formula (I) and pharmaceutically acceptable salts, solvates and prodrugs thereof, and to intermediates used for their preparation, (formula I) wherein R is selected from an alkyl group, an alkynyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted and * denotes a chiral centre. In particular, the present invention provides an efficient synthesis of (S)-pregabalin which is suitable for carrying out on an industrial scale.
5 [0001] The present invention relates to the preparation of gamma amino acids, and pharmaceutically acceptable salts, solvates and prodrugs thereof.

[0002] In particular, the invention relates to an preparation of both (S)- and (R)-enantiomers of gamma amino acids. In particular, the invention relates to the preparation of (S)-pregabalin and pharmaceutically acceptable salts, solvates and prodrugs thereof. The invention further relates to intermediates used in said preparations, processes for their synthesis and use thereof to prepare gamma amino acids.

BACKGROUND

15 [0003] (S)-pregabalin is an anticonvulsive drug which is also indicated in the treatment of generalised anxiety disorder (GAD) in adults, and the treatment of peripheral and central neuropathic pain in adults. Its chemical name is (3S)-3-(aminomethyl)-5-methylhexanoic acid or (S)-(+)\textmd{-}4-amino-3-(2-methylpropyl)butanoic acid, and it has the following chemical structure:

20 [0004] A synthesis of (S)-pregabalin is described by Hayashi et al. (Organic Letters, 2007, Vol. 9, No.25, 5307 - 5309). The synthesis comprises conjugate addition of nitromethane to \( \alpha,\beta \)-unsaturated aldehydes in the presence of a diphenylprolinol silyl ether catalyst to give an aliphatic nitro compound which undergoes oxidation followed by reduction to (S)-pregabalin (Scheme 1).

25 [0005] Scheme 1
The catalyst is prepared in six steps. The scale up of the synthesis is difficult making it unsuitable for use on an industrial scale.

The present invention provides an efficient method for preparing gamma amino acids such as (S)-pregabalin, preferably in high enantiomeric purity.

SUMMARY OF THE INVENTION

One aspect of the invention relates to a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{COOH} \\
\text{R}_1^* & \quad \text{(I)}
\end{align*}
\]

wherein:

- \(\text{R}_1^*\) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and * denotes a chiral centre;

which process comprises the step of reacting a compound of formula (IV) with nitromethane in the presence of a catalyst to provide a compound of formula (V):

\[
\begin{align*}
\text{R}_1^* & \quad \text{COOH} \\
\text{R}_1^* & \quad \text{(I)}
\end{align*}
\]

wherein:

- \(\text{R}_1^*\) and * are as defined above in relation to the compound of formula (I); \(\text{R}_2\) is an alkyl group or aryl group, each of which may be optionally substituted; and \(X\) is an electron withdrawing group.

A further aspect of the invention relates to a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{COOH} \\
\text{R}_1^* & \quad \text{(I)}
\end{align*}
\]

wherein:

- \(\text{R}_1^*\) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and * denotes a chiral centre;
which process comprises the step of preparing a compound of formula (IV) by reacting a compound of formula (III) with a compound of formula (II):

\[
\begin{array}{c}
\text{(III)} \\
\text{R}^1 \text{O} \text{N} \text{R}^2 \\
\text{X}
\end{array}
\begin{array}{c}
\text{(II)} \\
\text{R}^1 \text{H} \\
\end{array}
\begin{array}{c}
\text{(IV)} \\
\text{R}^1 \text{N} \text{O} \text{N} \text{R}^2 \\
\text{X}
\end{array}
\]

wherein:

R\(^1\) is defined above in relation to the compound of formula (I); R\(^2\) is an alkyl group or aryl group, each of which may be optionally substituted; and X is an electron withdrawing group.

[0010] A further aspect of the invention relates to a compound of formula (V), and salts, thereof,

\[
\begin{array}{c}
\text{(V)} \\
\text{R}^1 \text{O} \text{N} \text{R}^2 \\
\text{X}
\end{array}
\]

wherein:

R\(^1\) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; R\(^2\) is an alkyl group or an aryl group, each of which may be optionally substituted; * denotes a chiral centre; and X is an electron withdrawing group.

[0011] A further aspect of the invention relates to the use of a compound of formula (V):

which process comprises reacting a compound of formula (IV), with nitromethane in the presence of a catalyst:

\[
\begin{array}{c}
\text{(IV)} \\
\text{R}^1 \text{N} \text{O} \text{N} \text{R}^2 \\
\text{X}
\end{array}
\begin{array}{c}
\text{CH}_3 \text{NO}_2 \\
\end{array}
\begin{array}{c}
\text{(V)} \\
\text{R}^1 \text{N} \text{O} \text{N} \text{R}^2 \\
\text{X}
\end{array}
\]

wherein:

R\(^1\) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; * denotes a chiral centre; R\(^2\) is an alkyl group or aryl group, each of which may be optionally substituted; and X is an electron withdrawing group.

[0012] A further aspect of the invention relates to the use of a compound of formula (V):
wherein:

R¹ is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; * denotes a chiral centre; R² is an alkyl group or aryl group, each of which may be optionally substituted; and X is an electron withdrawing group for the preparation of a compound of formula (I), in particular (S)-pregabalin.

[0013] A further aspect of the invention relates to a compound of formula (IV), or salt, thereof,

wherein:

R¹ is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; R² is an alkyl group or aryl group, each of which may be optionally substituted; and X is an electron withdrawing group.

[0014] A further aspect of the invention relates to a process for the preparation of a compound of formula (IV), and salts thereof, which process comprises reacting a compound of formula (III) with a compound of formula (II):

wherein:

R¹ is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; R² is an alkyl group or aryl group, each of which may be optionally substituted; and X is an electron withdrawing group.

[0015] A further aspect of the invention relates to the use of compound (IV):

wherein:
[0015] A further aspect of the invention relates to a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\text{(I)} \quad \text{H}_2\text{N} - \overset{*}{R^1} - \text{COOH}
\]

wherein:

- \( R^1 \) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and * denotes a chiral centre;

\[
\text{(II)} \quad \text{H} - \overset{\text{O}}{R_1}
\]

\[
\text{(IIIA)} \quad \overset{\text{O}}{\text{N}} - \overset{\text{R_2}}{\text{R}}
\]

\[
\text{(IIIB)} \quad \overset{\text{O}}{\text{L}} - \overset{\text{O}}{\text{N}} - \overset{\text{R_2}}{\text{R}}
\]

wherein:

- \( L \) is a hydroxyl activating group, \( R^1 \) is defined above in relation to the compound of formula (I);
- \( R^2 \) is an alkyl group or aryl group, each of which may be optionally substituted;

\[
\text{(IIB)} \quad \overset{\text{OL}}{\text{O}} - \overset{\text{X}}{\text{N}} - \overset{\text{R_2}}{\text{R}}
\]

wherein:

- \( X \) is an electron withdrawing group; and converting the compound of formula (IIIB) to a compound of formula (IV).

[0016] A further aspect of the invention relates to a process for the preparation of a compound of formula (IV), and salts thereof, which process comprises reacting a compound of formula (IIIA) with a compound of formula (II) to form a compound of formula (IIIB):

\[
\text{(IIIC)} \quad \overset{\text{OL}}{\text{O}} - \overset{\text{X}}{\text{N}} - \overset{\text{R_2}}{\text{R}}
\]

wherein:

\[
\text{(IV)} \quad \text{R is selected from a n alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionall}
\]

\[
\text{y substituted; \emph{and} X is an electron withdrawing group for the preparation of a compound of formula (I), in particular (S)-}
\]

\[
\text{pregabalin.}
\]
wherein:

- L is a hydroxyl activating group, \( R^1 \) is defined above in relation to the compound of formula (I);
- and \( R^2 \) is an alkyl group or aryl group, each of which may be optionally substituted; and
- converting the compound of formula (IIIB) to a compound of formula (NIC):

\[
\text{OL} \quad \text{O} \quad \text{N} \quad \text{R}^2
\]

\[
\text{OL} \quad \text{O} \quad \text{N} \quad \text{R}^2
\]

\[
\text{X}
\]

\[
\text{X}
\]

wherein:

- \( X \) is an electron withdrawing group; and converting the compound of formula (IIIC) to a compound of formula (IV).

[0018] A further aspect of the present invention relates to a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\text{H}_2\text{N} \quad \text{COOH}
\]

\[
\text{R}^1 \quad \text{*}
\]

\[
\text{I}
\]

wherein:

- \( R^1 \) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and * denotes a chiral centre;
- which process comprises the step of reacting a compound of formula (IIA) with a compound of formula (III) in the presence of a catalyst to provide a compound of formula (V);

\[
\text{R}^1 \quad \text{NO}_2
\]

\[
\text{R}^2 \quad \text{X}
\]

\[
\text{R}^2 \quad \text{X}
\]

\[
\text{NO}_2
\]

\[
\text{R}^1 \quad \text{*} \quad \text{R}^2
\]

\[
\text{V}
\]

wherein:

- \( R^1 \) and * are as defined above in relation to the compound of formula (I); \( R^2 \) is an alkyl group or aryl group, each of which may be optionally substituted; and \( X \) is an electron withdrawing group.
[0019] A further aspect of the present invention relates to a process for the preparation of a compound of formula (V), and salts thereof, which process comprises reacting a compound of formula (IIA) with a compound of formula (III) in the presence of a catalyst:

\[
\begin{align*}
\text{(IIA)} & \quad \text{N} \quad \text{(III)} \\
R_1^1 \quad \text{NO}_2 & \quad R_2 \quad X \quad \text{N} \quad \text{O} \quad \text{NO}_2 \\
\end{align*}
\]

wherein:

- \( R_1^1 \) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted;
- \( R_2 \) is an alkyl group or an aryl group, each of which may be optionally substituted;
- and \( X \) is an electron withdrawing group.

[0020] A further aspect relates to the compounds of formula (IIA), (IMA), (IIIB) and (NIC) as defined herein above and their use in the preparation of a compound of formula (I), in particular (S)-pregabalin.

[0021] A further aspect of the invention relates to the following compounds and their use as catalysts in chemical processes:

wherein \( Y^- \) is a counterion. Examples of suitable counterions include fluoride, chloride, bromide and iodide. Preferably the counterion is bromide.

**DETAILED DESCRIPTION**

[0022] The present invention provides an efficient four step process for the preparation of gamma amino acids beginning from readily available starting materials (Schemes 2 and 3).

**Scheme 2**
Surprisingly, aqueous solvent has been demonstrated to be suitable for the reaction of compounds of formula (II) with compounds of formula (III). The ability to use solvents comprising water as a reaction solvent is preferable on an industrial scale as it is reduces cost and reduces the need to handle harmful solvents. This is advantageous in terms of safety and is beneficial for the environment.

The chiral centre is introduced by addition of nitromethane to compounds of formula (IV) in the presence of a catalyst. This reaction may proceed in high yield and, if a chiral catalyst is used, may proceed with high enantioselectivity. Preferably the reaction does not require stoichiometric quantities of catalyst.

Preferably, the catalysts employed are cheap and commercially available, or can be easily synthesized.

Preferably the process for the preparation of gamma amino acids of the present invention does not require chromatographic purification of the intermediates. This is preferable for a synthesis which may be carried out on an industrial scale.

General Definitions
As used herein, the term "alkyl" includes both saturated straight chain and branched alkyl groups which may be substituted (mono- or poly-) or unsubstituted. Preferably, the alkyl group is a C_{1-20} alkyl group, more preferably a C_{1-15} alkyl group, more preferably still a C_{1-10} alkyl group, more preferably still a C_{1-8} alkyl group, more preferably still a C_{1-6} alkyl group. Particularly preferred alkyl groups include, for example, methyl, ethyl, n-propyl, /so-propyl, n-butyl, sec-butyl, /so-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl.

As used herein, the term "cycloalkyl" refers to a cyclic alkyl group which may be substituted (mono- or poly-) or unsubstituted.

As used herein, the term "alkenyl" refers to a carbon chain containing one or more carbon-carbon double bonds, which may be branched or unbranched, and substituted (mono- or poly-) or unsubstituted. Preferably the alkenyl group is a C_{2-20} alkenyl group, more preferably a C_{2-15} alkenyl group, more preferably still a C_{2-10} alkenyl group, more preferably still a C_{2-8} alkenyl group, or more preferably still a C_{2-6} alkenyl group.

As used herein, the term "alkynyl" refers to a carbon chain containing one or more carbon-carbon triple bonds, which may be branched or unbranched, and substituted (mono- or poly-) or unsubstituted. Preferably the alkynyl group is a C_{2-20} alkynyl group, more preferably a C_{2-15} alkynyl group, more preferably still a C_{2-10} alkynyl group, more preferably still a C_{2-8} alkynyl group, or more preferably still a C_{2-6} alkynyl group.

As used herein, the term "aryl" refers to a C_{6}C_{6+} aromatic group which may be substituted (mono- or poly-) or unsubstituted. Preferably the aryl group is a C_{6,14} aryl group, more preferably a C_{6,10} aryl group. Typical examples include phenyl, naphthyl and anthracenyl.

The term "heteroaryl" refers to an aryl group as defined above which contains one or more heteroatoms. Suitable heteroatoms will be apparent to those skilled in the art and include, for example, sulphur, nitrogen, oxygen, phosphorus and silicon.

The term "alkoxy" refers to an O-alkyl group, wherein alkyl is as defined above. Preferably, the alkoxy group is a C_{1-20} alkoxy group, more preferably a C_{1-15} alkoxy group, more preferably still a C_{1-10} alkoxy group, more preferably still a C_{1-8} alkoxy group, more preferably still a C_{1-6} alkoxy group. Particularly preferred alkoxy groups include, for example, methoxy, ethoxy, /so-propoxy, propoxy, butoxy, /so-butoxy, pentoxy and hexoxy.

The term "electron withdrawing group" refers to any group capable of withdrawing electrons away from a reaction centre. These groups may be electron withdrawing either by the inductive effect or the mesomeric effect. In one embodiment the electron withdrawing group is electron withdrawing via the inductive effect. In another embodiment the electron withdrawing group is electron withdrawing via the mesomeric effect. Examples of suitable electron withdrawing groups include halogens, nitriles, nitro groups, esters and sulfones. Preferably the electron withdrawing group is selected from halogens, NO_2, CN, COOR^3 and S0_2R^3; wherein
each R\textsuperscript{3} group is independently H or an optionally substituted alkyl group. More preferably the electron withdrawing group is selected from NO\textsubscript{2}, CN, COOR\textsuperscript{3} and SO\textsubscript{2}R\textsuperscript{3}; wherein each R\textsuperscript{3} group is independently H or an optionally substituted alkyl group. More preferably, X is CN or NO\textsubscript{2}. More preferably, X is NO\textsubscript{2}.

[0035] As used herein the term "hydroxyl activating group" refers to an alkyl sulfonyl or aryl sulfonyl compound. Suitable hydroxyl activating groups include compounds of formula R\textsuperscript{*}-SO\textsubscript{2}\textsuperscript{r}, where R\textsuperscript{*} is an alkyl group or an aryl group. Suitable alkyl groups include C\textsubscript{1-6} alkyl optionally substituted with one or more, preferably 1-3, halogen atoms. Preferably the halogen is fluoro. Suitable aryl groups include phenyl optionally substituted with one or more, preferably 1-3, C\textsubscript{1-3} alkyl groups. Preferred alkyl and aryl sulfonyl compounds include methanesulfonyl, benzene sulfonyl, p-toluenesulfonyl and trifluoromethanesulfonyl.

[0036] Where a term defined above is described as substituted, examples of suitable substituents may include one or more of hydroxy, alkyl, aryl, halo, alkoxy, haloalkyl, haloalkoxy, amino, aminoalkyl, nitro and cycloalkyl.

[0037] It will be appreciated by those skilled in the art that the compounds of formula (I), (V), (VI) and (Vlb) contain a chiral centre (denoted as *) and thus exist in the form a pair of optical isomers (i.e. enantiomers). Thus the compounds of formula (I), (V), (VI) and (Vlb) may be either (S)-enantiomers or (R)-enantiomers or mixtures thereof including racemic mixtures.

Salts

[0038] The present invention relates to the preparation of all salts of the compounds described herein. The term "compound" is intended to include all such salts unless the context requires otherwise.

[0039] Acceptable salts of the compounds prepared herein include suitable acid addition or base salts thereof. A review of suitable pharmaceutical salts may be found in Berge et al., J. Pharm. Sci., 66: 1, 19 (1977). Salts are formed, for example with strong inorganic acids such as mineral acids, e.g. sulphuric acid, phosphoric acid or hydrohalic acids; with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted (e.g., by halogen), such as acetic acid; with saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or tetraphthalic; with hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid; with aminoacids, for example aspartic or glutamic acid; with benzoic acid; or with organic sulfonic acids, such as (CrC\textsuperscript{3}-alkyl- or aryl-sulfonic acids which are unsubstituted or substituted (for example, by a halogen) such as methane- or p-toluene sulfonic acid. Salts which are not pharmaceutically acceptable may still be valuable as intermediates.

Solvates
The present invention also includes the preparation of solvate forms, hydrated forms and anhydrous forms of the compounds of formula (I). The term "compound" is intended to include all such solvates unless the context requires otherwise.

Polymorphs

The invention furthermore encompasses the preparation of the compounds of formula (I) in their various polymorphic forms. It is well established within the pharmaceutical industry that chemical compounds may be isolated in any of such forms by slightly varying the method of purification and/or isolation from the solvents used in the synthetic preparation of such compounds. The term "compound" is intended to include all such polymorphs unless the context requires otherwise.

Prodrugs

The invention further includes the preparation of the compounds of formula (I) in prodrug form. Such prodrugs are generally compounds of formula (I) wherein one or more appropriate groups have been modified such that the modification may be reversed upon administration to a human or mammalian subject. Such reversion is usually performed by an enzyme naturally present in such subject, though it is possible for a second agent to be administered together with such a prodrug in order to perform the reversion in vivo. Examples of such modifications include esterification wherein the reversion may be carried out be an esterase etc. Other such systems will be well known to those skilled in the art. The term "compound" is intended to include all such prodrugs unless the context requires otherwise.

The Compounds of Formulae (I), (II), (HA), (III), (IDA), (NIB), (IIIC), (IV), (V), (VI) and (Vlb)

Throughout the specification, definitions of the substituents $R^1$, $R^2$ and $X$ apply to each of compounds formulae (I), (II), (HA), (III), (IIIA), (IIIC), (IV), (V), (VI) and (Vlb) unless the context requires otherwise.

Throughout the specification, where substituents $R^1$, $R^2$ and $R^3$ are defined as optionally substituted, examples of suitable substituents may include one or more of hydroxy, alkyl, aryl, halo, alkoxy, haloalkyl, haloalkoxy, amino, aminoalkyl and cycloalkyl. Preferably, suitable substituents are selected from one or more of hydroxy, alkyl, alkoxy, halo, haloalkoxy and aryl. More preferably, suitable substituents are selected from one or more of hydroxy, methyl, ethyl, methoxy, ethoxy, halo, CF$_3$ and phenyl.

In one embodiment $X$ is an electron withdrawing group. In another embodiment $X$ is an electron withdrawing group selected from halogens, nitriles, nitro groups, esters and sulfones. In another embodiment $X$ is an electron withdrawing group selected from halogens, NO$_2$, CN, COOR$^3$ and S0$_2$R$^3$; wherein each $R^3$ group is independently H or an optionally substituted alkyl.
In another embodiment X is an electron withdrawing group selected from N0₂, CN, COOR³ and S0₂R³; wherein each R³ group is independently H or an optionally substituted alkyl. Preferably, X is CN or N0₂. More preferably, X is N0₂.

[0046] In one embodiment R¹ is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted.

[0047] In one embodiment R² is selected from an alkyl group and a phenyl group, each of which may be optionally substituted.

[0048] Preferably, R¹ is an alkyl group, an alkenyl group or a cycloalkyl, each of which may be optionally substituted. More preferably R¹ is an optionally substituted alkyl group.

[0049] Preferably, R¹ and R² are independently selected C₁₂₀ alkyl groups, more preferably a C₁₁₅ alkyl groups, more preferably still a C₁₁₀ alkyl groups, more preferably still a C₁₈ alkyl groups, more preferably still a C₁₆ alkyl groups; which may optionally be substituted.

[0050] In one embodiment R¹ and R² are independently selected from methyl, ethyl, n-propyl, /so-propyl, n-butyl, sec-butyl, /so-butyl, fe/f-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl.

[0051] In one embodiment R¹ and R² are independently selected from methyl, ethyl, n-propyl, /so-propyl, n-butyl, sec-butyl, /so-butyl, fe/f-butyl.

[0052] In one embodiment R¹ is selected from methyl, ethyl, n-propyl, /so-propyl, n-butyl, sec-butyl, /so-butyl, fe/f-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl; and R² is methyl.

[0053] In one embodiment R¹ is selected from methyl, ethyl, n-propyl, n-butyl, /so-butyl, n-heptyl and n-octyl; and R² is methyl.

[0054] In a particularly preferred embodiment R¹ is /so-butyl and R² is methyl.

[0055] In a most preferred embodiment is R¹ /so-butyl, R² is methyl and X is N0₂.

The Catalyst

[0056] In one embodiment, the preparation of the compound of formula (V) is carried out in the presence of a catalyst.

[0057] In one embodiment the catalyst is a phase transfer catalyst. Examples of phase transfer catalysts include tetrabutylammonium salts such as tetrabutylammonium bromide and tetrabutylammonium iodide; tetrabutylammonium halides; arylation ammonium halides such as triphenylbutylammonium bromide; trialkylarylpheosphonium halides such as trimethylphenylphosphonium bromide; trialkylphosphonium halides such as tetrabutylphosphonium bromide; guanidinium salts; metal salen complexes; and crown ethers.

[0058] In one embodiment the catalyst is an organic amine for example a compound of formula N(Rz)₃, where Rz is independently selected from hydrogen and C₁₆ alkyl. Preferably, one and
more preferably two and more preferably three of Rz are C₄₋₉ alkyl. Most preferably the amine is triethyl amine.

[0059] In one embodiment the catalyst is a chiral catalyst.

[0060] In one embodiment the chiral catalyst is a cinchona alkaloid derivative.

[0061] In one embodiment the cinchona alkaloid derivatives may include, but are not limited to, compounds of formula (Vila) or (Vilb):

![Chemical Structures](Vila), (Vilb);

wherein, M is selected from H, hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, 0(CH₂)ₙ-heteroaryl, 0(CH₂)ₙ-cycloalkyl, amino, NR¹C(=0)R₁², C(=0)NR²R³, C(=0)R₁², 0(C=0)R₁², C(=0)OR₁², NR¹S₀₂R₁², and R₇; in which each aryl, heteroaryl and cycloalkyi groups may be optionally substituted.

[0062] Preferably M is selected from H, hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, 0(CH₂)ₙ-heteroaryl, 0(CH₂)ₙ-cycloalkyl and R₇; more preferably M is selected from H, hydroxy, alkoxy, O-alkenyl and R₇. Most preferably, M is selected from H, hydroxy and methoxy.

R₄ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, 0(CH₂)ₙ-heteroaryl, 0(CH₂)ₙ-cycloalkyl, amino, NR¹C(=0)R₁², C(=0)NR²R³, C(=0)R₁², 0(C=0)R₁², C(=0)OR₁², NR¹S₀₂R₁², and R₇; in which each aryl, heteroaryl and cycloalkyi groups may be optionally substituted.

[0063] Preferably R₄ is selected from hydroxy, alkoxy, O-alkenyl, optionally substituted 0(CH₂)ₙ-aryl, amino, NR¹S₀₂R₁², and R₇. More preferably, R₄ is selected from hydroxyl, alkoxy, O-alkenyl, R₇ and 0(CH₂)ₙ-aryl optionally substituted with one or more of halo, N0₂, Me, CF₃ and OMe. Most preferably, R₄ is selected from hydroxy, O-benzyl, O-bis(trifluoromethyl)benzyl, 0-2-nitro-4,5-dimethoxybenzyl and R₇.

[0064] R¹¹, R¹², R¹³ and R¹⁴ are independently selected from H, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group and a cycloalkyi group, each of which may be optionally substituted; or R¹³ and R¹⁴ may together define an optionally substituted C₅₋₁₅ cycloalkyi group or C₅₋₁₅ heteroaryl group.
Preferably \( R^{11} \) is selected from H and an alkyl group. More preferably, \( R^{11} \) is selected from H, methyl and ethyl.

Preferably \( R^{12}, R^{13} \) and \( R^{14} \) are independently selected from H, and optionally substituted alkyl groups, aryl groups, heteroaryl groups and cycloalkyl groups. More preferably, \( R^{12}, R^{13} \) and \( R^{14} \) are independently selected from H, alkyl, aryl and cycloalkyl.

In one embodiment \( R^{13} \) and \( R^{14} \) together define a piperidinyl, piperazinyl or a pyridyl group.

\( R^6 \) and \( R^{6\#} \) are independently selected from H, alkyl and alkenyl, each of which may be optionally substituted.

Preferably \( R^5 \) and \( R^{5\#} \) are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl. Most preferably \( R^5 \) and \( R^{5\#} \) are independently selected from H, ethyl and ethenyl.

\( R^6 \) is selected from an alkyl group, an alkenyl group, an alkynyl group, a heteroaryl group, a cycloalkyl group, an (CH\(_2\))\(_n\)-aryl group, a (CH\(_2\))\(_n\)-heteroaryl group and a (CH\(_2\))\(_n\)-cycloalkyl group; each of which may be optionally substituted.

Preferably \( R^6 \) is selected from optionally substituted (CH\(_2\))\(_n\)-aryl groups, (CH\(_2\))\(_n\)-heteroaryl groups and (CH\(_2\))\(_n\)-cycloalkyl groups. More preferably \( R^6 \) is an optionally substituted (CH\(_2\))\(_n\)-aryl group. More preferably, \( R^6 \) is a (CH\(_2\))\(_n\)-aryl group optionally substituted with one or more of halo, alkyl, N\(_2\), Me, CF\(_3\) and OMe. More preferably, \( R^6 \) is a (CH\(_2\))\(_n\)-aryl group optionally substituted with one or more of bromo, tert-butyl, Me and CF\(_3\). More preferably, \( R^6 \) is a (CH\(_2\))\(_n\)-aryl group optionally substituted with one or more of halo, N\(_2\), Me, CF\(_3\) and OMe.

More preferably, \( R^6 \) is a (CH\(_2\))\(_n\)-aryl group optionally substituted with one or more of halo, N\(_2\), Me, CF\(_3\) and OMe. More preferably, \( R^6 \) is selected from 3,5-bis(trifluoromethyl)benzyl, benzyl, 2-nitro-4,5-dimethoxybenzyl, 3,5-di-ferf-butyl-benzyl, 3,5-di-bromo-benzyl, 3,5-di-methyl-benzyl and 9-methylantracene. More preferably \( R^6 \) is selected from 3,5-bis(trifluoromethyl)benzyl, 3,5-di-tert-butyl-benzyl, 3,5-di-bromo-benzyl and 3,5-di-methyl-benzyl. Most preferably \( R^6 \) is selected from 3,5-bis(trifluoromethyl)benzyl, benzyl, 2-nitro-4,5-dimethoxybenzyl and 9-methylantracene.

\( n = 0 \) to 6. Preferably \( n = 0 \) to 3, more preferably \( n = 1 \).

\( R^7 \) is

\[
\begin{align*}
&\text{wherein } Q \text{ is } O \text{ or } S; \text{ and } R^8, R^9 \text{ and } R^{10} \text{ are independently selected from H, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group and a cycloalkyl group, each}
\end{align*}
\]
of which may be optionally substituted, or $R^8$ and $R^9$ may together define an optionally substituted $C_3$-$C_{20}$ cycloalkyl group or an optionally substituted $C_5$-$C_{15}$ heteroaryl group.

**[0074]** Preferably $R^8$ is selected from an alkyl group, an aryl group, a heteroaryl group and a cycloalkyl group each of which may be optionally substituted. More preferably, $R^8$ is selected from alkyl group, an aryl group and a cycloalkyl group; each of which may be optionally substituted. Most preferably, $R^8$ is selected from 3,5-bis(trifluoromethyl)phenyl, 2-nitro-4,5-dimethoxyphenyl, phenyl and cyclohexane.

**[0075]** Preferably $R^8$ and $R^9$ are independently selected from H and an alkyl group. More preferably, $R^8$ and $R^9$ are independently selected from H, methyl and ethyl.

**[0076]** In one embodiment $R^8$ and $R^9$ define an optionally substituted $C_3$-$C_{20}$ cycloalkyl group or $C_5$-$C_{15}$ heteroaryl group.

**[0077]** Preferably $R^8$ and $R^9$ define an optionally substituted, piperidinyl, piperazinyl or pyridyl group.

**[0078]** $Y^-$ is a counterion. Examples of suitable counterions may include fluoride, chloride, bromide and iodide.

**[0079]** In one embodiment the cinchona alkaloid derivatives are dimeric species of formula (Vile) or (VIlId) in which $R^{15}$ represents a linking group between two compounds of formula Vila or VIlb respectively:

![Diagram](VIIc) ![Diagram](VIlId)

wherein $M$, $R^5$, $R^{5a}$ are as defined above and $R^{15}$ is selected from $0(CH_2)_n$-$aryl$-$(CH_2)nO$, $0(CH_2)_n$-$heteroaryl$-$(CH_2)nO$; each of which may be optionally substituted. Preferably $R^{15}$ is selected from the following:

![Molecules](Molecules)

**[0080]** In one preferred embodiment, the catalyst is a compound of formula (Vila) wherein $M$ is selected from H, hydroxy, alkoxy, $0(CH_2)_n$-$aryl$, $0(CH_2)_n$-$heteroaryl$, $0(CH_2)_n$-$cycloalkyl$ and $R^7$;
R^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n^\text{-aryl}, C(=0)OR^{12}, amino, NR^{11}SO^{2}R^{12}, and R^7;

Q is S;

R^5 and R^6a are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;

R^8 is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more of halo, CF_3, Me and OMe;

R^9, R^{10}, R^{11} are independently selected from H and alkyl; and

R^{12} is selected from H and alkyl, aryl, cycloalkyl; each of which may be optionally substituted by one or more of halo, CF_3, Me and OMe.

[0081] In another preferred embodiment the catalyst is a compound of formula (Vila) wherein M is selected from H, hydroxy, methoxy and R^7;

R^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n^\text{-aryl}, C(=0)OR^{12}, amino, NR^{11}SO^{2}R^{12}, and R^7;

Q is S;

R^5 and R^6a are independently selected from H, methyl, ethyl, ethenyl;

R^8 and R^{10} are H; and R^8 is selected from an alkyl group, an aryl group and a cycloalkyl group;

[0082] In another preferred embodiment the catalyst is a compound of formula (Vila) wherein M is selected from H, hydroxy, methoxy and R^7;

R^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n^\text{-aryl}, C(=0)OR^{12}, amino, NR^{11}SO^{2}R^{12}, and R^7;

Q is S;

R^5 and R^6a are independently selected from H, methyl, ethyl, ethenyl;

R^8 and R^{10} are H; and R^8 is selected from an alkyl and aryl group optionally substituted by one or more of halo, CF_3, Me and OMe;

[0083] In another preferred embodiment, the catalyst is a compound of formula (Vllb) wherein M is selected from H, hydroxy, alkoxy, 0(CH_2)_n^\text{-aryl}, 0(CH_2)_n^\text{-heteroaryl}, 0(CH_2)_n^\text{-cycloalkyl} and R^7;

R^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n^\text{-aryl}, C(=0)OR^{12}, amino, NR^{11}SO^{2}R^{12}, and R^7;

Q is S;

R^5 and R^6a are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;

R^6 is selected from (CH_2)_n^\text{-aryl groups}, (CH_2)_n^\text{-heteroaryl groups and (CH_2)_n^\text{-cycloalkyl groups, each of which may optionally be substituted with one or more halo, NO}_2, CF_3, Me and OMe groups;
R is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe;

R⁸, R¹⁰, R¹¹ are independently selected from H and alkyl; and

R¹² is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe.

[0084] In another preferred embodiment, the catalyst is a compound of formula (VIIb) wherein M is selected from H, hydroxy, alkoxy, 0(CH₂)ₙ-aryl, 0(CH₂)ₙ-heteroaryl, 0(CH₂)ₙ-cycloalkyl and R⁷;

R⁴ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, C(=0)OR₁₂, amino, NR₁¹SR₂₁₂, and R⁷;

Q is S;

R⁵ and R⁶a are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;

R⁸ is selected from (CH₂)ₙ-aryl groups, (CH₂)ₙ-heteroaryl groups and (CH₂)ₙ-cycloalkyl groups, each of which may optionally be substituted with one or more halo, alkyl, NO₂, haloalkyl and methoxy groups;

R⁸ is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe;

R⁹, R¹⁰, R¹¹ are independently selected from H and alkyl; and

R¹² is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe.

[0085] In another preferred embodiment the catalyst is a compound of formula (VIIb) wherein M is selected from H, hydroxy, methoxy and R⁷;

R⁴ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, C(=0)OR₁₂, amino, NR₁¹SR₂₁₂, and R⁷;

Q is S;

R⁵ and R⁶a are independently selected from H, methyl, ethyl, ethenyl;

R⁸ is selected from a benzyl group which may be optionally substituted with one or more of halo, alkyl, NO₂, haloalkyl and alkoxy;

R⁸ and R¹⁰ are H; and R⁸ is selected from an alkyl and aryl group optionally substituted by one or more of halo, CF₃, Me and OMe;

[0086] In another preferred embodiment the catalyst is a compound of formula (VIIb) wherein M is selected from H, hydroxy, methoxy and R⁷;

R⁴ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, C(=0)OR₁₂, amino, NR₁¹SO₂R₁¹₂, and R⁷;
Q is S;
R^5^5 and R^6^6 are independently selected from H, methyl, ethyl, ethenyl;
R^6^6 is selected from a benzyl group which may be optionally substituted with one or more of halo, NO_2^2, CF_3^3, Me, tert-butyl and OMe;
5 R^9^9 and R^{10}^{10} are H; and R^8^8 is selected from an alkyl and aryl group optionally substituted by one or more of halo, CF_3^3, Me and OMe;

[0087] In another preferred embodiment the catalyst is a compound of formula (VIIb) wherein M is selected from H, hydroxy, methoxy and R^7^7;
R^4^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n-aryl, C(=0)OR_1^1, amino, NR^{11}R^{12}, and R^7^7;
10 Q is S;
R^5^5 and R^{6a}^{6a} are independently selected from H, methyl, ethyl, ethenyl;
R^6^6 is selected from a benzyl group which may be optionally substituted with one or more of halo, NO_2^2, CF_3^3, Me and OMe;
15 R^9^9 and R^{10}^{10} are H; and R^8^8 is selected from an alkyl and aryl group optionally substituted by one or more of halo, CF_3^3, Me and OMe;

[0088] In another preferred embodiment the catalyst is a compound of formula (VIIb) wherein M is selected from H, hydroxy, methoxy and R^7^7;
R^4^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n-aryl, C(=0)OR_1^1, amino, NR^{11}S_0^0 R^{12}, and R^7^7;
20 Q is S;
R^5^5 and R^{6a}^{6a} are independently selected from H, methyl, ethyl, ethenyl;
R^6^6 is selected from 3,5-di-tert-butyl-benzyl, 3,5-di-bromo-benzyl, 3,5-di-methyl-benzyl, 3,5-bis(trifluoromethyl)benzyl, 2-nitro-4,5-dimethoxybenzyl and benzyl;
25 R^9^9 and R^{10}^{10} are H; and R^8^8 is selected from an alkyl and aryl group optionally substituted by one or more of halo, CF_3^3, Me and OMe;

[0089] In another preferred embodiment the catalyst is a compound of formula (VIIb) wherein M is selected from H, hydroxy, methoxy and R^7^7;
R^4^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n-aryl, C(=0)OR_1^1, amino, NR^{11}S_0^0 R^{12}, and R^7^7;
30 Q is S;
R^5^5 and R^{6a}^{6a} are independently selected from H, methyl, ethyl, ethenyl;
R^6^6 is selected from 3,5-bis(trifluoromethyl)benzyl, 2-nitro-4,5-dimethoxybenzyl and benzyl;
R⁹ and R¹⁰ are H; and R⁸ is selected from an alkyl and aryl group optionally substituted by one or more of halo, CF₃, Me and OMe;

[0090] In another preferred embodiment the catalyst is selected from the following:
wherein $Y^-$ is a counterion. Examples of suitable counterions include fluoride, chloride, bromide and iodide. Preferably the counterion is bromide.

[0091] In another preferred embodiment the catalyst is selected from those catalysts in the preceding paragraph as well as the following:

wherein $Y^-$ is a counterion. Examples of suitable counterions include fluoride, chloride, bromide and iodide. Preferably the counterion is bromide.

[0092] In another embodiment the catalyst is selected from those of the preceding paragraph only.

[0093] In another embodiment the catalyst is selected from the following:
In another preferred embodiment the catalyst is selected from:

wherein $R$ is independently selected from terf-butyl, $CF_3$, Me and Br, and $M$ is selected from H and OMe; and wherein --- indicates either a double bond or single bond.

In another preferred embodiment the catalyst is selected from:

wherein $R$ is selected from H and $CF_3$, $R'$ is selected from H and $NO_2$ and $M$ is selected from H and OMe.

In another preferred embodiment the catalyst is selected from:
wherein R and R' are independently selected from Nₐ₂ and Oₑ, preferably R' is N₀₂ or H and R is OMe or H.

[0097] In another preferred embodiment the catalyst is selected from N-(3,5-ditrifluoromethylbenzyl)quinidinium bromide, /V-(3,5-ditertbutylbenzyl)quinidinium bromide, N-(3,5-ditertbutylbenzyl)dihydroquinidinium bromide, A/- (3,5-dimethylbenzyl)quinidinium bromide, A/- (3,5-dibromobenzyl)quinidinium bromide, /V-benzylcinchonidinium bromide, A/- (4,5-dimethoxy-2-nitrobenzyl)cinchonidinium bromide and /V-(3,5-bis(trifluoromethyl)benzyl)cinchonidinium bromide, /V-benzylquinidinium bromide, N-(2-nitro-4,5-dimethoxybenzyl)quinidinium bromide.

[0098] In another preferred embodiment the catalyst is selected from N-benzylcinchonidinium bromide, A/- (4,5-dimethoxy-2-nitrobenzyl)cinchonidinium bromide and /V-(3,5-bis(trifluoromethyl)benzyl)cinchonidinium bromide, N-benzylquinidinium bromide, A/- (4,5-dimethoxy-2-nitrobenzyl)quinidinium bromide. Preferably the catalyst is selected from /V-benzylquinidinium bromide, A/- (4,5-dimethoxy-2-nitrobenzyl)quinidinium bromide.

[0099] In another embodiment the catalyst is selected from N-(3,5-ditrifluoromethylbenzyl)quinidinium bromide, A/- (3,5-ditertbutylbenzyl)quinidinium bromide, N-(3,5-ditertbutylbenzyl)dihydroquinidinium bromide, A/- (3,5-dimethylbenzyl)quinidinium bromide, /V-(3,5-dibromobenzyl)quinidinium bromide, A/-benzylcinchonidinium bromide, A/- (4,5-dimethoxy-2-nitrobenzyl)cinchonidinium bromide and A/- (3,5-bis(trifluoromethyl)benzyl)cinchonidinium bromide, A/-benzylquinidinium bromide, /V-(2-nitro-4,5-dimethoxybenzyl)quinidinium bromide and tetrabutylammonium bromide, tetraethylammonium bromide, triphenylbutyrammonium bromide, trimethylphenylphosphonium bromide and tetrabutylphosphonium bromide.

[00100] Throughout the specification, where substituents M, R⁴,R⁵,R⁶,R⁸ to R⁴ are defined as optionally substituted, examples of suitable substituents may include one or more of hydroxy, alkyl, aryl, halo, alkoxy, haloalkyl, haloalkoxy, amino, aminoalkyl, nitro and cycloalkyl. Preferably, suitable substituents are selected from one or more of hydroxy, alkyl, alkoxy, halo,
haloalkoxy, nitro and aryl. More preferably, suitable substituents are selected from one or more hydroxy, methyl, ethyl, methoxy, ethoxy, halo, N02, CF3 and phenyl groups.

[00101] It will be appreciated by a person skilled in the art that the some of the above catalysts possess at least two chiral centres and thus give rise to diastereoisomers. Where stereochemistry is not specifically indicated it will be understood that all diastereoisomers are encompassed by the structures shown.

[00102] Preferably the catalysts are those of formulae VIIa-d which provide compounds of formula (V) with the S-configuration at the chiral centre denoted by *.

[00103] In one embodiment the catalyst loading with respect to the compound of formula (IV) is less than or equal to about 1:1. In another embodiment the catalyst loading with respect to the compound of formula (IV) is less than or equal to about 0.5:1. In another embodiment the catalyst loading with respect to the compound of formula (IV) is less than or equal to about 0.2:1. Preferably, the catalyst loading with respect to the compound of formula (IV) is about 0.05:1.

The Processes

[00104] In one aspect, the present invention provides a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\text{H}_2\text{N}\begin{array}{c} \text{R}^1 \ast \text{COOH} \\
\end{array}
\]

(I)

which process comprises the step of preparing a compound of formula (IV) by reacting a compound of formula (III) with a compound of formula (II):

\[
\begin{array}{c}
\text{R}^2 \text{X} \\
\end{array} \text{N} \begin{array}{c} \text{R}^1 \text{H} \\
\end{array} \text{R}^2
\]

(III)  (II)  (IV);

wherein R1, R2, and X are as defined herein above.
[00105] In one embodiment the reaction comprises a base. Preferably the base provides a source of hydroxide. Examples of suitable bases may include sodium hydroxide, lithium hydroxide and potassium hydroxide. Preferably, the base is sodium hydroxide.

[00106] Preferably, the reaction is conducted in the presence of an aqueous solvent, such as water, or a mixture of solvents comprising water. Preferably the solvent comprises water and a C_{1,6} alcohol, such as methanol or ethanol.

[00107] In another embodiment, the reaction comprises a further organic solvent. The further organic solvent may be selected from tetrahydrofuran, 1,4-dioxan, diethyl ether. Preferably, the further organic solvent is tetrahydrofuran.

[00108] In one embodiment the ratio of water to C_{1,6} alcohol is between 0.1:1 and 100:1. In another embodiment the ratio of water to C_{1,6} alcohol is between 0.1:1 and 50:1. In another embodiment the ratio of water to C_{1,6} alcohol is between 0.1:1 and 20:1. In another embodiment the ratio of water to C_{1,6} alcohol is between 1:1 and 20:1.

[00109] Preferably, the solvent is 9:1 water to C_{1,6} alcohol. Preferably the C_{1,6} alcohol is ethanol or methanol.

[00110] In another embodiment, the solvent is 7:3 water to C_{1,6} alcohol. Preferably the C_{1,6} alcohol is methanol.

[00111] Optionally, the coupling of a compound of formula (III) and a compound of formula (II) and subsequent dehydration to yield a compound of formula (IV) can be carried out in two stages with isolation of the intermediate compound of formula (IIa) (Scheme 4).

**Scheme 4**

![Scheme 4](image)

[00112] The dehydration stage may be carried out by first activating the hydroxyl group of a compound of formula (IIa) using any method commonly known in the art. In one embodiment, the hydroxyl group is mesylated with mesyl chloride in the presence of triethylamine. Elimination of methanesulfonic acid yields a compound of formula (IV).

[00113] Preferably the dehydration is carried out in the presence of a solvent. In one embodiment the solvent is selected from dichloromethane, tetrahydrofuran, 1,4-dioxan, diethyl ether, toluene, acetone, ethyl acetate. Preferably the solvent is dichloromethane.
In an alternative aspect the present invention provides a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\text{H}_2\text{N} - \text{COOH}
\]

(I)

wherein:

- \(R^1\) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and *

\(\text{denotes a chiral centre;}

which process comprises preparing a compound of formula (IV) by reacting a compound of formula (IIIA) with a compound of formula (II) to form a compound of formula (1MB):

\[
\text{H} - \text{O} \quad \text{O} - \text{N} - \text{R}_2 \\
\text{R}_1 \quad \text{R}_1 \\
(\text{II}) \quad (\text{IIIA}) \quad (\text{III}B)
\]

wherein:

- \(L\) is a hydroxyl activating group, \(R^1\) is defined above in relation to the compound of formula (I); and \(R^2\) is an alkyl group or aryl group, each of which may be optionally substituted; and

converting the compound of formula (1MB) to a compound of formula (NIC):

\[
\text{O} - \text{N} - \text{R}_2 \\
\text{O} - \text{L} \quad \text{R}_1 \\
(\text{III}B) \quad (\text{III}C)
\]

wherein:

- \(X\) is an electron withdrawing group; and converting the compound of formula (III) to a compound of formula (IV).

In one embodiment the reaction of (II) and (IIIA) is carried out in the presence of a base, such as LDA. In one embodiment the reaction of (II) and (IIIA) is carried out in the presence of a base and then the hydroxyl activating group is added with or without isolation of the intermediate hydroxyl compound.

In a preferred embodiment \(X\) in the compounds of formula (III) and (IMC) is nitro. In such an embodiment, suitable reagents for generation of \(\text{NO}_2^+\) will be apparent to the skilled person. Exemplary conditions include \(\text{HN0}_3/\text{H}_2\text{SO}_4\) and tetramethyl ammonium nitrate and trifluoroacetyc anhydride.
The conversion of the compound of formula (MIC) to the compound of formula (IV) may be carried out by any method known in the art. Preferably the reaction is carried out in the presence of an organic base, preferably the reaction is carried out in the presence of an amine such as triethylamine.

In one embodiment the process further comprises the step of reacting a compound of formula (IV) with nitromethane in the presence of a catalyst to provide a compound of formula (V):

\[
\begin{align*}
\text{R}^1 & \rightarrow \text{CH}_3\text{NO}_2 \\
\text{(IV)} & \rightarrow \text{(V)}
\end{align*}
\]

wherein \( R^1, R^2 \) and X are as defined hereinabove.

In one embodiment the reaction of the compound of formula (IV) with nitromethane is carried out in the presence of a base. Preferably the base is a source of carbonate. Examples of suitable bases include, but are not limited to, potassium carbonate, sodium carbonate and cesium carbonate. Preferably the base is potassium carbonate.

In one embodiment the reaction of the compound of formula (IV) with nitromethane is conducted at a temperature of between -70°C to 30°C. In another embodiment the reaction is conducted at a temperature of between -70°C to 0°C. In another embodiment the reaction is conducted at a temperature of between -50°C to -20°C. Preferably the reaction is conducted at a temperature of about -37°C.

In one embodiment the reaction of the compound of formula (IV) with nitromethane is conducted at a temperature of between -70°C to 50°C. In another embodiment the reaction is conducted at a temperature of between 0°C to 30°C. In another embodiment the reaction is conducted at a temperature of between 20°C to 30°C. Preferably the reaction is conducted at room temperature.

In one embodiment the reaction of the compound of formula (IV) with nitromethane provides a compound of formula (V) with an enantiomeric excess of greater than about 60%. In another embodiment the enantiomeric excess is greater than about 70%. In
another embodiment the enantiomeric excess is greater than about 80%. Preferably the enantiomeric excess is greater than about 90%.

[00124] In one embodiment compound of formula (V) is enantiomerically enriched by re-crystallization. In one embodiment re-crystallization is in isopropanol or mixtures of isopropanol and hexane.

[00125] In one embodiment the enantiomerically enriched compound of formula (V) has an enantiomeric excess of greater than about 90%, more preferably greater than about 95%, more preferably greater than about 99%.

[00126] In one embodiment the process further comprises the step of hydrolysing the compound of formula (V) to provide a compound of formula (VI)

\[
\begin{align*}
\text{(V)} & \quad \text{\rightarrow} \quad \text{(VI)}; \\
\end{align*}
\]

wherein \(R^1, R^2\) and \(X\) are as defined hereinabove.

[00127] In one embodiment the process further comprises the step of hydrolysing the compound of formula (Vlb) to provide a compound of formula (I)

\[
\begin{align*}
\text{(Vlb)} & \quad \text{\rightarrow} \quad \text{(I)}; \\
\end{align*}
\]

wherein \(R^1, R^2\) and \(X\) are as defined hereinabove; with the proviso that \(X\) is not NO₂.

[00128] The hydrolysis may be carried out by any method commonly known in the art.

[00129] In one embodiment the hydrolysis of compound (V) or (Vlb) is carried out in the presence of a base. Preferably the base is a source of hydroxide. Examples of suitable bases include, but are not limited to, sodium hydroxide, potassium hydroxide and lithium hydroxide. Preferably the base is sodium hydroxide, more preferably aqueous sodium hydroxide.

[00130] The hydrolysis may be performed in the presence of an organic solvent. Examples of suitable organic solvent include, but are not limited to, tetrahydrofuran, 1,4-dioxan and diethyl ether. Preferably the solvent is tetrahydrofuran.

[00131] In one embodiment the solvent is a mixture of organic solvent and water. Preferably, the solvent is a mixture of water and tetrahydrofuran.
In one embodiment the process further comprises the step of reducing the compound of formula (VI) to provide a compound of formula (I)

\[
\begin{align*}
\text{(VI)} & \quad \text{(I)}; \\
\end{align*}
\]

wherein \( R^1, R^2 \) and \( X \) are as defined hereinabove.

In one embodiment the process further comprises the step of reducing the compound of formula (V) to provide a compound of formula (Vlb)

\[
\begin{align*}
\text{(V)} & \quad \text{(Vlb)}; \\
\end{align*}
\]

wherein \( R^1, R^2 \) and \( X \) are as defined hereinabove; with the proviso that \( X \) is not \( \text{NO}_2 \).

The reduction may be accomplished by any commonly known method in the art. Examples of suitable reduction reactions include, but are limited to, hydrogenation, transfer hydrogenation or transition metal and acid reduction.

Preferably the reduction of a compound of formula (VI) or (V) is accomplished by catalytic hydrogenation. Optionally, the hydrogenation is conducted in the presence of an acid. Preferably the acid is hydrochloric acid.

Preferred hydrogenation catalysts include palladium on carbon and Raney nickel.

In one embodiment the reduction is conducted in a solvent. Suitable solvents include, but are not limited to ethanol, methanol and ethyl acetate. Preferably the solvent is ethanol.

In one embodiment the reduction may be performed accordingly to the procedure described in F. Felluga, G. Pitacco, E. Valentin, C. D. Venneri Tetrahedron: Asymm. 2008, 945.

In another aspect of the invention there is provided a process for the preparation of a compound of formula (IV), and salts thereof, which process comprises reacting a compound of formula (III) with a compound of formula (II):
as described hereinabove,
wherein \( R^1, R^2 \) and \( X \) are as defined above.

In another aspect of the invention, there is provided the use of a compound of formula (IV)

\[
\begin{align*}
\text{R}^1 \text{H} & \\
\text{R}^2 \text{O} & \\
\text{N} & \\
\text{X} & \\
\end{align*}
\]

wherein \( R^1, R^2 \) and \( X \) are as defined above in the preparation of a compound of formula (I).

Another aspect of the invention relates to a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\begin{align*}
\text{H}_2\text{N} & \\
\text{R}^1 \text{COOH} & \\
\end{align*}
\]

wherein:

\( R^1 \) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and \( * \) denotes a chiral centre;

which process comprises the step of reacting a compound of formula (IV) with nitromethane in the presence of a catalyst to provide a compound of formula (V):

\[
\begin{align*}
\text{R}^1 \text{O} & \\
\text{N} & \\
\text{X} & \\
\text{R}^2 & \\
\end{align*}
\]

wherein:

\( R^1 \) and \( * \) are as defined above in relation to the compound of formula (I); \( R^2 \) is an alkyl group or aryl group, each of which may be optionally substituted; and \( X \) is an electron withdrawing group.

In one embodiment the reaction is carried out in the presence of a base. Preferably the base is a source of carbonate. Examples of suitable bases include, but are not limited to, potassium carbonate, sodium carbonate and cesium carbonate. Preferably the base is potassium carbonate.
In one embodiment the reaction is carried out in a solvent. Examples of suitable solvents include tetrahydrofuran, 1,4-dioxan, toluene and xylene. Preferably, the solvent is toluene. In one embodiment the solvent is toluene recycled from previous reactions comprising reacting a compound of formula (IV) with nitromethane in the presence of a catalyst to provide a compound of formula (V).

[00144] In one embodiment the reaction is conducted at a temperature of between -70°C to 30°C. In another embodiment the reaction is conducted at a temperature of between -70°C to 0°C. In another embodiment the reaction is conducted at a temperature of between -50°C to -20°C. Preferably the reaction is conducted at a temperature of about -37°C.

[00145] In one embodiment the reaction is conducted at a temperature of between -70°C to 50°C. In another embodiment the reaction is conducted at a temperature of between 0°C to 30°C. In another embodiment the reaction is conducted at a temperature of between 20°C to 30°C. Preferably the reaction is conducted at room temperature.

[00146] In an alternative aspect the present invention provides a process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{COOH} \\
\text{R}^1\text{*} & \quad \text{(I)}
\end{align*}
\]

which process comprises the step of reacting a compound of formula (IIA) with a compound of formula (III) in the presence of a catalyst to provide a compound of formula (V);

\[
\begin{align*}
\text{R}_1\text{NO}_2 & \quad \text{+} \quad \text{R}_2\text{X} \\
\text{(IIA)} & \quad \text{R}_2\text{X} \quad \text{NO}_2 \quad \text{(III)} & \quad \text{(V)}
\end{align*}
\]

wherein \( R_1, R_2 \) and \( X \) are as defined hereinabove.

[00147] In one embodiment the reaction of the compound of formula (IIA) with a compound of formula (III) is carried out in the presence of a base. Preferably the base is a source of carbonate. Examples of suitable bases include, but are not limited to, potassium carbonate, sodium carbonate and cesium carbonate. Preferably the base is potassium carbonate.

[00148] In one embodiment the reaction provides a compound of formula (V) with an enantiomeric excess of greater than about 60%. In another embodiment the enantiomeric excess is greater than about 70%. In another embodiment the enantiomeric excess is greater than about 80%. Preferably the enantiomeric excess is greater than about 90%.
In one embodiment compound of formula (V) is enantiomerically enriched by re-crystallization. In one embodiment re-crystallization is in isopropanol or mixtures of isopropanol and hexane.

In one embodiment the enantiomerically enriched compound of formula (V) has an enantiomeric excess of greater than about 90%, more preferably greater than about 95%, more preferably greater then about 99%.

In one embodiment the compound of formula (IV) may be prepared by reacting a compound of formula (III) with a compound of formula (II):

\[
\begin{align*}
\text{(III)} & \quad \text{(II)} & \quad \text{(IV)}; \\
R^2 & \quad R^1 & \quad X
\end{align*}
\]

as described hereinabove.

In alternative embodiment the compound of formula (IV) may be prepared by reacting a compound of formula (IIIA) with a compound of formula (II) to form a compound of formula (MB):

\[
\begin{align*}
\text{(II)} & \quad \text{(IIIA)} & \quad \text{(1MB)} \\
R_1 & \quad O & \quad R_2
\end{align*}
\]

and converting the compound of formula (1MB) to a compound of formula (IIIC):

\[
\begin{align*}
\text{(1MB)} & \quad \text{(IIIC)} \\
R_1 & \quad O & \quad N & \quad R_2
\end{align*}
\]

and converting the compound of formula (IIIC) to a compound of formula (IV), as described hereinabove.

In one embodiment the compound of formula (V) may be prepared by reacting a compound of formula (IIA) with a compound of formula (III) in the presence of a catalyst:

\[
\begin{align*}
\text{(IIA)} & \quad \text{(III)} & \quad \text{(V)} \\
R_1 & \quad R_2 & \quad X & \quad R_1
\end{align*}
\]
as described hereinabove.

[00154] In one embodiment the process further comprises the step of hydrolysing the compound of formula (V) to provide a compound of formula (VI)

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{O} \\
\text{R}_1^* & \quad \text{R}^2 \\
(\text{V}) & \quad (\text{VI})
\end{align*}
\]

as described hereinabove.

[00155] In one embodiment the process further comprises the step of hydrolysing the compound of formula (Vlb) to provide a compound of formula (I);

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{COOH} \\
\text{R}_1 & \quad \text{R}^2 \\
(\text{Vlb}) & \quad (\text{I})
\end{align*}
\]

wherein R\text{I}, R\text{II} and X are as defined hereinabove; with the proviso that X is not N0\text{II}, as described hereinabove.

[00156] In one embodiment the process further comprises the step of reducing the compound of formula (VI) to provide a compound of formula (I)

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{H}_2\text{N} \\
\text{R}_1^* & \quad \text{R}^2 \\
(\text{VI}) & \quad (\text{I})
\end{align*}
\]

as described herein above.

[00157] In one embodiment the process further comprises the step of reducing the compound of formula (V) to provide a compound of formula (Vlb);

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{H}_2\text{N} \\
\text{R}_1 & \quad \text{R}^2 \\
(\text{V}) & \quad (\text{Vlb})
\end{align*}
\]

wherein R\text{I}, R\text{II} and X are as defined hereinabove; with the proviso that X is not N0\text{II}, as described hereinabove.
In another aspect of the invention there is provided a process for the preparation of a compound of formula (V), and salts thereof, which process comprises reacting a compound of formula (IV), with nitromethane in the presence of a catalyst:

\[
\begin{align*}
&\text{(IV)} \\
&\text{(V)}
\end{align*}
\]

as described hereinabove,

wherein \(R^1, R^2\) and \(X\) are as defined above.

In another aspect of the invention, there is provided the use of a compound of formula (V)

\[
\begin{align*}
&\text{(V)}
\end{align*}
\]

wherein \(R^1, R^2\) and \(X\) are as defined above, in the preparation of a compound of formula (I).

In the processes of the present invention the compound of formula (I) preferably has an enantiomeric excess of greater than about 60%. In another embodiment the enantiomeric excess is greater than about 70%. In another embodiment the enantiomeric excess is greater than about 80%. In another embodiment the enantiomeric excess is greater than about 90%. In another embodiment the enantiomeric excess is greater than about 95%. In another embodiment the enantiomeric excess is greater than about 99%.

In one embodiment compound of formula (I) is enantiomerically enriched by resolution. Any suitable resolving agent may be used, for example tartaric acid based resolving agents, mandelic acid based resolving agents and enzymes.

In one embodiment the enantiomerically enriched compound of formula (I) has an enantiomeric excess of greater than about 90%, more preferably greater than about 95%, more preferably greater than about 99%.

**EXAMPLES**

The following examples are intended to illustrate particular embodiments of the invention, and are not intended to limit the specification, including the claims in any manner.

It will be apparent to those skilled in the art that many modifications, both to the materials and the methods, may be made without departing from the spirit or scope of the invention.
Experimental

[00165] Scheme 5

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H}_2\text{O} - \text{EtOH} (9:1) \\
\text{NO}_2 & \quad \text{NaOH} (1 \text{ equiv}) \\
\text{O} & \quad \text{MeCl} (1.2 \text{ equiv}, \text{NBs} (2 \text{ equiv}) \\
\text{N} & \quad \text{K}_2\text{CO}_3 (5 \text{ eq}) \quad \text{toluene} (0.03 \text{M}) \\
\text{H}_2\text{C} & \quad \text{CH}_3\text{NO}_2 (5 \text{ eq}) \\
\text{NO}_2 & \quad 96\% \text{ yield, } 76\% \text{ ee}
\end{align*}
\]

NaOH (5 equiv) Acetone H$_2$O THF (1:4:1)

[00166] Scheme 6

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H}_2\text{O} - \text{EtOH} 9/1 \text{ mL} \\
\text{NO}_2 & \quad \text{NaOH} (1 \text{ equiv}) \\
\text{O} & \quad \text{H}_2\text{O} - \text{EtOH} 9/1 \text{ mL} \\
\text{H}_2\text{C} & \quad \text{DCM} \\
\text{NO}_2 & \quad 99\% \text{ yield}
\end{align*}
\]

[00167] Part A - Preparation of 3-methyl-5-(4-methyl-pent-1-enyl)-4-nitro-isoxazole (8): In a round bottomed flask fitted with a magnetic stirrer were dissolved 1.4 mmol of 3,5-dimethyl-4-nitroisoxazole 1 (200 mg) in water ethanol mixture (9:1, 0.8 mL). To the clear solution was added NaOH powder (40 mg, 1.4 mmol, 1 equiv). The solution turned deep yellow and was stirred at room temperature for 30 minutes before aldehyde 2 (146 mg, 1.7 mmol) was added in one portion. The reaction mixture was then stirred at room temperature for seven days, then quenched with saturated ammonium chloride and compound 8 extracted with dichloromethane (5 mL). The organic layer was washed with water (3 x 10 mL) and carried through the next step without further purification (290 mg, 1.26 mmol, 90% yield). Colorless liquid; $R_f = 0.2$ (Petroleum Ether/Ethyl Acetate, 90:10); $\delta_{H}$ (400 MHz, CDCl$_3$) 4.23-4.20 (1H, m), 3.36 (1H, dd, $J = 15$ $J = 4$), 3.29 (1H, dd, $J = 15$ $J = 7$), 2.55 (3H, s), 1.87-1.76 (1H, m), 1.58-1.53 (1H, m), 1.40-1.34 (1H, m), 0.95 (3H, d, $J = 7$), 0.93 (3H, d, $J = 7$); $\delta_C$ (100.6 MHz, CDCl$_3$)
[00168] **Part (A) preparation of 4-methyl-1-(3-methyl-4-nitro-isoxazol-5-yl)-pentan-2-ol (8):** In a 1000 mL conical flask fitted with a magnetic follower were put 3,5-dimethyl-4-nitroisoxazole 1 (100g, Mw=142, 704.2 mmol) and 150 mL of THF and the resulting solution stirred at 0°C. To this solution, were then added 200 mL of MeOH : H₂O (7 : 3). A freshly made solution of NaOH (5g, Mw = 40, 125 mmol) in 50 mL of H₂O was then charged in a dropping funnel and added drop wise over 10 minutes. Upon this addition, the solution becomes yellow to dark brown. It was noted the formation of a precipitate of sodium 3,5-dimethyl-4-nitroisoxolate that will dissolve during the course of the reaction. At this point, a solution of isovaleraldehyde 2 (151g, Mw = 86, 1755 mmol, 2.5 equiv.) in 100 mL of THF was added drop wise at 0°C over the period of 50 min. After this period the ice bath was removed and the reaction allowed reaching room temperature under vigorous stirring. Conversion was monitored after 2h (60%), 3h (83%), 3h30min (92%) since end of addition of aldehyde. A sample of the reaction mixture was kept under stirring for further two hours and conversion measured again (92%) indicating the reaction mixture had reached the equilibrium. The reaction was quenched with distilled H₂O (500 mL), stirred for 10 minutes, then extracted twice with DCM (300 mL + 200 mL). The organic layers were combined, washed with H₂O (300 mL at least to avoid formation of emulsion), then with sat NaHSO₃ (200 mL) then again with H₂O (300 mL). The organic layer was evaporated at the rotavapor (49°C, 44mb) to give 161g of material which contains the title compound alongside 7% of alkene 3, 8% of 3,5-dimethyl-4-nitroisoxazole and 5% of isovaleraldehyde. Estimated weight in title alcohol was 146g (91% yield). Colorless liquid; Rf= 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl₃) 4.23-4.20 (1H, m), 3.36 (1H, dd, J = 15 J = 4), 3.29 (1H, dd, J = 15 J = 7), 2.55 (3H, s), 1.87-1.76 (1H, m), 1.58-1.53 (1H, m), 1.40-1.34 (1H, m), 0.95 (3H, d, J = 7), 0.93 (3H, d, J = 7); δ_C (100.6 MHz, CDCl₃) 172.9, 155.8, 130.9, 68.0, 46.8, 36.1, 24.8, 23.3, 22.0, 11.8. HRMS: m/z found [M+H]+ 229.1 154, C₁₀H₁₀N₂O₃ requires 229.1 188.

[00169] **Part (B) preparation of 3-methyl-5-(4-methyl-pent-1-enyl)-4-nitro-isoxazole (3):** To a solution of alcohol 8 (39 mg, 0.17 mmol) in dichloromethane (1 mL) kept at 0°C by an ice-water bath was added methanesulfonyl chloride (30 mg, 0.20 mmol, 1.2 equiv) and then triethylamine (34.4 mg, 0.34 mmol, 2 equiv). The reaction was allowed to reach room temperature and then stirred for 1 hour. Then the reaction mixture was quenched with water (2 mL), the organic layer was extracted with dichloromethane (3 x 3 mL), washed with brine, dried over anhydrous Na₂SO₄, filtered and evaporated to give pure compound 3 (35mg, 99% yield). Colorless liquid; Rf= 0.8 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl₃) 7.12-7.00 (2H, m), 2.56 (3H, s), 2.29-2.26 (2H, m), 1.89-1.82 (1H, m), 0.97 (6H, d, J = 6), δ_C (100.6
MHz, CDCI$_3$ 167.0, 156.0, 130.1, 115.6, 43.0, 28.3, 22.5, 12.0. HRMS: m/z found [M]$^+$ 196.0815, C$_9$H$_{14}$N$_2$O$_3$ requires 196.0848.

[00170] Part (B) preparation of 3-methyl-5-(4-methyl-pent-1- enyl)-4-nitro-isoxazole (3): In a 3L round bottomed flask fitted with an overhead stirrer (to overcome difficult stirring caused by formation of solid HNET$_3$Cl through the reaction) were loaded 160g of 4-methyl-1-(3-methyl-4-nitro-isoxazol-5-yl)-pentan-2-ol 8 (about 90% pure, 144g, 633 mmol, Mw = 229) and 1000 mL of DCM. The solution was cooled at -30°C by adding liquid nitrogen to a methanol bath, then methanesulfonyl chloride (86.62g, Mw = 114, 760 mmol, 1.2 equiv) was added drop wise in 20 min. To the resulting solution was then added NEt$_3$ (127.9g, 1266 mmol, Mw = 101, 2.0 equiv) drop wise over the period of 1h i 5 min while maintaining the temperature between 0°C and -20°C. After the addition was completed the reaction was allowed to reach room temperature and stirred for 2h (from the end of addition of NEt$_3$). The reaction was quenched with H$_2$O (300 mL), washed with additional H$_2$O (2 x 500 mL), then with 5% NaOH in water, the organic layer dried over Na$_2$SO$_4$ and then evaporated under reduced pressure (47°C, Omb) to give 163g of crude product which was thinned with 50 mL of petroleum ether (40-60°C) and passed through a plug of silica gel (flash type) (10g) eluting with petroleum ether (40:60) (50 mL) to give 132g of title compound. Estimated purity of alkene is 92%. Pale yellow liquid; $R_f$ = 0.8 (Petroleum Ether/Ethyl Acetate, 90:10); $\delta$$_H$ (400 MHz, CDCI$_3$) 7.12 - 7.00 (2H, m), 2.56 (3H, s), 2.29-2.26 (2H, m), 1.89-1.82 (1H, m), 0.97 (6H, d, J = 6), $\delta$$_C$ (100.6 MHz, CDCI$_3$) 167.0, 156.0, 130.1, 115.6, 43.0, 28.3, 22.5, 12.0. HRMS: m/z found [M]$^+$ 196.0815, C$_9$H$_{14}$N$_2$O$_3$ requires 196.0848.

[00171] Note 1: Product 3 was obtained over 99.9% pure via distillation, collecting the fraction boiling over 120°C at 0.2mb. The yield was ca 65-70% of pure alkene.

[00172] Note 2: Purification via DMF wash: the alkene 3 may be obtained over 99.9% pure by dissolving it in a DMF : H$_2$O (20: 80) and then extracting with petroleum ether. Typically, 12 g of crude material were dissolved in 10 mL of DMF, then 40 mL of water were added and the resulting yellow solution was extracted with petroleum ether (40 : 60), (2x 50 mL).

Optionally, the alkene (20g) was dissolved in petroleum ether (40 : 60), (50 mL), then treated with 3 mL of DMF, stirred for 20 minutes, then washed with water (2 x 50 mL).

Alternative synthesis of alkenes 3'$

[00173] Scheme 7: alternative route to styrylisoxazoles 3'a-d.
An alternative route to styrylisoxazoles 3'a-d involves reaction of 3,5-dimethylisoxazole 1 with LDA followed by addition of suitable aldehydes 2'a-d. The resulting alcohols 8'a-d were mesylated using MsCl and triethylamine to give compounds 104a-d which in turn was nitrated to 105a-d. Treatment of 105a-d with triethylamine gave desired 3'a-d.

Table 1: Isolated yields of hydroxyl isoxazoles 8'a-d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Reactant Alk group</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2'a</td>
<td>Cyclohexane</td>
<td>8'a</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>2'b</td>
<td>CH(CH₂CH₃)CH₂CH₂CH₂CH₃</td>
<td>8'b</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>2'c</td>
<td>CH₂CH(CH₃)₂</td>
<td>8'c</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>2'd</td>
<td>CH₂CH₂CH₂CH₂CH₂CH₃</td>
<td>8'd</td>
<td>64</td>
</tr>
</tbody>
</table>

Table 2: Isolated yields of mesylated isoxazoles 104a-d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starter</th>
<th>Reactant Alk group</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8'a</td>
<td>Cyclohexane</td>
<td>104a</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>8'b</td>
<td>CH(CH₂CH₃)CH₂CH₂CH₂CH₃</td>
<td>104b</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>8'c</td>
<td>CH₂CH(CH₃)₂</td>
<td>104c</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>8'd</td>
<td>CH₂CH₂CH₂CH₂CH₂CH₃</td>
<td>104d</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 3: Isolated yields of nitro isoxazoles 105a-d

<table>
<thead>
<tr>
<th>Starter</th>
<th>Reactant Alk</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104a</td>
<td>Cyclohexane</td>
<td>105a</td>
</tr>
<tr>
<td>2</td>
<td>104b</td>
<td>CH(CH₂CH₃)CH₂CH₂CH₂CH₃</td>
<td>105b</td>
</tr>
<tr>
<td>3</td>
<td>104c</td>
<td>CH₂CH(CH₃)₂</td>
<td>105c</td>
</tr>
<tr>
<td>4</td>
<td>104d</td>
<td>CH₂CH₂CH₂CH₂CH₂CH₃</td>
<td>105d</td>
</tr>
</tbody>
</table>

Table 4: Isolated yields of aliphatic nitro isoxazoles 3'a-d

<table>
<thead>
<tr>
<th>Starter</th>
<th>Reactant Alk</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Typical procedure for preparation of hydroxy isoxazoies (Compounds 8'a-d)

[00179] Under an inert atmosphere, lithium diisopropyl amide (5ml, 10 mmol) was added dropwise to a stirred solution of isoxazole (1g, 10 mmol) in anhydrous tetrahydrofuran (10 mL) at -78°C using a liquid nitrogen/acetone bath. The resulting solution was stirred at the same temperature for 60 minutes. To this solution was then added the aliphatic aldehyde (1 eq, 10mmol) -78 °C over 60 minutes. The resulting reaction mixture was allowed to warm to room temperature over a period of 2h, with stirring magnetically. At the end of this time the solvent was evaporated off and the residue re-dissolved in DCM, quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted with DCM (2 x 20 mL). Combined organic extracts were washed with water followed by brine and dried over anhydrous sodium sulphate before evaporation under reduced pressure. The crude product was purified by column chromatography with 10% ethyl acetate in petroleum spirits as an eluent followed by 20 % ethyl acetate in petroleum ether to afford the pure title product.

[00180] 1-Cyclohexyl-2-(3-methyl-isoxazol-5-yl)-ethanol 8'a

![Diagram]

[00181] 1.5 g, 74% yield, yellow oil, R₇ = 0.4 (30%, EtOAc in Petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δ_H = 5.91 (1H, s, C=H), 3.61-3.69 (1H, m, CH₂CH), 2.84 (1H, dd, J = 15, J = 4, CH₂CH), 2.74 (1H, dd, J = 15, J = 9, CH₂CH), 2.18 (3H, s, CH₃C=N), 1.82-1.59 (5H, m, H Aliphatic), 1.35-1.27 (1H, m, H Aliphatic), 1.23-0.93 (5H, m, H Aliphatic); ¹³C NMR (100.6 MHz) δ_C = 168.1 (C=O), 160.0 (N=O-C=CH₂), 103.3, (C=O-H), 73.9 (C=O), 38.3 (CH-cyclohexane), 34.9 (CH₂-aliphatic), 29.1 (CH₂-cyclohexane), 27.8 (CH₂-cyclohexane), 26.2 (CH₂-cyclohexane), 14.0 (CH₃-aliphatic), 14.0 (CH₃-aliphatic), 11.4 (N=O-C=CH₂), HRMS found: [M-H⁺] 209.152, C₁₂H₁₉N>O₂ requires 209.146; m/z: 209 (100%, M-H⁺).
3-Ethyl-1-(3-methyl-isoxazol-5-yl)-heptan-2-ol 8\textsuperscript{b}

\[ \text{HO} \]
\[ \text{N} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]

\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]

1.24 g, 55% yield, yellow oil, \( R_f = 0.39 \) (30%, EtOAc in Petroleum spirits); \( ^1H \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta_H = 5.91 \) (1H, s, C=C-H), 3.61-3.69 (1H, m, CH\textsubscript{2}CH), 2.84 (1H, dd, \( J = 15, J = 4, \text{CH}_2\text{CH} \)), 7.74 (1H, dd, \( J = 15, J = 9, \text{CH}_2\text{CH} \)), 2.18 (3H, s, CH\textsubscript{3}C=N), 1.82-1.59 (5H, m, H Aliphatic), 1.35-1.27 (1H, m, H Aliphatic), 1.23-0.93 (5H, m, H Aliphatic), 0.92-0.82 (6H, m, \( \text{CH}_3 \text{CH}_2 \)), \( ^{13}C \) NMR (100.6 MHz) \( \delta_C = 170.94 \) (C=C-H), 159.9 (N=C-CH\textsubscript{3}), 103.0, (C=C-H), 71.4 (C=OH), 46.97 (CH-aliphatic), 44.9 (CH\textsubscript{2}-aliphatic), 30.6 (CH\textsubscript{2}-aliphatic), 28.2 (CH\textsubscript{2}-aliphatic), 23.4 (CH\textsubscript{2}-aliphatic), 21.3 (CH\textsubscript{2}-aliphatic), 14.0 (CH\textsubscript{3}-aliphatic), 14.0 (CH\textsubscript{3}-aliphatic), 11.7 (N=C-CH\textsubscript{3}); HRMS found: [M-H\textsuperscript{+}] 225.1733, C\textsubscript{13}H\textsubscript{22}NO\textsubscript{2} requires 225.1729; m/z. 225 (100%, M-H\textsuperscript{+}).

4-Methyl-1-(3-methyl-isoxazol-5-yl)-pentan-2-ol 8\textsuperscript{c}

\[ \text{HO} \]
\[ \text{N} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]
\[ \text{CH} \]

1.28 g, 70% yield, yellow oil, \( R_f = 0.4 \) (30%, EtOAc in petroleum spirits); \( ^1H \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta_H = 5.92 \) (1H, s, H isoxazole), 4.06-4.00 (1H, m CH\textsubscript{2}CH), 2.87 (1H, dd, \( J = 15, J = 4, \text{CH}_2\text{CH} \)), 2.79 (1H, dd, \( J = 15, J = 8, \text{CH}_2\text{CH} \)), 2.25 (3H, s, N=C-CH\textsubscript{3}), 1.84-1.74 (1H, m, CH\textsubscript{2} aliphatic), 1.49-1.42 (1H, m, CH\textsubscript{2} aliphatic), 1.30-1.23 (1H, m, CH\textsubscript{2} aliphatic), 0.91 (6H, t, \( J = 7, \text{CH}(\text{CH}_3)\)), 13C NMR (100.6 MHz) \( \delta_C = 170.2 \) (C=C-H), 159.9 (N=C-CH\textsubscript{3}), 103.2, (C=C-H), 67.95 (C=OH), 46.05 (CH\textsubscript{2}-aliphatic), 35.4 (CH\textsubscript{2}-aliphatic), 23.3 (CH\textsubscript{3}-aliphatic), 21.9 (CH\textsubscript{2}-aliphatic), 11.4 (CH\textsubscript{3}-aliphatic), 11.4 (N=C-CH\textsubscript{3}), HRMS found: [M-H\textsuperscript{+}] 183.1262, C\textsubscript{10}H\textsubscript{17}NO\textsubscript{2} requires 183.1259; m/z. 183 (100%, M-H\textsuperscript{+}).

1-(3-Methyl-isoxazol-5-yl)-octan-2-ol; compound with methane 8\textsuperscript{d}
1.35 g, 64% yield, yellow oil, R<sub>f</sub> = 0.42 (30%, EtOAc in petroleum spirits); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> = 5.87 (1H, s, C=C-H), 3.91-3.85 (1H, m, CH<sub>2</sub>CH), 2.82 (1H, dd, J = 15, J = 5, CH<sub>2</sub>CH), 2.75 (1H, dd, J = 15, J = 8, CH<sub>2</sub>CH), 2.18 (3H, s, CH<sub>3</sub>C=N), 1.46-1.34 (5H, m, H Aliphatic), 1.34-1.21 (5H, m, H Aliphatic), 0.91-0.87 (3H, t, J = 6, (CH<sub>3</sub>)<sub>2</sub>CH); <sup>13</sup>C NMR (100.6 MHz) δ<sub>c</sub> = 170.94 (C=C-H), 159.9 (N=C-CH<sub>3</sub>), 104.1 (C=C-H), 80.6 (C-CH), 38.35 (CH<sub>2</sub>-aliphatic), 34.48 (CH<sub>2</sub>-aliphatic), 31.7 (CH<sub>2</sub>-aliphatic), 28.2 (CH<sub>2</sub>-aliphatic), 25.2 (CH<sub>2</sub>-aliphatic), 21.3 (CH<sub>2</sub>-aliphatic), 14.0 (CH<sub>3</sub>-aliphatic), 11.4 (N=C-CH<sub>3</sub>); HRMS found: [M-H]<sup>+</sup> 211.1564, C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub> requires 211.1572; m/z: 211 (100%, M-H<sup>+</sup>).

Typical procedure for preparation of mesylated isoxazoles (compounds 104a-d)

Methane sulfonyl chloride (25mmol, 5 eq) and Et<sub>3</sub>N (25mmol, 5 eq) were sequentially added to a solution of starting alcohol (5mmol, 1 eq) in DCM (10ml) at 0°C. The reaction was then brought to room temperature and stirred for a further hour. The mixture was then diluted with water and the organic layer extracted, washed with brine and dried over MgSO<sub>4</sub> before evaporation under reduced pressure. The crude product was purified by column chromatography with 2% methanol in DCM as an eluent to afford the pure title product.

Methanesulfonic acid 1-cyclohexyl-2-(3-methyl-isoxazol-5-yl)-ethyl ester 104a

Methanesulfonic acid 1-cyclohexyl-2-(3-methyl-isoxazol-5-yl)-ethyl ester 104a

1.180 g, 82% yield, yellow oil, R<sub>f</sub> = 0.5 (30%, EtOAc in Petroleum spirits); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> = 6.00 (1H, s, C=C-H), 4.74 (1H, q, J = 5.6, CH<sub>2</sub>CH), 3.13 (2H, d, J = 6, CH<sub>2</sub>CH), 2.83 (3H, s, SO<sub>2</sub>CH<sub>3</sub>), 2.27 (3H, s, CH<sub>3</sub>C=N), 1.86-1.61 (6H, m, H Aliphatic), 1.29-1.15 (5H, m, H Aliphatic); <sup>13</sup>C NMR (100.6 MHz) δ<sub>c</sub> = 168.1 (C=C-H), 160.0 (N=C-CH<sub>3</sub>),
104.4, (C=C-H), 84.50 (C-OS0 2CH₃), 41.13 (C-OSOACh), 38.3 (CH-cyclohexane), 37.7 (CH₂-aliphatic), 29.3 (CH₂-cyclohexane), 28.3 (CH₂-cyclohexane), 25.8 (CH₂-cyclohexane), 11.4 (N=C-CH₃); HRMS found: [M-H⁺] 287.1 195, C₁₃H₂₅NO₄S requires 287.1 191; m/z: 287 (100%, M-H⁺).

[00191] Methanesulfonic acid 2-ethyl-1-[3-methyl-isoxazol-5-ylmethyl]-hexyl ester 104b:

![Diagram of 104b]

[00192] 1.33 g, 88% yield, yellow oil, Rᵢ = 0.52 (30%, EtOAc in petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δ_H = 5.97 (1H, s, C=C-H), 4.95-4.90 (1H, m, CH₂CH), 3.04 (2H, d, J = 6, CH₂CH), 2.75 (3H, s, S0₂CH₃), 2.21 (3H, s, C=C-CH₃), 1.65-1.58 (1H, m, CH aliphatic), 1.58-1.24 (8H, m, (CH₃)₂, 13C NMR (100.6 MHz) δ_C = 170.94 (C=C-H), 159.9 (N=C-CH₃), 103.0, (C=C-H), 82.6 (C-OSO₂CH₃), 46.76 (CH-aliphatic), 43.3 (CH₂-aliphatic), 38.3 (SO₂CH₃), 31.5 (CH₂-aliphatic), 28.2 (CH₂-aliphatic), 25.2 (CH₂-aliphatic), 21.3 (CH₂-aliphatic), 14.0 (CH₃-aliphatic), 14.0 (CH₃-aliphatic), 11.7 (N=C-CH₃) HRMS found: [M-H⁺] 303.1512, C₁₄H₂₅NO₄S requires 303.1504; m/z: 303 (100%, M-H⁺).

[00193] Methanesulfonic acid 3-methyl-1-(3-methyl-isoxazol-5-ylmethyl)-butyl ester 104c

![Diagram of 104c]

[00194] 1.11 g, 85% yield, yellow oil, Rᵢ = 0.48 (30%, EtOAc in petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δ_H = 5.95 (1H, s, H isoxazole), 4.97-4.92 (1H, m), 3.12 (1H, dd, J = 16, J = 5, CH₂CH), .303 (1H, dd, J = 16, J = 6, CH₂CH), 2.81 (3H, s, S0₂CH₃), 2.21 (3H, s, N=C-CH₃), 1.73-1.61 (2H, m, CH₂ aliphatic), 1.42-1.38 (1H, m CH aliphatic), 0.89 (6H, t, J = 7,
CH(CH₃)₂, 13C NMR (100.6 MHz) δC = 170.1 (C=C-H), 158.2 (N=C-CH₃), 103.2, (C=C-H), 68.0 (C-OSO₂CH₃), 46.1 (CH₂-aliphatic), 34.6 (CH₂-aliphatic), 34.2 (SO₂CH₃), 24.4 (CH₂-aliphatic), 23.9 (CH₃-aliphatic), 22.3 (CH-aliphatic), 12.5 (N=C-CH₃), HRMS found: [M-H⁺] 261.1039, C₁₁H₁₉N₂O₄S requires 261.1035; m/z: 261 (100%, M-H⁺).

[00195] Methanesulfonic acid 1-(3-methyl-isoxazol-5-ylmethyl)-heptyl ester 104d

![Methanesulfonic acid 1-(3-methyl-isoxazol-5-ylmethyl)-heptyl ester 104d](image)

[00196] 1.3 g, 90% yield, yellow oil, Rₜ = 0.5 (30%, EtOAc in petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δH = 6.02 (1H, s, C=H), 4.97-4.91 (1H, m, CH₂CH), 3.15 (2H, dd, J = 5, J = 3, CH₂CH), 2.89 (3H, s, SO₂CH₃), 2.29 (3H, s, C=C-CH₃), 1.82-1.66 (2H, m, CH₂ aliphatic), 1.48-1.24 (8H, m, (CH₂)₄ aliphatic), 0.91-0.87 (3H, t, J = 6, (CH₃)₃, ¹³C NMR (100.6 MHz) δC = 170.94 (C=C-H), 159.9 (N=C-CH₃), 104.1, (C=H), 80.6 (C-OSO₂CH₃), 38.35 (SO₂CH₃), 34.48 (CH₂-aliphatic), 31.7 (CH₂-aliphatic), 28.2 (CH₂-aliphatic), 25.2 (CH₂-aliphatic), 24.2 (CH₂-aliphatic), 21.3 (CH₂-aliphatic), 14.0 (CH₃-aliphatic), 11.4 (N=C-CH₃); HRMS found: [M-H⁺] 289.1350, C₁₃H₂₃N₂O₄S requires 289.1348; m/z: 289 (100%, M-H⁺).

Typical procedure for preparation of nitro isoxazoles (Compounds 105a-d)

[00197] Under a N₂ gas blanket at room temperature, triflic anhydride (2mmol, 2eq) was added dropwise to a stirred suspension of tetra methyl ammonium nitrate (2mmol, 2eq) in 2ml of anhydrous DCM, a slight temperature rise was observed. After stirring for at least 1.5 hours at room temperature, the stirred suspension was cooled to -78°C using an acetone/liquid nitrogen bath. The aliphatic isoxazole (1mmol, 1 eq) was dissolved in 3ml of anhydrous DCM and subsequently added to the stirred nitronium triflate suspension keeping the temperature at -65°C or lower. The reaction suspension was kept under N₂, the cooling bath removed and the reaction was stirred at room temperature for 24 hours.

[00198] The reaction was quenched using NaHCO₃ to give an aqueous layer of PH 8, the lower DCM layer was then separated and washed with 5 x 20ml of water. The combined water washes were back extracted with 2 X 20ml of DCM. The combined DCM portions were then dried over MgSO₄. DCM removal by rotary evaporation gave the crude product. The crude product was purified by column chromatography starting with 10 % EtOA in petroleum spirits as the eluent followed by 20 % EtOA in petroleum spirits to give the pure product.
Methanesulfonic acid 1-cyclohexyl-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl ester 105a

0.26 g, 79% yield, yellow oil; Rf = 0.65 (30%, EtOAc in Petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δ_H = 4.97 (1H, m, CH₂), 3.60 (1H, dd, J = 15, J = 4, CH₂CH), 3.47 (1H, dd, J = 15, J = 9, ChbCH), 2.91 (3H, s, SO₂CH₃), 2.57 (3H, s, CH₃C=N), 1.90-1.70 (6H, m, H Aliphatic), 1.30-1.18 (5H, m, H Aliphatic); ¹³C NMR (100.6 MHz) δ_C = 170.9 (C=C-N₂), 155.9 (N=C-CH₃), 110.9, 110.9 (C=C-N₂), 81.90 (C-OSO₂CH₃), 42.3 (C-OSO₂CH₃), 38.5 (CH-cyclohexane), 31.54 (CH₂-aliphatic), 30.7 (CH₂-cyclohexane), 28.1 (CH₂-cyclohexane), 25.8 (CH₂-cyclohexane), 11.6 (N=C-CH₃); HRMS found: [M-H⁺] 348.1360, C₁₃H₂₀N₂O₅S requires 348.1355; m/z: 332 (100%, M-H⁺).

Methanesulfonic acid 2-ethyl-1-(3-methyl-4-nitro-isoxazol-5-ylmethyl)-hexyl ester 105b

0.26 g, 75% yield, yellow oil, Rf = 0.62 (30%, EtOAc in petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δ_H = 5.20-5.16 (1H, m, CH₂), 3.48 (2H, d, J = 6, CH₂CH), 3.47 (3H, s, SO₂CH₃), 2.55 (3H, s, C=C-CH₃), 1.65-1.58 (1H, m, CH aliphatic), 1.58-1.24 (8H, m, CH² aliphatic), 0.92-0.82 (6H, m, CH₃), ¹³C NMR (100.6 MHz) δ_C = 171.05 (C=C-H), 155.9 (N=C-CH₃), 103.0, 103.0 (C=C-N₂), 79.9 (C-OSO₂CH₃), 44.5 (CH-aliphatic), 38.3 (SO₂CH₃), 31.54 (CH₂ aliphatic), 29.9 (CH₂ aliphatic), 29.4 (CH₂ aliphatic), 28.57 (CH₂ aliphatic), 22.8 (CH₂ aliphatic), 14.0 (CH₃ aliphatic), 14.0 (CH₃ aliphatic), 11.8 (N=C-CH₃); HRMS found: [M-H⁺] 348.1360, C¹₄H₂₆N₂O₆S requires 348.1355; m/z: 348 (100%, M-H⁺).
[00203] Methanesulfonic acid 3-methyl-1-(3-methyl-4-nitro-isoxazol-5-ylmethyl)butyl ester 105c

![Chemical Structure]

0.21 g, 70% yield, yellow oil, R\text{f} = 0.67 (30%, EtOAc in petroleum spirits); 'H NMR (400 MHz, CDCl\textsubscript{3}): δ\textsub{H} = 5.23-5.17 (1H, m), 3.62 (1H, dd, J = 15, J = 4, CH\textsubscript{2}CH), 3.50 (1H, dd, J = 15, J = 8, CH\textsubscript{2}CH), 2.95 (3H, s, S0 \textsubscript{2}CH\textsubscript{3}), 2.58 (3H, s, N=C-CH\textsubscript{3}), 1.84-1.75 (2H, m, CH\textsubscript{2} aliphatic), 1.57-1.49 (1H, m, CH aliphatic), 0.99 (6H, t, J = 7, CH(CH\textsubscript{3})\textsubscript{2}), 13C NMR (100.6 MHz) δ\textsub{C} = 170.1 (C=C-H), 158.2 (N=C-CH\textsubscript{3}), 103.2, (C=C-N0\textsubscript{2}), 68.0 (C-OS0\textsubscript{2}CH\textsubscript{3}), 46.1 (CH\textsubscript{2} aliphatic), 34.2 (S0 \textsubscript{2}CH\textsubscript{3}), 26.0 (CH\textsubscript{2} aliphatic), 24.4 (CH\textsubscript{3} aliphatic), 23.9 (CH\textsubscript{3} aliphatic), 22.3 (CH aliphatic), 12.5 (N=C-CH\textsubscript{3}), HRMS found: [M-H\textsuperscript{+}] 306.0387, C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{8}S requires 306.0386; m/z: 306 (100%, M-H\textsuperscript{+}).

[00205] Methanesulfonic acid 1-(3-methyl-4-nitro-isoxazol-5-ylmethyl)-heptyl ester 105d

![Chemical Structure]

0.27 g, 80% yield, yellow oil, R\text{f} = 0.67 (30%, EtOAc in petroleum spirits); 'H NMR (400 MHz, CDCl\textsubscript{3}): δ\textsub{H} = 5.06-5.01 (1H, m, CH\textsubscript{2}CH), 3.54 (1H, dd, J = 15, J = 4, CH\textsubscript{2}CH), 3.50 (1H, dd, J = 15, J = 8, CH\textsubscript{2}CH), 2.89 (3H, s, S0 \textsubscript{2}CH\textsubscript{3}), 2.51 (3H, s, N=C-CH\textsubscript{3}), 1.82-1.66 (2H, m, CH\textsubscript{2} aliphatic), 1.48-1.24 (8H, m, CH\textsuperscript{A} aliphatic), 0.89 (3H, t, J = 6, CH\textsubscript{3}), 13C NMR (100.6 MHz) δ\textsub{C} = 170.19 (C=C-H), 155.82 (N=C-CH\textsubscript{3}), 102.21, (C=C-N0\textsubscript{2}), 78.05 (C-OS0\textsubscript{2}CH\textsubscript{3}), 38.35 (S0 \textsubscript{2}CH\textsubscript{3}), 34.48 (CH\textsubscript{2} aliphatic), 31.7 (CH\textsubscript{2} aliphatic), 29.6 (CH\textsubscript{2} aliphatic), 28.2 (CH\textsubscript{2} aliphatic), 25.2 (CH\textsubscript{2} aliphatic), 22.50 (CH\textsubscript{2} aliphatic), 14.0 (CH\textsubscript{3} aliphatic), 11.81 (N=C-CH\textsubscript{3}); HRMS found: [M-H\textsuperscript{+}] 334.1203, C\textsubscript{16}H\textsubscript{19}N\textsubscript{2}O\textsubscript{8}S requires 334.1199; m/z: 334 (100%, M-H\textsuperscript{+}).

Typical procedure for preparation of aliphatic styrlisoxazoles (Compounds 3’a-d)
Et₃N (2.5 mmol, 2.5 eq) was added to nitro styryl isoxazole (1 mmol, 1.0 eq) in DCM (15 ml) and stirred at room temperature for approximately 1 hour. The reaction mixture was then quenched with NH₄Cl and diluted with water (10 mL). The organic layer was separated and dried over Na₂SO₄, filtered and evaporated to yield the crude compound. The crude product was purified by column chromatography using 100% DCM as the eluent.

5-(2-Cyclohexyl-vinyl)-3-methyl-4-nitro-isoxazole 3'a

0.19 g, 82% yield, yellow oil; Rf = 0.75 (20%, EtOAc in Petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δH = 6.97 (1H, dd, J = 16, CH=CH), 6.91 (1H, d, J = 16, CH=CH), 2.49 (3H, s, CH₃), 2.26-2.23 (1H, m, CH Aliphatic), 1.80-1.62 (5H, m, H Aliphatic), 1.34-1.11 (5H, m, H Aliphatic); ¹³C NMR (100.6 MHz) δC = 170.8 (C=N=CH₂), 156.0 (N=CH=CH), 111.1, (C=NO₂), 138.2 (C=C), 129.5 (C=C), 35.0 (CH-cyclohexane), 31.5 (CH₂-cyclohexane), 27.5 (CH₂-cyclohexane), 25.0 (CH₂-cyclohexane), 11.4 (N=CH=CH); HRMS found: [M-H⁺] 236.161, C₁₂H₁₆N₂O₃ requires 236.161; m/z: 236 (100%, M-H⁺).

5-(3-Ethyl-hept-1-enyl)-3-methyl-4-nitro-isoxazole 3'b

0.22 g, 88% yield, yellow oil, Rf = 0.77 (20%, EtOAc in petroleum spirits); ¹H NMR (400 MHz, CDCl₃): δH = 6.94 (1H, d, J = 16, CH=CH), 6.80 (1H, d, J = 16, CH=CH), 2.49 (3H, s, N=C-CH₃), 1.65-1.58 (1H, m, CH Aliphatic), 1.58-1.24 (8H, m, (CH₂)₄ Aliphatic), 0.92-0.82 (6H, m, (CH₃)₂), ¹³C NMR (100.6 MHz) δC = 171.05 (C=CH), 155.9 (N=CH=CH), 103.0, (C=NO₂), 135.6 (CH=CH), 136.9 (CH=CH), 40.3 (CH Aliphatic), 31.54 (CH₂-Aliphatic), 29.4 (CH₂-Aliphatic), 28.57 (CH₂-Aliphatic), 22.8 (CH₂-Aliphatic), 14.0 (CH₃-Aliphatic), 14.0 (CH₃-Aliphatic), 11.8 (N=CH=CH); HRMS found: [M-H⁺] 252.1462, C₁₃H₂₀N₂O₃ requires 252.1474; m/z: 252 (100%, M-H⁺).
3-Methyl-5-(4-methyl-pent-1-enyl)-4-nitro-isoxazole 3'c

NMR (400 MHz, CDCl₃): δ_H = 7.08 (1H, dd, J = 16, J = 6, CH=CH), 7.03 (1H, dd, J = 21, J = 16, CH=CH), 2.53 (3H, s, N=C-CH₃), 2.26 (2H, t, J = 6, CH₂ aliphatic), 1.89-1.79 (1H, m, CH aliphatic), 0.95 (6H, d, J = 7, CH(CH₃)₂), 13C NMR (100.6 MHz) δ_C = 170.1 (C=C-H), 158.2 (N=C-CH₃), 133.0 (CH=CH), 127.0 (CH=CH), 103.2, (C=C-NO₂), 42.1 (CH₂-aliphatic), 24.4 (CH₃-aliphatic), 23.9 (CH₃-aliphatic), 22.3 (CH-aliphatic), 12.5 (N=C-CH₃), HRMS found: [M-H⁻] 210.1008, C₁₀H₁₄N₂O₃ requires 210.1004; m/z 210 (100%, M-H⁻).

3-Methyl-4-nitro-5-oct-1-enyl-isoxazole 3'd

NMR (400 MHz, CDCl₃): δ_H = 7.10 (1H, dd, J = 16, J = 6, CH=CH), 7.06 (1H, dd, J = 26, J = 16, CH=CH), 2.54 (3H, s, C=C-CH₃), 2.38 (2H, q, J =6, CH₂ aliphatic), 1.57-1.50 (2H, m, CH₂ aliphatic), 1.37-1.28 (6H, m, (CH₂)₃), 0.89 (3H, t, J = 6, (CH₃), 13C NMR (100.6 MHz) δ_C = 155.82 (N=C-CH₃), 135.6 (CH=CH), 126.9 (CH=CH), 102.21, (C=C-NO₂), 34.48 (CH₂ aliphatic), 31.7 (CH₂-aliphatic), 28.2 (CH₂-aliphatic), 25.2 (CH₂-aliphatic), 22.50 (CH₂-aliphatic), 14.0 (CH₃-aliphatic), 11.81 (N=C-CH₃); HRMS found: [M-H⁻] 238.1302, C₁₀H₁₆N₂O₃ requires 238.1317; m/z 238 (100%, M-H⁻).

Procedure for the preparation of 3-methyl-5-(4-methyl-2-nitromethyl-pentyl)-4-nitro-isoxazole (5)
[00216] **Procedure A**: In a round bottomed flask, fitted with a magnetic stirrer were sequentially added compound 3 (196 mg, 1 mmol) toluene (33 mL), \(\alpha\)-benzyl-quinidinium bromide 4a (R=H) (23 mg, 0.05 equiv, 5 mol%), and nitromethane (300 mg, 5 mmol, 5 equiv). Finally, \(\text{K}_2\text{CO}_3\) (690 mg, 5 mmol, 1 equiv) was added in one portion. The reaction was stirred at 0°C for 60 hours, then quenched with sat \(\text{NH}_4\text{Cl}\) (10 mL), extracted with toluene (2 x 10 mL), dried over MgSO\(_4\), filtered over celite and evaporated to give pure compound 5 in 96% yield and 65% ee.

[00217] **Procedure B**: In a round bottomed flask, fitted with a magnetic stirrer were sequentially added compound 3 (196 mg, 1 mmol) toluene (33 mL), \(\alpha\)-((4,5-dimethoxybenzyl-2-nitrobenzyl)quinidinium bromide 4b (R= R\(_1\)=NO\(_2\), R\(_2\)=OCH\(_3\), R\(_3\)=OCH\(_3\)) (12 mg, 0.02 equiv, 2 mol%), and nitromethane (300 mg, 5 mmol, 5 equiv). Finally, \(\text{K}_2\text{CO}_3\) (690 mg, 5 mmol, 1 equiv) was added in one portion. The reaction was stirred at 0°C for 24 hours, then quenched with sat \(\text{NH}_4\text{Cl}\) (10 mL), extracted with toluene (2 x 10 mL), dried over MgSO\(_4\), filtered over celite and evaporated to give pure compound 5 in 96% yield and 76% ee.

[00218] Compound 5: Colorless liquid; \(R_f=0.2\) (Petroleum Ether/Ethyl Acetate, 90:10); \(\delta_H\) (400 MHz, CDCl\(_3\)) 4.38 (2H, d, \(J=6\)), 3.35 (1H, dd, \(J=15, J=6\)), 3.28 (1H, dd, \(J=15, J=7\)), 2.87 (1H, sept, \(J=7\)), 2.56 (3H, s), 1.68 (1H, sept, \(J=7\)), 1.36-1.23 (2H, m), 0.92 (3H, d, \(J=4\)), 0.90 (3H, d, \(J=4\)), 22.3, 11.7. HRMS: \(m/z\) found [M+H\(^+\)]\(^{272.1212}\), \(\text{C}_{18}\text{H}_{18}\text{N}_{3}\text{O}_{5}\) requires 272.1212.

[00219] **Recrystallisation of compound 5 from 68-86%ee to enantiopure +99ee**: Purified compound 5 (4g) was dissolved in minimum amounts of hot isopropanol or hot mixtures of isopropanol hexane (1:1), which were typically 3-10 mL. The resulting solution was cooled at -20°C to give compound 5 as needles, which were filtered, dried weighted 2.5-3.2g.

[00220] **Procedure C**: In a round bottomed flask, fitted with a magnetic stirrer were sequentially added alkene 3 (20 mg, 0.096 mmol) toluene (9.6 mL), catalyst A-E (see below)
(0.1 equiv, 10mol%), and nitromethane (30mg, 0.48 mmol, 5 equiv). The temperature was made 0°C using an ice water bath, then K₂CO₃ (66mg, 0.48 mmol, 5 equiv) was added in one portion. The reaction was stirred at 0-3°C for 32 hours, then quenched with sat NH₄Cl (10 mL), extracted with toluene (2 x 10 mL), dried over MgSO₄, filtered over celite and evaporated to give pure compound in yield and ee listed in table 1.

**Table 1: catalyst screening**

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<th>Entry</th>
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<th>Conv% of 3</th>
<th>Yield% of 5</th>
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<tr>
<td>2</td>
<td>B</td>
<td>100</td>
<td>97</td>
<td>86</td>
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<tr>
<td>3</td>
<td>C</td>
<td>100</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>E</td>
<td>100</td>
<td>91</td>
<td>62</td>
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</table>

**Procedure D:** In a round bottomed flask, fitted with a magnetic stirrer were sequentially added alkene 3 and toluene as indicated in table 2, catalyst B (0.05 equiv, 5mol%) and nitromethane (3-5 equiv). The temperature was made 0°C using an ice water bath, then K₂CO₃ (3-5 equiv) was added in one portion. The reaction was stirred at 0-3°C for time indicated in table 2, then quenched with sat NH₄Cl, extracted with toluene, dried over MgSO₄, filtered over celite and evaporated to give pure compound in yield and ee as listed in table 2.

**Table 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>CH₃N₂O</th>
<th>K₂CO₃ (mmol)</th>
<th>Alkene 3 (mg)</th>
<th>Alkene 3 (mmol)</th>
<th>Cone. (M)</th>
<th>Toluene (mL)</th>
<th>Conv. % of 3</th>
<th>Ee% of 5</th>
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<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>0.096</td>
<td>20</td>
<td>0.01M</td>
<td>9.6</td>
<td>89% (96h)</td>
<td>86%</td>
</tr>
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<td>2</td>
<td>1.5</td>
<td>5</td>
<td>10</td>
<td>2100</td>
<td>0.08M</td>
<td>125</td>
<td>30% (96h)</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>5</td>
<td>10</td>
<td>2100</td>
<td>0.16M</td>
<td>62.5</td>
<td>41% (96h)</td>
<td>79%</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>5</td>
<td>2.4</td>
<td>500</td>
<td>0.04M</td>
<td>60</td>
<td>20% (24h)</td>
<td>81%</td>
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<tr>
<td>5</td>
<td>5</td>
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<td>2.4 (p)</td>
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<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>2.4 (p)</td>
<td>500</td>
<td>0.08M</td>
<td>30</td>
<td>80% (20h)</td>
<td>83%</td>
</tr>
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<tr>
<td>7</td>
<td>5</td>
<td>5</td>
<td>2.4 (p)</td>
<td>500</td>
<td>0.16M</td>
<td>15</td>
<td>83% (20h)</td>
<td>80%</td>
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<tr>
<td>8</td>
<td>5</td>
<td>5</td>
<td>2.4 (p)</td>
<td>500</td>
<td>0.32M</td>
<td>7.5</td>
<td>92% (19h)</td>
<td>74%</td>
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<tr>
<td>9</td>
<td>3</td>
<td>3</td>
<td>2.4 (p)</td>
<td>500</td>
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<td>15</td>
<td>57% (17h)</td>
<td>80%</td>
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<tr>
<td>10</td>
<td>3</td>
<td>3</td>
<td>1.7 (p)</td>
<td>500</td>
<td>0.32M</td>
<td>5.3</td>
<td>75% (17h)</td>
<td>74%</td>
</tr>
</tbody>
</table>

(a (p) refers to alkene 3 over 98% pure.

[00224] Procedure E: In a round bottomed flask, fitted with a magnetic stirrer were sequentially added alkene 3 (25g, 119 mmol) and toluene (750 ml), then catalyst B (3.6g, 0.05 equiv, 5mol%) and nitromethane (36.3g, 595 mmol, 5 equiv). The temperature was made 0°C using an ice water bath, then K₂CO₃ (82g, 595 mmol, 5 equiv) was added in one portion. The reaction was stirred at 0-3°C for 30 hours, then quenched water (250 mL), the organic layer separated and the aqueous treated with diluted HCl to pH ~ 3; the aqueous layer was extracted with toluene (2 x 50 mL); the organic layer were combined, evaporated and the residue passed through a plug of silica eluting with DCM. The product was obtained in 93% yield (30g) as a sticky liquid and in 80% ee. Compound 5: Colorless solid, mp = 43°C (isopropanol Hexane 1 : 1) ; Rf = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); νₒ(H) (400 MHz, CDCl₃) 4.38 (2H, d, J = 6), 3.35 (1H, dd, J = 15, J = 6), 3.28 (1H, dd, J = 15, J = 1), 2.87 (1H, sept, J = 7), 2.56 (3H, s), 1.68 ( 1H, sept, J = 7), 1.36-1.23 ( 2H, m), 0.92 (3H, d, J = 4), 0.90 (3H, d, J = 4), νₒ (100.6 MHz, CDCl₃) 172.1, 122.9, 78.5, 40.9, 33.9, 30.0, 25.1, 22.4, 22.3, 11.7. HRMS: m/z found [M+H]⁺ 272.1212, C₁₁H₁₆N₃O₅ requires 272.1246.

[00225] Procedure F: In a round bottomed flask, fitted with an overhead stirrer were charged toluene (330 mL) and K₂CO₃ (75.9g, 550 mmol, 2.5 equiv). A solution of alkene 3 (46.2g, 220 mmol), nitromethane (26.8g, 440 mmol, 2 equiv) and catalyst B (5.33g, 0.04 equiv, 4mol%) in toluene (110 mL) was charged in a dropping funnel and added drop wise over a 2h period. The reaction was stirred at room temperature (21°C) for 28h, then quenched with water (500 mL) and the organic layer separated. The aqueous layer was treated with HCl cone to pH ~ 3; the aqueous layer was extracted with toluene (2 x 100 mL); the organic layer were combined, evaporated and the residue passed through a plug of silica eluting with DCM. The product was obtained in 92% yield (54.8g) as a sticky liquid and in 68% ee.

NOTE 1: the reaction may have a induction period depending on purity of alkene 3.

NOTE 2: the reaction carried out by adding the solution of alkene/nitromethane/catalyst over a period of 16 hours gave only 16% conversion in the same time.
Procedure G (Preparation of racemic compound 5): In a round bottomed flask, fitted with an overhead stirrer were charged toluene (330 mL) and K₂CO₃ (75.9g, 550 mmol, 2.5 equiv). A solution of alkene 3 (46.2g, 220 mmol), nitromethane (26.8g, 440 mmol, 2 equiv) and N-tetrabutyl ammonium bromide (2.82g, 0.04 equiv, 4mol%) in toluene (110 mL) was charged in a dropping funnel and added drop wise over a 2h period. The reaction was stirred at room temperature (21 °C) for 28h, then quenched with water (500 mL) and the organic layer separated. The aqueous layer was treated with HCl cone to pH ~ 3; the aqueous layer was extracted with toluene (2 x 100 mL); the organic layer were combined, evaporated and the residue passed through a plug of silica eluting with DCM. The product was obtained in 94% yield (56g) as a sticky liquid.

Alternative preparation of 3-methyl-5-(4-methyl-2-nitromethyl-pentyl)-4-nitro-isoxazole (5).

![Diagram of reaction](image)

Table 11

<table>
<thead>
<tr>
<th>entry</th>
<th>B (equiv)</th>
<th>Solvent</th>
<th>Base</th>
<th>Catalyst</th>
<th>Conv. A</th>
<th>Yield % C</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>2.25 mL</td>
<td>K₂CO₃</td>
<td>NE₅₃ (1 equiv)</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>2.25 mL</td>
<td>K₂CO₃ (5 equiv)</td>
<td>I (0.1 equiv)</td>
<td>100</td>
<td>70 (5% e.e.)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>2.25 mL</td>
<td>K₂CO₃ (5 equiv)</td>
<td>II (0.1 equiv)</td>
<td>100</td>
<td>20 (7% e.e.)</td>
</tr>
</tbody>
</table>

4-Methyl-1-nitro-pent-1-ene (Alkene A) was prepared via condensation of isovaleraldehyde and nitromethane in presence of base according to a literature procedure [Liu, J-m; Wang, X.; Ge, Z-m; Sun, Q.; Cheng, T-m, Li, R-t Tetrahedron, 201 1, 67, 636].

Procedure: To a solution of 4-methyl-1-nitro-pent-1-ene A (0.5 mmol) in dichloromethane (2.25 mL) were sequentially added 3,5-dimethyl-4-nitroisoxazole (5 equiv), catalyst and base as indicated in table 11. The resulting mixture was then stirred at room temperature for 16 h, then quenched with sat ammonium chloride (3 mL). The organic layer was separated, the solvent evaporated and the crude material purified via flash chromatography to give desired 3-methyl-5-(4-methyl-2-nitromethyl-pentyl)-4-nitro-isoxazole 5.
Preparation of the Catalysts

[00229] /V-benzyl-quinidinium bromide (4a): To a suspension of quinidine (650 mg, 2.0 mmol, 1.0 eq.) in THF (12.0 mL) benzyl bromide (0.31 mL, 2.6 mmol, 1.3 eq.) was added. The resulting mixture was heated at 60 °C for 16 h. The reaction was diluted with CH2Cl2 (10 mL) and washed with H2O (3 x 15 mL). The organic phase was dried over Na2SO4 and the solvent evaporated under reduced pressure. The crude material was purified by column chromatography (chloroform/methanol 95:5) affording the title compound as a purple solid (512 mg, 52% yield). δH (400 MHz, CDCl3): 8.60 (d, J = 4.4, 1H), 7.95 (d, J = 9.2, 1H), 7.81 (d, J = 4.4, 1H), 7.72-7.70 (m, 2H), 7.36 (d, J = 2.8, 1H), 7.35-7.18 (m, 4H), 6.73-6.71 (m, 1H), 6.57-6.56 (m, 1H), 6.02-5.89 (m, 2H), 5.25-5.19 (m, 3H), 4.67-4.55 (m, 1H), 3.95-3.90 (m, 2H), 3.85 (s, 3H), 3.44-3.41 (m, 1H), 2.98-2.95 (m, 1H), 2.45-2.35 (m, 2H), 1.90-1.80 (m, 3H), 1.09-1.01 (m, 1H); m.p.: 198-202°C.

[00230] yV-(4,5-dimethoxybenzyl-2-nitrobenzyl)quinidinium bromide (4b): To a suspension of quinidine (650 mg, 2.0 mmol, 1.0 eq.) in THF (12.0 mL) 1-bromomethyl-4,5-dimethoxy-2-nitro-benzene (0.31 mL, 2.6 mmol, 1.3 eq.) was added. The resulting mixture was heated at 60 °C for 16 h. The reaction was diluted with CH2Cl2 (10 mL) and washed with H2O (3 x 15 mL). The organic phase was dried over Na2SO4 and the solvent evaporated under reduced pressure. The crude material was purified by column chromatography (chloroform/methanol 95:5) affording the title compound as a purple solid (650 mg, 90% yield). δH (400 MHz, CDCl3): 8.80 (m, 1H), 8.30 (m, 1H), 8.10 (d, J = 9.2, 1H), 7.90 (d, J = 4.4, 1H), 7.72-7.70 (m, 2H), 7.10 (m 1H), 6.93-6.71 (m, 3H), 6.57-6.56 (m, 1H), 6.80-5.73 (m, 1H), 5.25-5.19 (m, 2H), 4.95-4.90 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.44-3.41 (m, 1H), 2.98-2.95 (m, 1H), 2.45-2.35 (m, 2H), 1.90-1.80 (m, 3H), 1.09-1.01 (m, 1H); m.p.: 202-205°C.

[00231] /V-benzyl-cinchonidinium bromide: To a flame-dried flask equipped with a magnetic stirring bar and a reflux condenser was added cinchonine (1.00 g, 3.4 mmol), THF (50 mL), and desired benzyl bromide derivative (3.4 mmol). The mixture was heated to reflux until judged to be complete by TLC-analysis (CH2Cl2/MeOH 9:1) and then cooled to room temperature and poured onto Et2O (150 mL) with stirring. The resulting suspension was stirred for 1 h and the precipitated solids were isolated by filtration, which was recrystallized from MeOH/Et2O as follows: to the crude product was added 5-10 mL MeOH until the solid just dissolves at reflux and then the mixture was placed at room temperature. To the warmed solution was quickly added Et2O until crystal formation was initiated and then the solution was allowed to cool slowly to room temperature over night. Removal of the mother liquid and washing with Et2O afforded the product as crystal. Prepared according to the general procedure, cinchonine (1.00 g, 3.4 mmol) and benzyl bromide (0.58 g, 3.4 mmol) gave the
product as colourless crystals 1.37 g (reaction time 4.5 h). Isolated yield 86.9% after recrystallisation. mp 259-261°C (dec); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.84 (1H, d, \(J = 5\)), 8.34 (1H, d, \(J = 8\)), 7.93 (1H, d, \(J = 4\)), 7.64 (1H, d, \(J = 8\)), 7.58 (2H, d, \(J = 7.0\)), 7.22 - 6.98 (5H, m), 6.83 - 6.70 (1H, m), 6.50 (1H, bs), 6.18 - 6.03 (1H, m), 5.89 - 5.76 (1H, m), 5.41 - 5.26 (1H, m), 5.26 - 5.11 (2H, m), 4.49 - 4.38 (1H, m), 4.20 - 4.02 (2H, m), 3.29 (1H, t, \(J = 12\) Hz), 2.74 (1H, dd, \(J = 21, J = 10\)), 2.27 (1H, dd, \(J = 17, J = 9\) Hz), 2.13 - 2.01 (1H, m), 1.82 - 1.63 (3H, m), 0.77 - 0.63 (1H, m); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 149.1, 146.6, 144.9, 135.2, 134.0, 129.9, 129.2, 128.6, 128.25, 127.3, 126.9, 123.5, 123.3, 119.7, 118.1, 118.2, 66.7, 65.7 61.4, 56.3, 53.6, 53.4, 38.0, 27.2, 23.8, 21.8.

\[00232]\] **W-(3,5-bis(trifluoromethyl)benzyl) cinchonidinium bromide**: To a stirred suspension of cinchonidine (294.4 mg, 1.0 mmol) in toluene (4.0 mL), 3.5-bis(trifluoromethyl)benzyl bromide (220 \(\mu\)L, 1.2 mmol) was added. The resulting mixture was then heated at 80°C, and stirred for 24 h at the same temperature. After cooling to r.t., the precipitate was collected by Buckner filtration and washed several times with Et\textsubscript{2}O, affording the title compound as a white solid in 75% yield. [a]D\textsubscript{20} = -126 (c = 0.81 in CH\textsubscript{2}OH); 1H NMR (CD\textsubscript{3}OD, 400 MHz) \(\delta\) 8.94 (d, \(J = 4.6\) Hz, 1H), 8.46 (s, 2H), 8.36-8.32 (m, 1H), 8.23 (s, 1H), 8.14-8.10 (m, 1H), 7.95 (d, \(J = 4.5\) Hz, 1H), 7.88-7.89 (m, 2H), 6.66 (d, \(J = 1.6\) Hz, 1H), 5.68 (ddd, \(J = 17.3, 10.5, 6.8\) Hz, 1H), 5.41 (d, \(J = 12.7\) Hz, 1H), 5.31 (d, \(J = 12.7\) Hz, 1H), 5.17 (dt, \(Jd = 17.2\) Hz, \(Jt = 1.0\) Hz, 1H), 4.99 (dt, \(Jd = 10.5\) Hz, \(Jt = 1.1\) Hz, 1H), 4.58 (tdtd, \(Jt = 11.3\) Hz, \(Jt = 8.3, 5.1, 3.0\) Hz, 1H), 4.05 (dd, \(J = 9.7, 8.8\) Hz, 1H), 3.80 (ddd, \(J = 12.4, 7.9, 4.7, 3.3\) Hz, 1H), 3.46 (dd, \(J = 12.3, 10.6\) Hz 1H), 3.38 (dt, \(Jt = 11.4\) Hz, \(Jd = 4.8\) Hz, 1H), 2.73 (bs, 1H), 2.37-2.19 (m, 1H), 2.08 (bs, 1H), 1.96-1.84 (m, 1H), 1.48-1.37 (m, 1H), 0.83-0.73 (m, 1H); \textsuperscript{13}C NMR (CD\textsubscript{3}OD, 100 MHz) \(\delta\) 149.9, 147.6, 146.1, 137.3, 134.3 (q, \(J = 4\) Hz), 132.5 (q, \(J = 36\) Hz), 130.9, 130.0, 129.2, 128.7, 128.1, 128.0, 125.1, 124.9, 123.3 (q, \(J = 275\) Hz), 123.0, 120.1, 116.5, 69.1, 65.1, 62.2, 60.7, 51.8, 37.9, 26.7, 24.7, 21.3; 19F NMR (CD\textsubscript{3}OD, 156 MHz) \(\delta\) -64.6; ESI-MS: 521 [M\textsuperscript{+}].

**General procedure for the preparation of catalysts A-E**
[00233] In a round bottomed flask fitted with a magnetic stirrer and a reflux condenser were put sequentially quinidine (1.0 equiv), the appropriate benzyl bromide (1.05 equiv) and acetone to make a 0.18-0.20M solution. It was noted that at 50-55°C the reaction became clear. The resulting solution was heated at 60-65°C for 2h. The reaction mixture was then allowed to reach room temperature, the solvent evaporated to give a solid which was suspended in petroleum ether, stirred for 30 minutes, then filtered and dried to give pure quinidinium bromides A-E. Optionally compounds A-B may be dissolved in the minimum quantity of DCM and then precipitated by addition of Et₂O.

NOTE 1: Commercial sources of quinidine always contain variable amounts of dihydroquinidine. This implies that Catalysts A-B and D-E may contain variable amounts of the corresponding dihydroquinidinium salt.

NOTE 2: In the synthesis of compounds C-E, it was noted the formation of a precipitate from hot acetone, minutes from refluxing at 60-65°C.

NOTE 3: Compounds A-B may form sticky viscous oils when wet (Acetone, DCM); Drying under reduce pressure (rotavapor) gave compounds A-E as a fine powder.

[00234] Catalyst A: W-(3,5-ditrifluoromethylbenzyl)quinidinium bromide: light yellow powder; δ H (400 MHz, CDCl₃) 8.39-8.36 (1H, m), 8.25-8.24 (2H, m), 7.74 (1H, s), 7.67 (1H, d, J = 8 Hz), 7.61 (1H, d, J = 4 Hz), 7.49 (1H, d, J = 4 Hz), 6.95-6.92 (1H, m), 6.48-6.47 (1H, m), 6.12-6.09 (1H, m), 6.10 (1H, d, J = 8 Hz), 5.82 (1H, d, J = 8 Hz), 5.80-5.74 (1H, m), 5.16-5.10 (2H, m), 4.56-4.50 (1H, m), 4.34-4.29 (1H, m), 4.15-4.10 (1H, m), 3.68 (3H, s), 3.08-3.02 (1H, m), 2.64-2.59 (1H, m), 2.39-2.19 (2H, m), 1.77-1.73 (9H, m), 0.85-0.82 (1H, m); δ C (100.6 MHz, CDCl₃) 157.9, 147.0, 144.0, 142.0, 134.9, 133.9, 132.6, 132.3, 131.6, 130.4, 126.0, 123.9, 121.2, 120.4, 120.0, 118.5, 103.2, 68.1, 67.1, 60.4, 60.2, 56.5, 56.3, 54.5, 37.9, 27.0, 23.8, 21.9.
Catalyst B: W-(3,5-ditertbutylbenzyl)quinidinium bromide: colourless powder; δ H (400 MHz, CDCl3) 8.61-8.59 (1H, m), 7.97-7.94 (1H, m), 7.68-7.67 (1H, m), 7.60-7.59 (1H, m), 7.53-7.51 (1H, m), 7.3-7.26 (2H, m), 6.79-6.77 (1H, m), 6.58-6.55 (1H, m), 6.00-5.92 (1H, m), 5.83-5.80 (1H, m), 5.19-5.15 (2H, m), 4.85-4.76 (1H, m), 4.62-4.57 (1H, m), 4.10-4.04 (1H, m), 3.93 (3H, s), 3.88-3.83 (1H, m), 3.50-3.44 (1H, m), 3.07-3.02 (1H, m), 1.89-1.85 (1H, m), 1.80-1.75 (1H, m), 1.08-1.01 (1H, m); δ C (100.6 MHz, CDCl3) 157.9, 152.0, 147.4, 144.2, 143.0, 135.8; 131.8, 128.3, 126.2, 126.1, 124.4, 121.0, 120.5, 118.1, 102.2, 68.4, 65.3, 64.3, 56.8, 56.0, 54.2, 38.3, 35.0, 31.4, 18.2, 27.8, 24.2, 21.5.

Catalyst C: W-(3,5-ditertbutylbenzyl)dihydroquinidinium bromide: colourless powder; δ H (400 MHz, CDCl3) 8.69-8.68 (1H, m), 8.03-8.00 (1H, m), 7.75-7.74 (1H, m), 7.59-7.58 (2H, m), 7.54-7.53 (1H, m), 7.63-7.29 (2H, m), 6.82-6.80 (1H, m), 6.66-6.62 (1H, m), 4.76-4.73 (1H, m), 4.42-4.35 (1H, m), 3.94 (3H, s), 3.74-3.65 (2H, m), 3.55-3.46 (1H, m), 3.14-3.06 (1H, m), 2.54-2.48 (1H, m), 1.94-1.88 (1H, m), 1.81-1.77 (1H, m), 1.69-1.55 (3H, m), 0.88-0.84 (1H, m); δ C (100.6 MHz, CDCl3) 158.0, 152.1, 147.7, 144.3, 143.1, 132.2, 128.3, 126.2, 126.0, 124.5, 120.6, 120.5, 102.3, 68.9, 64.9, 64.6, 57.1, 56.0, 55.9, 36.2, 35.0, 31.4, 31.3, 24.9, 24.6, 24.3, 21.3, 11.4.

Catalyst D: W-(3,5-dimethylbenzyl)quinidinium bromide: colourless powder; δ H (400 MHz, CDCl3) 8.45-8.43 (1H, m), 7.89-7.86 (1H, m), 7.71-7.70 (1H, m), 7.20-7.19 (1H, m), 7.20-7.17 (2H, m), 6.89-6.88 (1H, m), 6.69-6.67 (1H, m), 6.47-6.45 (1H, m), 5.89-5.81 (1H, m), 5.73-5.69 (1H, m), 5.17-5.12 (2H, m), 4.53-4.48 (1H, m), 3.91-3.86 (1H, m), 3.80 (3H, s), 3.43-3.38 (1H, m), 2.93-2.90 (1H, m), 2.39-2.34 (2H, m), 2.30 (6H, s), 1.80-1.65 (4H, m), 0.93-0.80 (1H, m); δ C (100.6 MHz, CDCl3) 157.8, 147.3, 144.3, 142.6, 138.7, 135.6, 131.9, 131.7, 131.4, 126.8, 126.4, 120.7, 120.6, 118.0, 102.8, 68.0, 66.9, 62.9, 56.6, 56.0, 54.0, 38.2, 27.2, 24.0, 21.7, 21.3.

Catalyst E: W-(3,5-dibromobenzyl)quinidinium bromide: colourless powder; δ H (400 MHz, CDCl3) 8.36-8.35 (1H, m), 7.82-7.74 (4H, m), 7.66-7.65 (1H, m), 7.04-7.01 (1H, m), 6.58-6.56 (1H, m), 6.44-6.40 (1H, m), 6.17-6.15 (1H, m), 5.86-5.79 (1H, m), 5.64-5.59 (1H, m), 5.28-5.22 (2H, m), 4.55-4.52 (1H, m), 4.27-4.25 (2H, m), 3.70 (3H, s), 3.23-3.20 (1H, m), 2.79-2.76 (1H, m), 2.40-2.38 (1H, m), 2.25-2.21 (1H, m), 1.85-1.77 (3H, m), 0.93-0.85 (1H, m); δ C (100.6 MHz, CDCl3) 157.7, 147.0, 144.1, 142.0, 136.2, 135.1, 135.0, 131.6, 131.1, 126.3, 123.5, 120.5, 119.5, 118.2, 103.8, 67.7, 59.8, 56.3, 56.0, 54.2, 37.9, 27.0, 23.8, 22.0, 15.3.

[00239] Preparation of 5-Methyl-3-nitroethyl-hexanoic acid (6) (Procedure A): A solution of adduct 5, (0.25 mmol) in THF (0.5 mL) was charged in a round bottomed flask and treated with an aqueous solution of NaOH (1N, 1.35 mL, 5.5 equiv.). The resulting deep yellow solution was refluxed (T of the oil bath = 100°C) for 1h, then allowed to reach room
temperature, the THF evaporated in vacuo and the aqueous solution so obtained was made acidic (pH = 2) by addition of 6N aqueous HCl. The aqueous solution obtained was evaporated in vacuo to give a solid which was then washed with DCM (2 x 10 mL). Compound 6 was obtained as solid in 70% yield upon evaporation of the DCM solution. $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 4.50 (1H, dd, J = 12, J = 7), 4.44 1H, dd, J = 12, J = 6) 2.67 (1H, sep J = 6 Hz), 2.49 (2H, d, J = 6), 1.66 (1H, sept, J = 7), 1.28 (2H, m), 0.93 (3H, d, J = 7), 0.91 (3H, d, J = 7). $^{13}$C NMR 6c(100.1 MHz, CDCl$_3$) 177.6, 78.4, 40.3, 35.6, 31.7, 24.9, 22.3, 22.0.

[00240] Preparation of 5-Methyl-3-nitromethyl-hexanoic acid (6) (Procedure B): To a solution of adduct 5, (0.25 mmol) in THF (0.5 mL) was added dropwise a solution of KMnO$_4$ (3 equiv) in H$_2$O: Acetone (4:1 ) 4.5mL. The reaction mixture was stirred for 1 hour at room temperature and then a Na$_2$S$_2$O$_3$ saturated solution (5 mL) was added to destroy the excess of KMnO$_4$: the formation of a brown precipitate was observed (MnO$_2$). The mixture was then acidified with HCl 6 M until pH = 3. At this point it was noted that the solution became clear. The mixture was then extracted with DCM (3 x 1mL) and the combined organic phases were evaporated. Compound 6 was obtained as solid in 90% yield upon evaporation of the DCM solution.

[00241] Preparation of 5-Methyl-3-nitromethyl-hexanoic acid (6) (Procedure C): A solution of adduct 5, (39.2g 144 mmol) in THF (100mL) was charged in a round bottomed flask and treated with a freshly made aqueous solution (1N, 720 mL, 5 equiv.) of NaOH (28.8g, 720 mmol). The resulting dark solution was refluxed (T = 60-65°C) for 16h, then allowed to reach room temperature, the THF evaporated in vacuo and the aqueous solution so obtained was extracted with toluene (300 mL). the aqueous layer was made cold (0°C) by an ice water bath, then HCl cone was added drop wise with stirring until pH ~ 2-3. This addition must be done carefully to avoid formation of side products. The aqueous solution was then extracted with toluene (3 x 200 mL), the organic layer washed with water (2 x 150 mL) and concentrated in vacuo to give acid 6 as a yellow brown viscous oil (25.2, 93% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 4.50 (1H, dd, J = 12, J = 7), 4.44 1H, dd, J = 12, J = 6) 2.67 (1H, sep J = 6 Hz), 2.49 (2H, d, J = 6), 1.66 (1H, sept, J = 7), 1.28 (2H, m), 0.93 (3H, d, J = 7), 0.91 (3H, d, J = 7). $^{13}$C NMR 5c(100.1 MHz, CDCl$_3$) 177.6, 78.4, 40.3, 35.6, 31.7, 24.9, 22.3, 22.0.

NOTE 1: starting from adduct 5 68% ee enantioenriched, compound 6 was obtained in 68% ee; starting from adduct 5 85% ee enantioenriched, compound 6 was obtained in 85% ee.

Preparation of (S)-Pregabalin (7) - Reduction of compound 6 using Pd/C: In a round bottomed flask were charged compound 6 (50g, 264 mmol, Mw=189, 80% ee), methanol (260 mL) and Pd/C (10%, 15g). The suspension obtained was stirred at room temperature for 24h under an atmosphere of H₂ (1 atm) then filtered through a pad of celite and the solution evaporated to give a white solid which was washed with hexane (20 mL) to give (S)-pregabalin (40.3g, 96% yield).

NOTE 1: the reduction could be carried out under pressure at room temperature (18°C).

Preparation of (S)-Pregabalin (7) - Reduction of compound 6 using Ni/Ra:

Preparation of (S)-Pregabalin (7) - Crystallisation of enantiopure (S)-Pregabalin:

Enantioenriched (S)-pregabalin (30g, 68-86% ee) was dissolved in hot isopropanol (100 mL), then water (35 mL) added and the mixture allowed to reach room temperature (18°C) and then cooled at 0°C, to give a precipitate of (S)-pregabalin (60% to 80% yield).

Preparation of (S)-Pregabalin (7) - Partial resolution of (S)-Pregabalin: To a solution of enantioenriched (S)-pregabalin (30g, 68-86% ee) in hot isopropanol (120 mL) water (25 mL) was added (R)-(−)-mandelic acid (0.2-0.1 equiv) and the solution refluxed for 30 minutes, then allowed to reach room temperature (18°C) and finally cooled at 0°C, to give a precipitate of (R)-pregabalin/(R)-(−)-mandelic acid. The filtrate was concentrated to give enantiopure (S)-pregabalin in 84-92% yield.

Analogs of compound 8 were prepared using a similar method to that above and are exemplified below.

1-(3-Weithyl-4-nitro-isoxazol-5-yl)-propan-2-ol (9)

Colorless liquid; Rf = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δH (400 MHz, CDCl₃) 4.38-4.33 (1H, m), 3.37 (1H, dd, J = 15 J = 7), 3.35 (1H, dd, J = 15 J = 4), 2.56 (3H, s), 1.35 (3H, d, J =
6);5c (100.6 MHz, CDCl₃) 172.6, 155.8, 66.1, 37.1, 23.8, 11.8. HRMS: m/z found [M+H]^+ 187.0742, C₇H₁₁N₂O₄ requires 187.0719.

[00248] 1-(3-Methyl-4-nitro-isoxazol-5-yl)-butan-2-ol (10)

Colorless liquid; R_f = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl₃) 4.09-4.06 (1H, m), 3.36 (1H, dd, J = 15 J = 4), 3.35 (1H, dd, J = 15 J = 6), 2.56 (3H, s), 1.66-1.59 (2H, m), 1.03 (3H, t, J = 7); δ_C (100.6 MHz, CDCl₃) 172.9, 155.8, 66.1, 37.1, 23.8, 1.8. HRMS: m/z found [M+H]^+ 201.0851, C₉H₁₅N₂O requires 201.0875.

[00249] 1-(3-Methyl-4-nitro-isoxazol-5-yl)-pentan-2-ol (11)

Colorless liquid; R_f = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl₃) 4.17-4.10 (1H, m), 3.38 (1H, dd, J = 15 J = 4), 3.33 (1H, dd, J = 15 J = 6), 2.58 (3H, s), 1.62-1.21 (6H, m), 0.86 (3H, t, J = 7); δ_C (100.6 MHz, CDCl₃) 172.9, 155.8, 69.9, 39.8, 35.7, 18.8, 13.9, 11.8. HRMS: m/z found [M+H]^+ 215.1011, C₁₀H₁₉N₂O requires 215.1032.

[00250] 1-(3-Methyl-4-nitro-isoxazol-5-yl)-hexan-2-ol (12)

Colorless liquid; R_f = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl₃) 4.16-4.10 (1H, m), 3.38 (1H, dd, J = 15 J = 4), 3.33 (1H, dd, J = 15 J = 6), 2.58 (3H, s), 1.62-1.21 (6H, m), 0.86 (3H, t, J = 7); δ_C (100.6 MHz, CDCl₃) 172.9, 155.8, 69.9, 37.5, 35.7, 27.7, 22.6, 21.2, 14.1, 11.8. HRMS: m/z found [M+H]^+ 229.1 196, C₁₀H₁₇N₂O₄ requires 229.1 188.

[00251] 1-(3-Methyl-4-nitro-isoxazol-5-yl)-nonan-2-ol (13)
Colorless liquid; R_f = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl_3) 4.15-4.12 (1H, m), 3.38 (1H, dd, J = 15 J = 4), 3.33 (1H, dd, J = 15 J = 6), 2.56 (3H, s), 1.60-1.57 (2H, m), 1.38-1.20 (10H, m), 0.88 (3H, t, J = 7); δ_C (100.6 MHz, CDCl_3) 172.9, 155.8, 130.8, 69.9, 37.8, 35.7, 31.9, 29.8, 29.4, 25.5, 22.8, 14.2, 11.8. HRMS: m/z found [M+H]^+ 271.1669, C_{13}H_{23}N_2O_4 requires 271.1658.

[00252] 1-(3-Methyl-4-nitro-isoxazol-5-yl)-decan-2-ol (14)

Colorless liquid; R_f = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl_3) 4.17-4.12 (1H, m), 3.38 (1H, dd, J = 15 J = 4), 3.33 (1H, dd, J = 15 J = 6), 2.56 (3H, s), 1.62-1.56 (2H, m), 1.38-1.20 (12H, m), 0.88 (3H, t, J = 7); δ_C (100.6 MHz, CDCl_3) 172.9, 155.8, 130.9, 69.9, 37.8, 35.7, 31.9, 29.6, 29.5, 25.5, 22.8, 14.2, 11.8. HRMS: m/z found [M+H]^+ 285.1828, C_{14}H_{25}N_2O_4 requires 285.1814.

[00253] Analogues of compound 3 were prepared using a similar method to that above and are exemplified below.

[00254] 3-Methyl-4-nitro-5-propenyl-isoxazole (15)

Colorless liquid; R_f = 0.8 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl_3) 7.10-7.06 (2H, m), 2.55 (3H, s), 2.08-2.06 (3H, m); δ_C (100.6 MHz, CDCl_3) 167.1, 156.0, 144.0, 116.1, 19.7, 12.0. HRMS: m/z found [M]^+ 168.0554, C_7H_8N_2O_3 requires 168.0535.

[00255] 5-But-1-enyl-3-methyl-4-nitro-isoxazole (16)

Colorless liquid; R_f = 0.8 (Petroleum Ether/Ethyl Acetate, 90:10); δ_H (400 MHz, CDCl_3) 7.18-7.01 (2H, m), 2.56 (3H, s), 2.44-2.38 (2H, m), 1.17 (3H, t, J = 7); δ_C (100.6 MHz, CDCl_3) 167.3,
HRMS: m/z found [M]+ 182.0648, C₈H₁₀N₂O₃ requires 182.0691.

3-Methyl-4-nitro-5-pent-1-enyl-isoxazole (17)

Colorless liquid; Rᵣ = 0.8 (Petroleum Ether/Ethyl Acetate, 90:10); δₜ (400 MHz, CDCl₃) 7.11-7.00 (2H, m), 2.54 (3H, s), 2.38-2.33 (2H, m), 1.62-1.53 (2H, m), 0.98 (3H, t, J = 7); δc (100.6 MHz, CDCl₃) 167.1, 156.0, 148.8, 144.7, 35.8, 21.6, 13.8, 11.9. HRMS: m/z found [M]+ 210.1016, C₁₀H₁₄N₂O₃ requires 210.1004.

5-Hex-1-enyl-3-methyl-4-nitro-isoxazole (18)

Colorless liquid; Rᵣ = 0.8 (Petroleum Ether/Ethyl Acetate, 90:10); δₜ (400 MHz, CDCl₃) 7.12-7.00 (2H, m), 2.55 (3H, s), 2.41-2.35 (2H, m), 1.56-1.48 (2H, m), 1.43-1.38 (2H, m), 0.94 (3H, t, J = 7); δc (100.6 MHz, CDCl₃) 167.2, 156.0, 149.0, 114.6, 33.5, 30.4, 22.4, 16.9, 11.9. HRMS: m/z found [M]+ 252.1448, C₁₃H₂₀N₂O₃ requires 252.1474.

3-Methyl-4-nitro-5-non-1-enyl-isoxazole (19)

Colorless liquid; Rᵣ = 0.8 (Petroleum Ether/Ethyl Acetate, 90:10); δₜ (400 MHz, CDCl₃) 7.13-6.95 (2H, m), 2.56 (3H, s), 2.40-2.35 (2H, m), 1.56-1.50 (2H, m), 1.37-1.25 (8H, m), 0.87 (3H, t, J = 7); δc (100.6 MHz, CDCl₃) 167.2, 156.0, 149.2, 114.6, 33.9, 31.9, 29.8, 29.3, 29.2, 28.3, 22.8, 14.2, 12.0. HRMS: m/z found [M]+ 252.1448, C₁₃H₂₀N₂O₃ requires 252.1474.

5-Dec-1-enyl-3-methyl-4-nitro-isoxazole (20)
Colorless liquid; $R_f = 0.8$ (Petroleum Ether/Ethyl Acetate, 90:10); $\delta_H$ (400 MHz, CDCl$_3$) 7.13-6.95 (2H, m), 2.57 (3H, s), 2.45-2.38 (2H, m), 1.65-1.20 (12H, m), 0.89 (3H, t, $J = 7$); $\delta_C$ (100.6 MHz, CDCl$_3$) 167.2, 156.0, 149.2, 114.6, 33.9, 31.9, 29.5, 29.3, 28.3, 22.8, 14.2, 11.9. HRMS: $m/z$ found [M$^+$] + 266.1630, C$_{14}$H$_{22}$N$_2$O$_3$ requires 266.1630.

Analogues of compound 5 were prepared using a similar method to that above and are exemplified below.

**3-Methyl-5-(2-methyl-3-nitro-propyl)-4-nitro-isoxazole (21)**

Compound 21: Procedure B, 91% yield, 93% ee Colorless liquid; $R_f = 0.2$ (Petroleum Ether/Ethyl Acetate, 90:10); $\delta_H$ (400 MHz, CDCl$_3$) 4.44 (1H, dd, $J = 12$, $J = 6$), 4.37 (1H, dd, $J = 12$, $J = 6$), 3.35 (1H, dd, $J = 15$, $J = 7$), 3.26 (1H, dd, $J = 15$, $J = 7$), 2.96 (1H, sept, $J = 6$), 2.59 (3H, s), 1.15 (3H, d, $J = 7$); $\delta_C$ (100.6 MHz, CDCl$_3$) 172.2, 156.0, 78.1, 37.4, 29.8, 11.8, 10.8. HRMS: $m/z$ found [M$^+$] + 230.0714, C$_8$H$_{14}$N$_2$O$_5$ requires 230.0777.

**3-Wlefth-4-nitro-5-(2-nitromethyl-butyl)-isoxazole (22)**

Compound 22: Procedure B, 91% yield, 93% ee Colorless liquid; $R_f = 0.2$ (Petroleum Ether/Ethyl Acetate, 90:10); $\delta_H$ (400 MHz, CDCl$_3$) 4.47 (1H, dd, $J = 13$, $J = 6$), 4.42 (1H, dd, $J = 13$, $J = 6$), 3.38 (1H, dd, $J = 15$, $J = 7$), 3.28 (1H, dd, $J = 15$, $J = 7$), 2.76 (1H, sept, $J = 6$), 2.58 (3H, s), 1.32-1.27 (2H, m), 1.03 (3H, t, $J = 7$); $\delta_C$ (100.6 MHz, CDCl$_3$) 172.2, 156.0, 78.1, 37.4, 29.8, 24.7, 11.8, 10.8. HRMS: $m/z$ found [M$^+$] + 244.0968, C$_9$H$_{14}$N$_2$O$_5$ requires 244.0933.

**3-3-Methyl-4-nitro-5-(2-nitromethyl-pentyl)-isoxazole (23)**
Compound 23: Procedure A 92% yield, 84% ee; Procedure B, 91% yield, 92% ee

Colorless liquid; Rf = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δH (400 MHz, CDCl3) 4.45 (1H, dd, J = 12, J = 6), 4.40 (1H, dd, J = 12, J = 6), 3.37 (1H, dd, J = 15, J = 7), 3.30 (1H, dd, J = 15, J = 7), 2.82 (1H, sept, J = 6), 2.58 (3H, s). 1.46-1.40 (4H, m), 0.94 (3H, t, J = 7); δC (100.6 MHz, CDCl3) 172.2, 156.0, 78.4, 35.8, 129.2, 29.8, 19.7, 13.7, 11.8. HRMS: m/z found [M+H]+ 272.1280, C10H8N2O5 requires 272.1246.

3-Methyl-4-nitro-5-(2-nitromethyl-pentyl)-isoxazole (24)

Compound 24: Procedure A 92% yield, 84% ee; Procedure B, 91% yield, 93% ee

Colorless liquid; Rf = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δH (400 MHz, CDCl3) 4.43 (1H, dd, J = 12, J = 6), 4.40 (1H, dd, J = 12, J = 6), 3.37 (1H, dd, J = 15, J = 7), 3.30 (1H, dd, J = 15, J = 7), 2.81 (1H, sept, J = 6), 2.58 (3H, s), 1.50-1.27 (4H, m), 0.88 (3H, t, J = 7); δC (100.6 MHz, CDCl3) 172.3, 156.0, 129.2, 78.4, 36.0, 31.4, 29.9, 28.5, 22.6, 14.0, 11.8. HRMS: m/z found [M+H]+ 272.1280, C11H18N2O5 requires 272.1246.

3-Methyl-4-nitro-5-(2-nitromethyl-nonyl)-isoxazole (25)

Compound 25: procedure A: 96% yield, 80% ee; procedure B, 91% yield, 91% ee.

Colorless liquid; Rf = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δH (400 MHz, CDCl3) 4.45 (1H, dd, J = 8, J = 6), 4.40 (1H, dd, J = 8, J = 6), 3.37 (1H, dd, J = 15, J = 7), 3.30 (1H, dd, J = 15, J = 7), 2.81 (1H, sept, J = 6), 2.58 (3H, s), 1.50-1.27 (12H, m), 0.88 (3H, t, J = 7); δC (100.6 MHz, CDCl3) 172.3, 156.0, 78.4, 36.0, 31.8, 31.7, 29.9, 29.4, 29.1, 26.3, 22.7, 14.2, 11.8. HRMS: m/z found [M+H]+ 314.1745, C14H26N2O5 requires 314.1716.

3-Methyl-4-nitro-5-(2-nitromethyl-decyl)-isoxazole (26)
Compound 26: procedure A: 96% yield, 84% ee; procedure B, 91% yield, 94% ee. Colorless liquid; R = 0.2 (Petroleum Ether/Ethyl Acetate, 90:10); δ$_H$ (400 MHz, CDCl$_3$) 4.45 (1H, dd, J = 8, J = 6), 4.40 (1H, dd, J = 8, J = 6), 3.36 (1H, dd, J = 15, J = 7), 3.30 (1H, dd, J = 15, J = 7), 2.81 (1H, sept., J = 6), 2.58 (3H, s), 1.48-1.26 (14H, m), 0.86 (3H, t, J = 7); δ$_C$ (100.6 MHz, CDCl$_3$) 172.3, 156.0, 78.4, 36.0, 31.9, 31.7, 29.9, 29.8, 28.4, 29.4, 26.3, 22.7, 14.2, 11.8. HRMS: m/z found [M+H]$^+$ 328.1849, C$_{15}$H$_{26}$N$_3$O$_5$ requires 328.1872.
Claims

1. A process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

$$\text{(I)}$$

wherein:

$R^1$ is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and

$*$ denotes a chiral centre;

which process comprises the step of reacting a compound of formula (IV) with nitromethane in the presence of a catalyst to provide a compound of formula (V);

$$\text{(IV)} \quad \text{CH}_3\text{NO}_2 \rightarrow \text{(V)}$$

wherein $R^1$ and $*$ are as defined above and $R^2$ is an alkyl group or aryl group, each of which may be optionally substituted; and

$X$ is an electron withdrawing group.

2. A process for the preparation of a compound of formula (I), as defined in claim 1, which process comprises the step of reacting a compound of formula (IIA) with a compound of formula (III) in the presence of a catalyst to provide a compound of formula (V);

$$\text{(IIA)} \quad \text{(III)} \rightarrow \text{(V)}$$

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

3. A process according to claim 1 or claim 2 wherein the catalyst is a chiral catalyst.
4. A process according to any one of claims 1-3 wherein the catalyst is a cinchona alkaloid derivative.

5. A process according to any one of claims 1 to 4 wherein the catalyst is a compound of formula (Vila) or (VIIb)

wherein, $M$ is selected from H, hydroxy, alkoxy, O-alkenyl, 0(CH$_2$)$_n$-aryl, 0(CH$_2$)$_n$-heteroaryl, 0(CH$_2$)$_n$-cycloalkyl, amino, NR$^{11}$C(=O)R$^{12}$, C(=O)NR$^{13}$R$^{14}$, C(=O)R$^{12}$, 0(C=O)R$^{12}$, C(=O)OR$^{12}$, NR$^{11}$SO$_2$R$^{12}$, and $R^7$; in which each aryl, heteroaryl and cycloalkyl groups may be optionally substituted;

$R^4$ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH$_2$)$_n$-aryl, 0(CH$_2$)$_n$-heteroaryl, 0(CH$_2$)$_n$-cycloalkyl, amino, NR$^{11}$C(=O)R$^{12}$, C(=O)NR$^{13}$R$^{14}$, C(=O)R$^{12}$, 0(C=O)R$^{12}$, C(=O)OR$^{12}$, NR$^{11}$SO$_2$R$^{12}$, and $R^7$; in which each aryl, heteroaryl and cycloalkyl groups may be optionally substituted;

$R^{11}$, $R^{12}$, $R^{13}$ and $R^{14}$ are independently selected from H, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group and a cycloalkyl group, each of which may be optionally substituted; or $R^{13}$ and $R^{14}$ may together define an optionally substituted C$_3$-C$_{20}$ cycloalkyl group or C$_5$-C$_{15}$ heteroaryl group;

$R^5$ and $R^5'$ are independently selected from H, alkyl and alkenyl, each of which may be optionally substituted;

$R^6$ is selected from an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group, a cycloalkyl group, a (CH$_2$)$_n$-aryl group, a (CH$_2$)$_n$-heteroaryl group and a (CH$_2$)$_n$-cycloalkyl group, each of which may be optionally substituted;

$n = 0$ to 6;

$R^7$ is
wherein Q is O or S; and R⁸, R⁹ and R¹⁰ are independently selected from H, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group and a cycloalkyl group, each of which may be optionally substituted, or R⁸ and R⁹ may together define an optionally substituted C₃-C₂₀ cycloalkyl group or an optionally substituted C₅-C₁₅ heteroaryl group; and

Y⁻ is a counterion.

6. A process according to any one of the preceding claims wherein the catalyst is a compound of formula (Vila) wherein:

M is selected from H, hydroxy, alkoxy, 0(CH₂)ₙ-aryl, 0(CH₂)ₙ-heteroaryl, 0(CH₂)ₙ-cycloalkyl and R⁷;

R⁴ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, C(=0)OR₁₂, amino, NR¹¹S₀₂R¹₂, and R⁷;

Q is S;

R⁵ and R⁶⁰ are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;

R⁸ is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe;

R⁹, R¹⁰, R¹¹ are independently selected from H and alkyl; and

R¹₂ is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe.

7. A process according to any one of claims 1 to 5 wherein the catalyst is a compound of formula (Villb) wherein:

M is selected from H, hydroxy, alkoxy, 0(CH₂)ₙ-aryl, 0(CH₂)ₙ-heteroaryl, 0(CH₂)ₙ-cycloalkyl and R⁷;

R⁴ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, C(=0)OR₁₂, amino, NR¹¹S₀₂R¹₂, and R⁷;

Q is S;
R⁵ and R⁹ are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;
R⁶ is selected from (CH₂)ₙ-aryl groups, (CH₂)ₙ-heteroaryl groups and (CH₂)ₙ-cycloalkyl groups, each of which may optionally be substituted with one or more halo, alkyl, NO₂, haloalkyl and methoxy groups;
R⁸ is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more halo, CF₃, Me and OMe;
R⁸, R¹⁰, R¹¹ are independently selected from H and alkyl; and
R¹² is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more halo, CF₃, Me and OMe.

8. A process according to any preceding claim wherein the catalyst is selected from:
wherein $Y^-$ is a counterion.

9. A process according to any one of claims 1 to 5, 7 and 8 wherein the catalyst is selected from $\Lambda^/-(3,5$-dinitrobenzyl)quinidinium bromide, $\Lambda^/-(3,5$-dimethylbenzyl)quinidinium bromide, $\Lambda^/-(3,5$-dibromobenzyl)quinidinium bromide, $\Lambda^/-(3,5$-ditertbutylbenzyl)quinidinium bromide, $\Lambda^/-(3,5$-ditrifluoromethylbenzyl)quinidinium bromide, $\Lambda^/-(2$-nitro-4,5-dimethoxybenzyl)quinidinium bromide, $\Lambda^/-(3,5$-bis(trifluoromethyl)benzyl)cinchonidinium bromide, $\Lambda^/-$benzylquinidinium bromide, $\Lambda^/-$benzylcinchonidinium bromide, $N^/-(4,5$-dimethoxy-2-nitrobenzyl)cinchonidinium bromide, $N^/-(3,5$-dibromobenzyl)quinidinium bromide, $A^/-$benzylcinchonidinium bromide, $A^/-$benzylquinidinium bromide, $A^/-$benzylquinidinium bromide, $A^/-$(3,5-dimethylbenzyl)quinidinium bromide, $A^/-$(3,5-ditertbutylbenzyl)quinidinium bromide, $A^/-$(3,5-ditrifluoromethylbenzyl)quinidinium bromide.

10. A process according to any preceding claim wherein the reaction further comprises a base.

11. A process according to claim 10 wherein the base is a source of carbonate.
12. A process according to claim 11 wherein the source of carbonate is selected from sodium carbonate, potassium carbonate and cesium carbonate.

13. A process according to any preceding claim wherein the compound of formula (IV) is prepared by reacting a compound of formula (III) with a compound of formula (II):

\[
\begin{align*}
(\text{III}) & \quad \text{\textit{R}^1} \quad \text{\textit{R}^2} \\
(\text{II}) & \quad \text{\textit{R}'}
\end{align*}
\]

wherein \( \text{\textit{R}^1}, \text{\textit{R}^2} \) and \( X \) are as defined in claim 1.

14. A process according to claim 12 wherein the reaction of compounds (III) and (II) further comprises an aqueous solvent.

15. A process accordingly to any one of claims 12 and 13 wherein the reaction of compounds (III) and (II) further comprises a base.

16. A process according to any of claims 1-12 wherein the compound of formula (IV) is prepared by reacting a compound of formula (III A) with a compound of formula (II) to form a compound of formula (III B):

\[
\begin{align*}
(\text{II}) & \quad \text{\textit{R}'} \\
(\text{III A}) & \quad \text{\textit{R}^1} \quad \text{\textit{R}^2}
\end{align*}
\]

\[
\begin{align*}
(1\text{MB}) & \quad \text{\textit{R}^1} \quad \text{\textit{R}^2}
\end{align*}
\]

converting the compound of formula (III B) to a compound of formula (NIC);

\[
\begin{align*}
(\text{III B}) & \quad \text{\textit{R}^1} \quad \text{\textit{R}^2}
\end{align*}
\]

\[
\begin{align*}
(\text{NIC}) & \quad \text{\textit{R}^1} \quad \text{\textit{R}^2}
\end{align*}
\]

and; converting the compound of formula (III C) to a compound of formula (IV).
17. A process accordingly to any preceding claim which further comprises the step of hydrolysing the compound of formula (V) to provide a compound of formula (VI)

\[
\begin{align*}
\text{(V)} & \quad \xrightarrow{\text{hydrolysing}} \quad \text{(VI)} \\
\end{align*}
\]

wherein \(R^1, R^2\) and \(X\) are as defined in claim 1.

18. A process according to claim 17 wherein the hydrolysis of compound (V) is effected in the presence of a base.

19. A process accordingly to any one of claims 1 to 16 which further comprises the step of reducing the compound of formula (V) to provide a compound of formula (Vlb)

\[
\begin{align*}
\text{(V)} & \quad \xrightarrow{\text{reducing}} \quad \text{(Vlb)} \\
\end{align*}
\]

wherein \(R^1, R^2\) and \(X\) are as defined hereinabove; with the proviso that \(X\) is not \(\text{NO}_2\).

20. A process according to claim 18 wherein the compound of formula (V) is reduced by hydrogenation.

21. A process according to any one of claims 17 and 18 which further comprises the step of reducing the compound of formula (VI) to the compound of formula (I):

\[
\begin{align*}
\text{(VI)} & \quad \xrightarrow{\text{reducing}} \quad \text{(I)} \\
\end{align*}
\]

wherein \(R^1\) is defined in claim 1.
22. A process according to claim 21 wherein the compound of formula (VI) is reduced by hydrogenation.

23. A process according to any one of claims 19 and 20 which further comprises the step of hydrolysing the compound of formula (VIb) to provide a compound of formula (I)

\[
\begin{align*}
\text{(VIb)} & \quad \text{(I)}; \\
& \quad \text{wherein } R^1, R^2 \text{ and } X \text{ are as defined hereinabove; with the proviso that } X \text{ is not } N_2.
\end{align*}
\]

24. A process according to claim 23 wherein the hydrolysis of compound (VIb) is effected in the presence of a base.

25. A process for the preparation of a compound of formula (I), and pharmaceutically acceptable salts, solvates and prodrugs thereof:

\[
\begin{align*}
\text{(I)}
\end{align*}
\]

wherein:

- R\textsuperscript{1} is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and
- * denotes a chiral centre;

which process comprises the step of preparing a compound of formula (IV) by reacting a compound of formula (III) with a compound of formula (II):

\[
\begin{align*}
\text{R}^2 & \quad X & \quad \text{R}^1 & \quad \text{O} \\
\text{R}^2 & \quad X & \quad \text{R}^1 & \quad \text{O}
\end{align*}
\]
26. A process according to claim 25 wherein the reaction further comprises an aqueous solvent.

27. A process accordingly to any one of claims 25 and 26 wherein the reaction is effected in the presence of a base.

28. A process for the preparation of a compound of formula (I) as defined in claim 25 which comprises preparing a compound of formula (IV) by reacting a compound of formula (IMA) with a compound of formula (II) to form a compound of formula (IIIB):

\[
\text{(II)} + \text{(IIIA)} \rightarrow \text{(IIIB)}
\]

wherein \(L\) is a hydroxyl activating group, and \(R^1\) and \(R^2\) are as defined in claim 25, converting the compound of formula (IIIB) to a compound of formula (IIIC):

\[
\text{(IIIB)} \rightarrow \text{(IIIC)}
\]

wherein \(X\) as defined in claim 25; and converting the compound of formula (IIIC) to a compound of formula (IV).

29. A process according to any one of claims 25 to 28 which further comprises the step of reacting a compound of formula (IV) with nitromethane in the presence of a catalyst to form a compound of formula (V)
wherein R\textsuperscript{1}, R\textsuperscript{2} and X are as defined in claim 1.

30. A process according to claim 29 wherein the catalyst is a cinchona alkaloid derivative.

31. A process according to any one of claims 29 and 30 wherein the catalyst is a compound of formula (Vila) or (VIIb)

wherein, M is selected from H, hydroxy, alkox, O-alkenyl, 0(CH\textsubscript{2})\textsubscript{n}-aryl, 0(CH\textsubscript{2})\textsubscript{n}-heteroaryl, 0(CH\textsubscript{2})\textsubscript{n}-cycloalkyl, amino, NR\textsuperscript{11}C(=0)R\textsuperscript{12}, C(=0)NR\textsuperscript{13}R\textsuperscript{14}, C(=0)R\textsuperscript{12}, 0(C=0)R\textsuperscript{12}, C(=0)OR\textsuperscript{12}, NR\textsuperscript{11}S0\textsubscript{2}R\textsuperscript{12}, and R\textsuperscript{7}; in which each aryl, heteroaryl and cycloalkyl groups may be optionally substituted;

R\textsuperscript{4} is selected from hydroxy, alkox, O-alkenyl, 0(CH\textsubscript{2})\textsubscript{n}-aryl, 0(CH\textsubscript{2})\textsubscript{n}-heteroaryl, 0(CH\textsubscript{2})\textsubscript{n}-cycloalkyl, amino, NR\textsuperscript{11}C(=0)R\textsuperscript{12}, C(=0)NR\textsuperscript{13}R\textsuperscript{14}, C(=0)R\textsuperscript{12}, 0(C=0)R\textsuperscript{12}, C(=0)OR\textsuperscript{12}, NR\textsuperscript{11}S0\textsubscript{2}R\textsuperscript{12}, and R\textsuperscript{7}; in which each aryl, heteroaryl and cycloalkyl groups may be optionally substituted;

R\textsuperscript{1}, R\textsuperscript{12}, R\textsuperscript{13} and R\textsuperscript{14} are independently selected from H, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group and a cycloalkyl group, each of which may be optionally substituted; or R\textsuperscript{13} and R\textsuperscript{14} may together define an optionally substituted C\textsubscript{3}-C\textsubscript{20} cycloalkyl group or C\textsubscript{5}-C\textsubscript{15} heteroaryl group;

R\textsuperscript{5} and R\textsuperscript{6a} are independently selected from H, alkyl and alkenyl, each of which may be optionally substituted;

R\textsuperscript{6} is selected from an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group, a cycloalkyl group, a (CH\textsubscript{2})\textsubscript{n}-aryl group, a (CH\textsubscript{2})\textsubscript{n}-heteroaryl group and a (CH\textsubscript{2})\textsubscript{n}-cycloalkyl group; each of which may be optionally substituted;

n = 0 to 6;

R\textsuperscript{7} is
wherein Q is O or S; and R, R and R are independently selected from H, an alkyl group, an alkenyl group, an alkyne group, an aryl group, a heteroaryl group and a cycloalkyl group, each of which may be optionally substituted, or R and R may together define an optionally substituted C-C cycloalkyl group or an optionally substituted C-C heteroaryl group; and Y is a counterion.

32. A process according to any one of claims 29 to 31 wherein the catalyst is a compound of formula (Vila) wherein:

- M is selected from H, hydroxy, alkoxy, 0(CH) n -aryl, 0(CH) n -heteroaryl, 0(CH) n -cycloalkyl and R;
- R is selected from hydroxy, alkoxy, O-alkenyl, 0(CH) n -aryl, C(=0)OR, amino, NR 1 S 0 2 R, and R;
- Q is S;
- R and R are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;
- R is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more of halo, CF, Me and OMe;
- R, R, and R are independently selected from H and alkyl; and
- R is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more of halo, CF, Me and OMe.

33. A process according to any one of claims 29 to 31 wherein the catalyst is a compound of formula (Vilb) wherein:

- M is selected from H, hydroxy, alkoxy, 0(CH) n -aryl, 0(CH) n -heteroaryl, 0(CH) n -cycloalkyl and R;
- R is selected from hydroxy, alkoxy, O-alkenyl, 0(CH) n -aryl, C(=0)OR, amino, NR 1 S 0 2 R, and R;
- Q is S;
R⁵ and R⁹ are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;
R⁶ is selected from (CH₂)ₙ-aryl groups, (CH₂)ₙ-heteroaryl groups and (CH₂)ₙ-cycloalkyl groups, each of which may optionally be substituted with one or more halo, alkyl, NO₂, haloalkyl and methoxy groups;
R⁸ is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe;
R⁹, R¹⁰, R¹¹ are independently selected from H and alkyl; and
R¹² is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe.

34. A process according to any one of claims 29 to 33 wherein the catalyst is selected from:
wherein \( Y^- \) is a counterion.

A process according to any one of claims 29 to 31, 33 and 34 wherein the catalyst is selected from the 
following:

- \( W\)-\{(3,5-ditrifluoromethyl)benzyl\}quinidinium bromide,
- \( N\)-(3,5-ditertbutylbenzyl)quinidinium bromide,
- \( \Lambda\)-(3,5-ditertbutylbenzyl)dihydroquinidinium bromide,
- \( N\)-(3,5-dimethylbenzyl)quinidinium bromide,
- \( \Lambda\)/(3,5-dibromobenzyl)quinidinium bromide,
- \( \Lambda\)/-benzylcinchonidinium bromide,
- \( \Lambda\)/(4,5-dimethoxy-2-nitrobenzyl)cinchonidinium bromide,
- \( \Lambda\)/(3,5-bis(trifluoromethyl)benzyl)cinchonidinium bromide,
- \( \Lambda\)/-benzylquinidinium bromide,
- \( \Lambda\)/-(2-nitro-4,5-dimethoxybenzyl)quinidinium bromide.

A process according to any one of claims 29 to 35 wherein the reaction of compounds of formula (IV) with nitromethane further comprises a base.
37. A process accordingly to any one of claims 29 to 36 which further comprises the step of hydrolysing the compound of formula (V) to provide a compound of formula (VI)

\[
\text{(V)} \rightarrow \text{(VI)}
\]

wherein \(R^1, R^2 \text{ and } X\) are as defined in claim 1.

38. A process according to claim 37 wherein the hydrolysis of compound (V) further comprises a base.

39. A process accordingly to any one of claims 29 to 37 which further comprises the step of reducing the compound of formula (V) to provide a compound of formula (Vlb)

\[
\text{(V)} \rightarrow \text{(Vlb)}
\]

wherein \(R^1, R^2 \text{ and } X\) are as defined hereinabove; with the proviso that \(X\) is not \(N\)02.

40. A process according to claim 39 wherein the compound of formula (V) is reduced by hydrogenation.

41. A process according to any one of claims 37 and 38 which further comprises the step of reducing the compound of formula (VI) to the compound of formula (i):

\[
\text{(VI)} \rightarrow \text{(i)}
\]

wherein \(R^1\) is as defined in claim 1.
42. A process according to claim 41 wherein the compound of formula (VI) is reduced by hydrogenation.

43. A process according to any one of claims 39 and 40 which further comprises the step of hydrolysing the compound of formula (VIIb) to provide a compound of formula (I)

\[
\begin{align*}
\text{(VIIb)} & \quad \text{(I)}; \\
\end{align*}
\]

wherein \( R^1, R^2 \) and \( X \) are as defined hereinabove; with the proviso that \( X \) is not \( \text{NO}_2 \).

44. A process according to claim 43 wherein the hydrolysis of compound (VIIb) is effected in the presence of a base.

45. A process according to any preceding claim wherein \( R^1 \) is an optionally substituted alkyl group.

46. A process according to any preceding claim wherein \( R^1 \) and \( R^2 \) are independently selected from methyl, ethyl, \( \text{iso-} \)propyl, \( \text{iso-} \)propyl, \( \text{n-} \)butyl, sec-butyl, \( \text{iso-} \)butyl, \( \text{tert-} \)butyl, \( \text{n-} \)pentyl, \( \text{n-} \)hexyl, \( \text{n-} \)heptyl and \( \text{n-} \)octyl.

47. A process according to claim 46 wherein \( R^1 \) is \( \text{iso-} \)butyl and \( R^2 \) is methyl.

48. A process according to any preceding claim wherein \( X \) is a group selected from \( \text{NO}_2, \text{CN}, \text{COOR}^3 \) and \( \text{SO}_2R^3 \); wherein each \( R^3 \) group is independently \( \text{H} \) or an optionally substituted alkyl group.

49. A process according to any preceding claim wherein \( X \) is \( \text{NO}_2 \).
50. A process according to any preceding claim wherein the compound of formula (I) is (S)-pregabalin.

51. A process according to any preceding claim wherein the isolated compound of formula (I) has an enantiomeric excess of greater than about 70%, preferably greater than about 80%, even more preferably greater than about 90%.

52. A compound of formula (V), and salts, thereof,

\[ \text{(V)} \]

wherein:

R\(^1\) is selected from an alkyl group, an alkenyl group, an alkynyl group and a cycloalkyl group, each of which may be optionally substituted; and

R\(^2\) is selected from an alkyl group and an aryl group, each of which may be optionally substituted; and

* denotes a chiral centre; and

X is an electron withdrawing group.

53. A compound according to claim 52 wherein R\(^1\) is an optionally substituted alkyl group.

54. A compound according to any one of claims 52 to 55 wherein R\(^1\) and R\(^2\) are independently selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl.

55. A compound according to any one of claims 52 to 54 wherein R\(^1\) is isobutyl and R\(^2\) is methyl.

56. A compound according to any claims 52 to 55 wherein X is a group selected from NO\(_2\), CN, COOR\(^3\) and SO\(_2\)R\(^3\); wherein each R\(^3\) group is independently H or an optionally substituted alkyl group.

57. A compound according to any one of claims 52 to 55 wherein X is NO\(_2\).
58. A compound according to any one of claims 52 to 57 which has an enantiomeric excess of greater than about 70%, preferably greater than about 80%, even more preferably greater than about 90%.

59. A process for the preparation of a compound of formula (V), and salts thereof, as defined in claim 49 which comprises reacting a compound of formula (IV),

\[
\text{(IV)}
\]

with nitromethane in the presence of a catalyst;

wherein \( R^1 \) and \( R^2 \) are as defined hereinabove.

60. A process according to claim 59 wherein the catalyst is a cinchona alkaloid derivative.

61. A process according to any one of claims 59 and 60 wherein the catalyst is a compound of formula (VIIa) or (VIIb)

\[
\text{M} \quad \text{N} \quad \text{M}
\]

\[
\text{R}^1 \quad \text{R}^2 \quad \text{R}^4 \\
\text{R}^5 \quad \text{R}^6
\]

(VIIa)

\[
\text{M} \quad \text{N} \quad \text{M}
\]

\[
\text{R}^1 \quad \text{R}^2 \quad \text{R}^4 \\
\text{R}^5 \quad \text{R}^6
\]

(VIIb);

wherein, \( M \) is selected from H, hydroxy, alkoxy, O-alkenyl, 0(CH\(_2\)\(_n\)-aryl, 0(CH\(_2\)\(_n\)-heteroaryl, 0(CH\(_2\)\(_n\)-cycloalkyl, amino, NR\(_1\)C(=0)R\(_{12}\), C(=0)NR\(_3\)R\(_{14}\), G(=0)R\(_{12}\), 0(C=0)R\(_{12}\), C(=0)OR\(_{12}\), NR\(_{11}\)SO\(_2\)R\(_{12}\), and R\(_7\); in which each aryl, heteroaryl and cycloalkyl groups may be optionally substituted;

\( R^4 \) is selected from hydroxy, alkoxy, O-alkenyl, 0(CH\(_2\)\(_n\)-aryl, 0(CH\(_2\)\(_n\)-heteroaryl, 0(CH\(_2\)\(_n\)-cycloalkyl, amino, NR\(_1\)C(=0)R\(_{12}\), C(=0)NR\(_3\)R\(_{14}\), C(=0)R\(_{12}\), 0(C=0)R\(_{12}\), C(=0)OR\(_{12}\), NR\(_{11}\)SO\(_2\)R\(_{12}\), and R\(_7\); in which each aryl, heteroaryl and cycloalkyl groups may be optionally substituted;
R¹, R², R³ and R⁴ are independently selected from H, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group and a cycloalkyi group, each of which may be optionally substituted; or R¹ and R⁴ may together define an optionally substituted C₃-C₂₀ cycloalkyi group or C₅-C₁₅ heteroaryl group;

R⁵ and R⁵a are independently selected from H, alkyl and alkenyl, each of which may be optionally substituted;

R⁶ is selected from an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group, a cycloalkyi group, a (CH₂)ₙ-aryl group, a (CH₂)ₙ-heteroaryl group and a (CH₂)ₙ-cycloalkyi group; each of which may be optionally substituted;

n = 0 to 6;

R⁷ is

\[
\begin{array}{c}
\text{N} \\
\text{R}^8 \text{N} \text{O} \text{R}^9 \\
\text{R}^10
\end{array}
\]

wherein Q is O or S; and R⁸, R⁹ and R¹₀ are independently selected from H, an alkyl group, an alkenyl group, an alkynyl group, an aryl group, a heteroaryl group and a cycloalkyi group, each of which may be optionally substituted, or R⁸ and R⁹ may together define an optionally substituted C₃-C₂₀ cycloalkyi group or an optionally substituted C₅-C₁₅ heteroaryl group; and

Y⁻ is a counterion.

A process according to any one of claims 59 to 61 wherein the catalyst is a compound of formula (Vila) wherein:

M is selected from H, hydroxy, alkoxy, 0(CH₂)ₙ-aryl, 0(CH₂)ₙ-heteroaryl, 0(CH₂)ₙ-cycloalkyi and R⁷;

R⁴ is selected from hydroxy, alkoxy, O-alkenyl, 0(CH₂)ₙ-aryl, C(=O)OR¹₂, amino, NR¹¹SO₂R¹₂, and R⁷;

Q is S;

R⁵ and R⁵a are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;

R⁶ is selected from an alkyl group, an aryl group and a cycloalkyi group each of which may be optionally substituted by one or more of halo, CF₃, Me and OMe;
R^9, R^{10}, R^{11} are independently selected from H and alkyl; and

R^{12} is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more of halo, CF_3, Me and OMe.

63. A process according to any one of claims 59 to 61 wherein the catalyst is a compound of formula (VIIb) wherein:

M is selected from H, hydroxy, alkoxy, 0(CH_2)_n-aryl, 0(CH_2)_n-heteroaryl, 0(CH_2)_n-cycloalkyl and R^7;

R^4 is selected from hydroxy, alkoxy, O-alkenyl, 0(CH_2)_n-aryl, C(=0)OR12, amino, NR^{11}SO_2R^{12}, and R^7;

Q is S;

R^5 and R^{6a} are independently selected from H, methyl, ethyl, propyl, ethenyl, propenyl;

R^6 is selected from (CH_2)_n-aryl groups, (CH_2)_n-heteroaryl groups and (CH_2)_n-cycloalkyl groups, each of which may optionally be substituted with one or more halo, alkyl, NO_2, haloalkyl and methoxy groups;

R^8 is selected from an alkyl group, an aryl group and a cycloalkyl group each of which may be optionally substituted by one or more of halo, CF_3, Me and OMe;

R^9, R^{10}, R^{11} are independently selected from H and alkyl; and

R^{12} is selected from H, alkyl, aryl and cycloalkyl; each of which may be optionally substituted by one or more of halo, CF_3, Me and OMe.

64. A process according to any one of claims 59 to 63 wherein the catalyst is selected from:
wherein $Y^-$ is a counterion.

65. A process according to any one of claims 59 to 61, 63 and 64 wherein the catalyst is selected from $N$-(3,5-ditrifluoromethylbenzyl)quinidinium bromide, $N$-(3,5-diterbutylbenzyl)quinidinium bromide, $N$-(3,5-ditertbutylbenzyl)dihydroquinidinium bromide, $N$-(3,5-dimethylbenzyl)quinidinium bromide, $N$-(3,5-dibromobenzyl)quinidinium bromide, $N$-benzylcinchonidinium bromide, $N$-(4,5-dimethoxy-2-nitrobenzyl)cinchonidinium bromide, $N$-(3,5-bis(trifluoromethyl)benzyl)cinchonidinium bromide, $N$-benzylquinidinium bromide, $N$-(2-nitro-4,5-dimethoxybenzyl)quinidinium bromide.

66. A process according to any one of claims 59 to 65 wherein the reaction further comprises a base.

67. Use of a compound of formula (V) for the preparation of a compound of formula (I).
68. Use according to claim 67 wherein the compound of formula (I) is (S)-pregabalin.

69. A compound of formula (IV), and salts, thereof,

\[
\begin{array}{c}
\text{O} \\
\text{R'} \end{array} \begin{array}{c}
\text{R}^2 \\
\text{X} \\
\text{N} \\
\end{array}
\]

(IV)

wherein:

- \( R^1, R^2 \) and \( X \) are as defined in claim 52.

70. A compound according to claim 69 wherein \( R^1 \) is an optionally substituted alkyl group.

71. A compound according to any one of claims 69 and 70 wherein \( R^1 \) and \( R^2 \) are independently selected from methyl, ethyl, n-propyl, /so-propyl, n-butyl, sec-butyl, /so-butyl, ferf-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl.

72. A compound according to any one of claims 69 to 71 wherein \( R^1 \) is /so-butyl and \( R^2 \) is methyl.

73. A compound according to any one of claims 69 to 72 wherein \( X \) is a group selected from \( \text{NO}_2, \text{CN}, \text{COOR}^3 \) and \( \text{SO}_2 \text{R}^3 \), wherein each \( R^3 \) group is independently \( \text{H} \) or an optionally substituted alkyl group.

74. A compound according to any one of claims 69 to 73 wherein \( X \) is \( \text{NO}_2 \).

75. A process for the preparation of a compound of formula (IV), and salts thereof, as defined in claim 69, which comprises reacting a compound of formula (III) with a compound of formula (II):

\[
\begin{array}{c}
\text{O} \\
\text{R}^2 \\
\text{X} \\
\text{N} \\
\end{array} \begin{array}{c}
\text{R}^1 \\
\text{H} \\
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{R'} \end{array} \begin{array}{c}
\text{R}^2 \\
\text{X} \\
\text{N} \\
\end{array}
\]

(III) (II) (IV)
76. A process according to claim 75 wherein the reaction further comprises an aqueous solvent.

77. A process accordingly to any one of claims 75 and 76 wherein the reaction further comprises a base.

78. Use of a compound of formula (IV) for the preparation of a compound of formula (I).

79. Use according to claim 78 wherein the compound of formula (I) is (S)-pregabalin.

80. A compound selected from:

\[
\begin{align*}
\text{Formula (I)} & \quad \text{Formula (II)} & \quad \text{Formula (III)}
\end{align*}
\]

wherein \(Y^-\) is a counterion.

81. Use of a compound according to claim 80 as catalyst in a chemical process.

82. Use according to claim 81 wherein the chemical process is as defined in any one of claims 1, 26 and 56.
**INTERNATIONAL SEARCH REPORT**

**PCT/EP2012/073420**

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<th>A. CLASSIFICATION OF SUBJECT MATTER</th>
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**ADD.**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

- C07D C07C

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

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

- EPO-Internal, WPI Data, CHEM ABS Data, BEI LSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>PEI, QING-LAN ET AL: &quot;Catalytic asymmetric 1,6-Mi chael addition of Aryl thiolesto 3-Methyl -4-ni tro-5-al kenyl -i soxazoles with Bi functional Catalysts&quot; , JOURNAL OF ORGANIC CHEMISTRY , 76(19) , 7849-7859 CODEN : JOCEAH ; ISSN : 0022-3263 , 30 August 2011 (2011-08-30) , XP002694843 , table 2: compound 3o page 7859 , footnote (10) ---- 69,73-75</td>
<td></td>
</tr>
</tbody>
</table>

* Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search: 16 April 2013

Date of mailing of the international search report: 26/04/2013

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentilaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer:

Fitz, Wolfgang
<table>
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<th>Category</th>
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<tr>
<td>X</td>
<td>KRISHNAMURTHY, A. ET AL: &quot;I soxazolyl sul fani l ami des&quot;, INDIAN JOURNAL OF APPLIED CHEMISTRY, 35(4-6), 90-2 CODEN : IJACAN; ISSN : 0019-5065, 1972 , XP008161179, page 91, table 1: SI . No. 3 page 90, column 1 , l ine 21 - l ine 24</td>
<td>69,73-75</td>
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<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages</td>
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<td>X</td>
<td>MURTY, A. KRISHNA ET AL: &quot;Spectroscopic evidence for the formation of 5-styryl 3,5-dimethyl -4-ni tro sox azol es with al dehydes&quot;, INDIAN JOURNAL OF CHEMISTRY, 11(10), 1074-6 CODEN: IJOCAP; ISSN: 0019-5103, page 1075; compound VIII, page 1075, col umn 2, last two lines - page 1076, col umn 1, line 9</td>
<td>69,70, 73-75,77</td>
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<td>Y</td>
<td>BASCHI ERI, ANDREA ET AL: &quot;Catalyti c Asymmetri c Conjugate Additi on of Ni troal kanes to 4-Ni tro-5-styryl i sox azol es&quot;, ANGEWANDTE CHEMIE, INTERNATIONAL EDITION, 48(49), 9342-9345, S9342/1-S9342/50 CODEN: ACIEF5; ISSN: 1433-7851, 2009, XP002694846, schemes 1,3,4</td>
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<tr>
<td>X,P</td>
<td>DEL FIANDRA, CLAUDIA ET AL: &quot;Phase transfer catalyzed enanti ose lcti ve cycl opropanati on of 4-ni tro-5-styryl i sox azol es&quot;, CHEMICAL COMMUNICATIONS (CAMBRIDGE, UNITED KINGDOM), 48(32), 3863-3865 CODEN: CHC0FS; ISSN: 1359-7345, 24 February 2012 (2012-02-24), XP002694847, table e 3: compound lk, page 3864, col umn 1, lines 2-5</td>
<td>69-71, 73-75</td>
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