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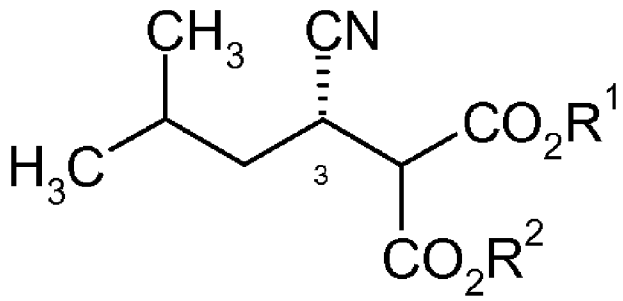
(54) Title: MALONATE ESTERS



(I)

(57) Abstract: The invention provides a compound of formula (I), in an enantiomerically enriched form; wherein R^1 and R^2 are each independently selected from optionally substituted alkyl, cycloalkyl, aryl-alkyl and aryl, wherein the 3S-enantiomer is present in excess and the enantiomeric excess is at least 10%. There is also provided a method of preparing, in an enantiomerically enriched form, the compound of formula (I). Use of a compound of formula (I) in a method of preparing pregabalin is also discussed.

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MALONATE ESTERS

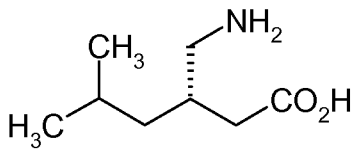
Field of the Invention

The present invention relates to certain 2-(1-cyanoalkyl)-malonate esters, and to methods and materials for preparing these esters. More specifically, the invention relates to 2-((1*S*)-1-cyano-3-methylbutyl)-malonate esters. These malonates are particularly useful for preparing pregabalin, a γ-amino acid that exhibits binding affinity to the human $\alpha_2\delta$ calcium channel subunit.

Background to the Invention

1. Pregabalin

Pregabalin, or (*S*)-(+)-3-aminomethyl-5-methyl-hexanoic acid,



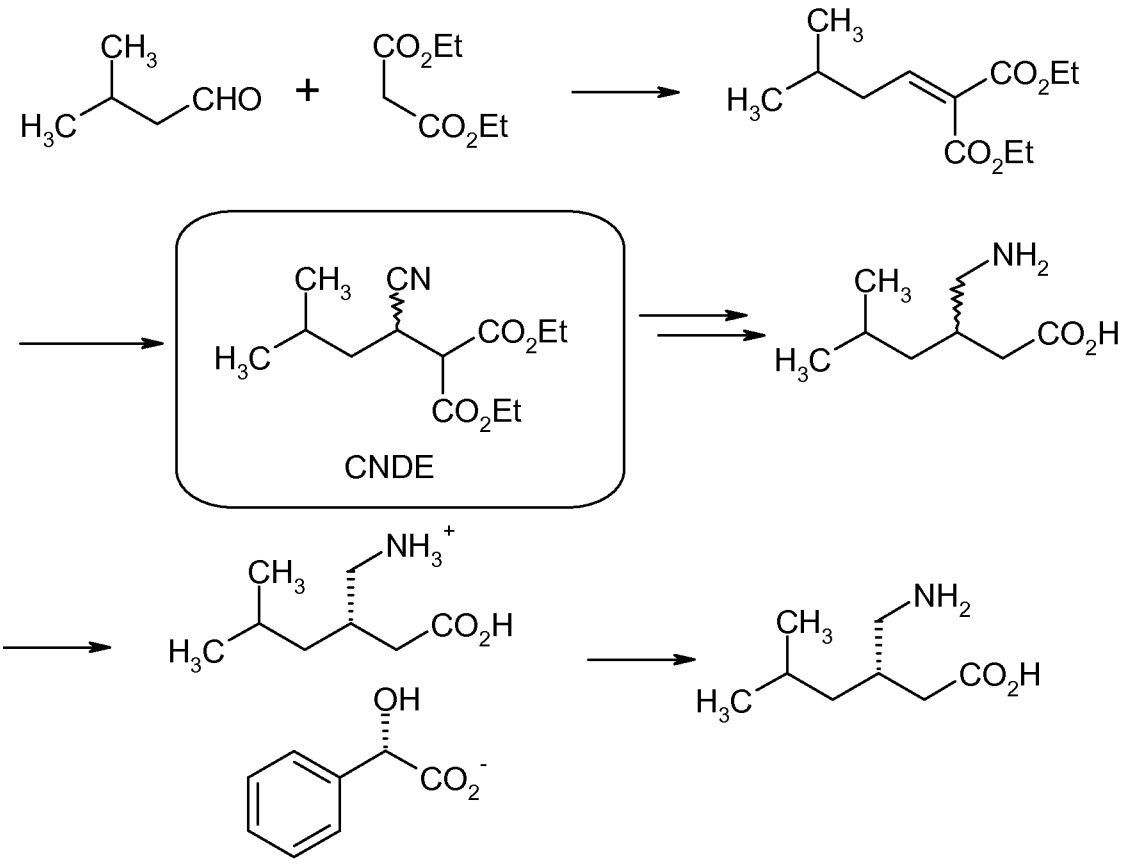
is the active agent in Lyrica®, which is approved for the treatment of epilepsy, neuropathic pain, fibromyalgia and generalized anxiety disorder. It exhibits anti-seizure activity, as discussed in U.S. Patent US 5,563,175, and anti-nociceptive activity, as discussed in U.S. Patent US 6,001,876. It is hypothesised that the pharmacological activity of pregabalin is the result of binding to the alpha-2-delta ($\alpha_2\delta$) subunit of a calcium channel. Pregabalin is also described as having utility in other conditions, such as physiological conditions associated with psychomotor stimulants, inflammation, gastrointestinal damage, alcoholism, insomnia, and various psychiatric disorders, including anxiety, depression, mania, and bipolar disorder.

It will be recognized that 3-aminomethyl-5-methyl-hexanoic acid has a single chiral centre and so exists as two optical isomers. As indicated above, pregabalin is the (*S*)-enantiomer, and a key consideration in the commercial manufacture of pregabalin is the strategy by which optically pure material is obtained.

2. Manufacturing methods involving resolution

Pregabalin has been prepared in various ways. A common strategy shared by many syntheses has been the resolution of the final product or of an earlier intermediate into its *R*- and *S*-enantiomers. Such methods may involve an azide intermediate (e.g., U.S. Patent US 5563175), or a Hoffman synthesis (e.g. U.S. Patents US 5629447, and US 5616793). A route involving a malonate intermediate (e.g., U.S. Patents US 6046353, US 5840956, and US 5637767) has also been utilised (Scheme 1). This route starts with the condensation of isovalderaldehyde with diethyl malonate to give an α,β-unsaturated diethyl ester, which is reacted with cyanide to give a β-cyanodiester (CNDE). This intermediate is subsequently hydrolysed, decarboxylated and reduced to give racemic pregabalin which is resolved with S-(+)-mandelic acid.

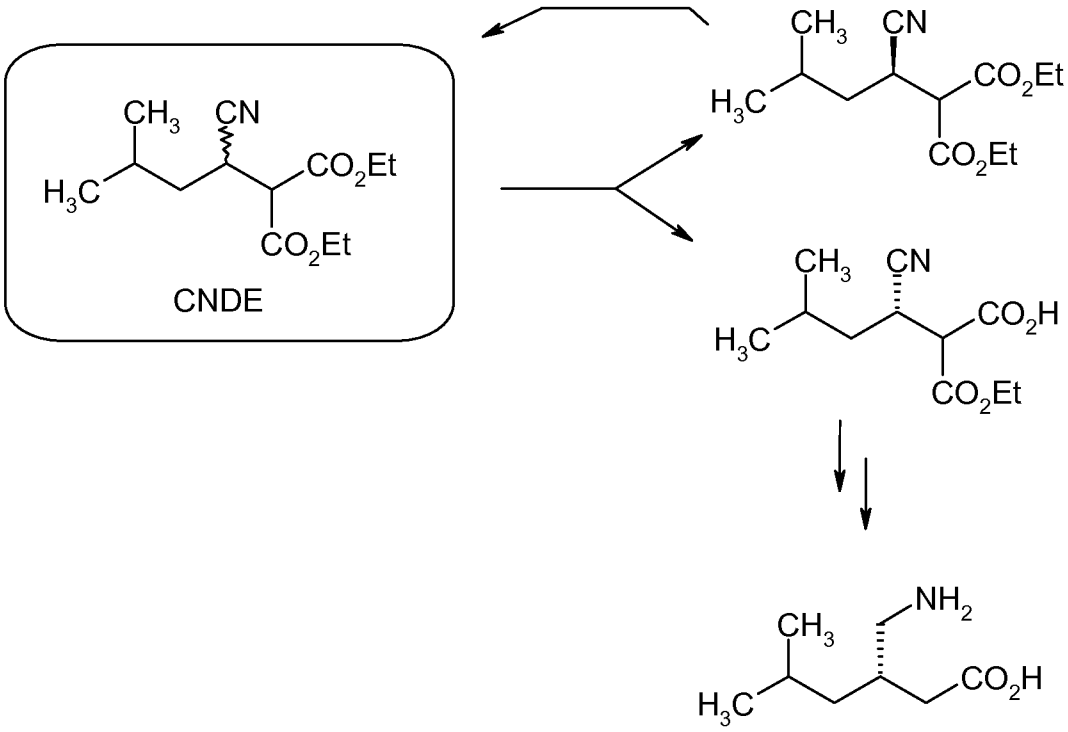
Scheme 1



An improvement of this method is described in International Patent Application WO 2006/000904. In this improved method the racemic CNDE intermediate is treated

with an ester that selectively hydrolyses one of the ester groups of (*S*)-CNDE while leaving the (*R*)-CNDE unchanged. The (S) acid is taken on to make Pregabalin while the (R)-CNDE is recycled by racemization (Scheme 2).

Scheme 2



3. Manufacturing methods involving chiral synthesis

In general, chiral synthesis is an attractive alternative to methods involving resolution in that the formation of the undesired enantiomer is avoided and potentially the overall yield can be doubled.

An asymmetric hydrogenation of a cyano-substituted olefin to produce a chiral cyano precursor of (S)-3-aminomethyl-5-methylhexanoic acid has also been used to prepare pregabalin, see e.g. U.S. Patent US 6891059. The cyano precursor is subsequently reduced to give pregabalin. The asymmetric hydrogenation employs a chiral catalyst that is comprised of a transition metal bound to a bisphosphine ligand, such as (*R*,*R*)-Me-DUPHOS. However biphosphine ligands may be difficult and costly to prepare. Asymmetric hydrogenation also requires the use of special equipment capable of handling H_2, which can add to the capital costs of carrying out a large-scale synthesis.

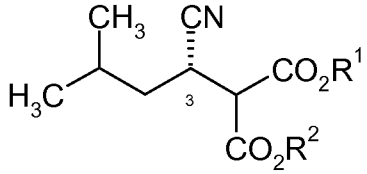
Pregabalin has also been synthesized directly using a chiral auxiliary, (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone: see, e. g., U.S. Patents US 6359169, US 6028214, US 5847151, US 5710304, US 5684189, US 5608090, and US 5599973. Although these methods provide pregabalin in high enantiomeric purity, they are less desirable for large-scale synthesis because they employ comparatively costly reagents (e. g., the chiral auxiliary) that are difficult to handle, as well as special cryogenic equipment to reach required operating temperatures, which can be as low as -78°C.

The use of a chiral oxazolidinone has also been reported in the synthesis of the antipode of pregabalin (see Convine and Popkin, Synlett, 2006, (10), 1589-1591). The addition of cyanide to an α,β-unsaturated oxazolidinone derivative afforded a chiral cyano precursor of pregabalin. However, the oxazolidinone derivative derived from the naturally occurring isomer of valine gives the cyano intermediate with the incorrect stereochemistry for pregabalin as the major diastereomer. In addition, a stoichiometric amount of the chiral oxazolidinone auxiliary was needed to prepare the α,β-unsaturated oxazolidinone derivative, as was a samarium-based catalyst, making this route financially unviable and environmentally undesirable, especially for a large-scale synthesis.

4. Need for new manufacturing methods

Still further improved syntheses of pregabalin are sought. It is especially desirable to provide a process which is cost effective and safe. In particular, it is important to provide a synthesis of pregabalin which can be carried out on a commercial scale and which uses readily available starting materials and cheap reagents.

We identified the cyano diester intermediate CNDE and its analogues as key targets for chiral synthesis. It would thus be highly advantageous to provide a direct method for the synthesis of a compound of formula (I)



(I)

in an enantiomerically enriched form, wherein the 3*S*-enantiomer is present in excess. A process for the large-scale manufacture of pregabalin which uses a compound of formula (I) which is enriched in the desired 3*S*-enantiomer as an early intermediate would bring about significant benefits. For instance, later intermediates formed in subsequent steps of the synthesis would themselves be enantiomerically enriched in the required 3*S*-enantiomer. The overall yield of pregabalin would substantially increase as there would be fewer molecules with the incorrect stereochemical configuration reacting in subsequent steps. Processing to remove the undesired 3*R*-enantiomer and subsequent disposal of this waste would also be minimised.

5. Chiral conjugate addition and Phase transfer catalysis

One method for the synthesis of the compounds of formula (I) that we describe in this specification requires a conjugate addition reaction in the presence of a chiral catalyst, particularly a chiral phase transfer catalyst.

Catalytic asymmetric conjugate additions of cyanide to α,β-unsaturated carboxylic derivatives such as imides (see Jacobsen et al, *J. Am. Chem. Soc.,* 2003, 125, 4442, and *J. Am. Chem. Soc.,* 2004, 126, 9928) and *N*-acylpyrroles (see Mita et al, *J. Am. Chem. Soc.,* 2005, 127, 514) have been reported. The former synthesis required chiral aluminium salen catalysts, whilst the catalyst used for the hydrocyanation of α,β-unsaturated *N*-acylpyrroles was a chiral gadolinium complex. However, such methods are not especially amenable to being carried out on a large scale, as both systems used TMSCN, which is relatively expensive, as a source for the cyanide ions.

Phase transfer catalysis is primarily employed in the reaction of an anion, which is usually soluble in water and not in organic solvents, with an organic substrate which is not usually soluble in water. The advantages of phase transfer catalysis are manifold. Higher reactivity may be achieved as the reactants are in the same phase with less hydration in an ion pair. With the right choice of a PTC, e.g. a quaternary ammonium catalyst, almost any anion may be extracted into almost any

organic medium, giving flexibility in choosing or eliminating the solvent. The PTC may also bring about a lower energy of activation, allowing for reduced reaction temperature and time.

Asymmetric phase transfer catalysis using chiral tetraalkylammonium salts or crown ethers may be used for the nucleophilic addition of an inorganic anion to prochiral electrophiles (see K. Maruoka and T. Ooi, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222). The asymmetric hydrocyanation of aldehydes using a phase transfer catalyst has been reported (see, e.g., S. Juliá and A. Ginebre, *Tetrahedron Lett.* **1979**, 2171). The Strecker reaction, i.e. the hydrocyanation of imines, using a PTC has also been carried out asymetrically (see, e.g., T. Ooi, Y. Uematsu, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 2548). However, there have been no reported instances of the successful asymmetric cyanide additions to α,β-unsaturated esters under PTC conditions.

6. Chiral cyanohydrin formation and elaboration

A second method for the synthesis of the compounds of formula (I) that we describe in this specification requires the elaboration of a chiral cyanohydrin.

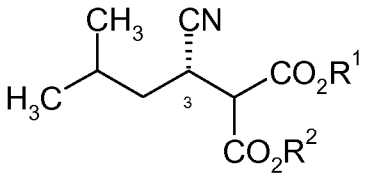
The reaction of an aldehyde with a cyanide equivalent (such as HCN, NaCN or Me_3SiCN) is well known. The reaction can be carried out in the presence of a suitable enzyme or chiral catalyst to give a chiral cyanohydrin (e.g. EP-0326063-A; Aspinall et al., *Tetrahedron Letters* 1999,40, 1763-1766; Nanda et al., Tetrahedron Asymmetry 2006,17, 735-741). Both the (*R*)- and (*S*)-enantiomers of isovaleraldehyde cyanohydrin (2-hydroxy-4-methylpentanenitrile) can be made using these methods.

Treating these chiral cyanohydrins with a sulfonyl chloride leads to the formation of the corresponding sulfonate with retention of configuration. The sulfonate can then be displaced with a nucleophilic agent. Oxygen-, sulphur- and nitrogen-based nucleophiles have all been reported (e.g Effenberger & Stelzer, *Chem. Berichte* 1993,126, 779-786; Effenberger et al., *Tetrahedron Asymmetry* 1996,7, 607-618; Effenberger & Gaupp, *Tetrahedron Asymmetry* 1999,10, 1765-1775). The reaction

of these sulfonates with carbon nucleophiles does not appear to have been reported, although the reaction of racemic 2-bromopropanenitrile with di-*tert*-butyl malonate has been reported (Dowd et al., *J. Org. Chem.* 1985, 50, 882-885).

Summary of the Invention

In a first aspect, the invention provides a compound of formula (I),



(I)

in an enantiomerically enriched form, wherein

R^1 and R^2 are the same or different and are each independently selected from hydrogen, C_1-C_{12}-alkyl, C_3-C_{12} cycloalkyl, aryl-C_1-C_6-alkyl and aryl, said alkyl, cycloalkyl and aryl being optionally substituted by one or more groups selected from halo, C_1-C_6-alkoxy and tri(C_1-C_3-alkyl)silyl;

or wherein R^1 and R^2 together are $-C(R^3)(R^4)-$, where R^3 and R^4 are the same or different and are each independently H or C_1-C_6-alkyl optionally substituted by one or more groups selected from halo, C_1-C_6-alkoxy and tri(C_1-C_3-alkyl)silyl;

or R^3 and R^4 together are $-(CH_2)_n-$ where n is 2, 3, 4, 5 or 6;

wherein the 3*S*-enantiomer is present in excess and the enantiomeric excess is at least 10%.

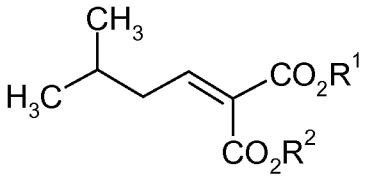
In a preferred embodiment, R^1 and R^2 are the same or different and are each independently selected from C_1-C_{12}-alkyl and benzyl. More preferably R^1 and R^2 are the same. Yet more preferably R^1 and R^2 are selected from C_1-C_4-alkyl.

In a particularly preferred embodiment, R^1 and R^2 are both ethyl.

In another preferred embodiment R^1 and R^2 together are $-C(R^3)(R^4)-$; and R^3 and R^4 are the same or different and are each independently H or C_1-C_6-alkyl; or R^3 and R^4 together are $-(CH_2)_n-$ where n is 2, 3, 4, 5 or 6. More preferably, R^3 and R^4 are both H or both methyl, or R^3 and R^4 together are $-(CH_2)_n-$ where n is 4 or 5.

In preferred embodiments, the enantiomeric excess is at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99%.

In a second aspect, the invention provides a method for the preparation of a compound of formula (I) as defined above comprising reacting a compound of formula (II)

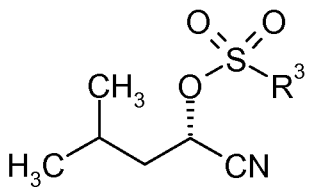


(II),

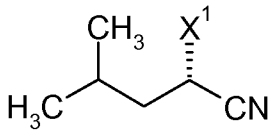
wherein R^1 and R^2 are as defined in formula (I) with a cyanide source in the presence of a chiral catalyst.

In a preferred embodiment the catalyst is a chiral phase transfer catalyst and the reaction is carried out in a two-phase system comprising water and a water-immiscible solvent.

In a third aspect, the invention provides a method for the preparation of a compound of formula (I) as defined above comprising reacting a compound of formula (III*A*) or (III*B*)

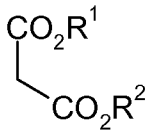


(III*A*)



(III*B*),

wherein R^3 is selected from C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, and phenyl optionally substituted with C_1-C_4 alkyl, halo or NO_2; and X^1 is selected from Cl and Br with a compound of formula (IV)



(IV),

wherein R^1 and R^2 are as defined in formula (I) in the presence of a base.

In a fourth aspect, the invention provides method for the preparation of pregabalin, comprising the steps of:

(i) preparing an enantiomerically enriched compound of formula (I) as defined above, and

(ii) converting the enantiomerically enriched compound of formula (I) into pregabalin.

Detailed Description of Preferred Embodiments

The term "alkyl" means a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

The term "aryl" means a phenyl or naphthyl group.

The term "aryl-alkyl'' means a straight-chain or branched-chain saturated aliphatic hydrocarbon radical in which an aryl group is substituted for an alkyl hydrogen atom. An example of an aryl-alkyl group is benzyl.

The term "cycloalkyl" means a saturated carbocyclic ring containing the specified number of carbon atoms. Examples of carbocyclic rings include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "enantiomeric excess'', sometimes abbreviated as "e.e.'', is a measure, for a given sample, of the excess of one enantiomer in excess of its antipode and is expressed as a percentage. Enantiomeric excess is defined as:

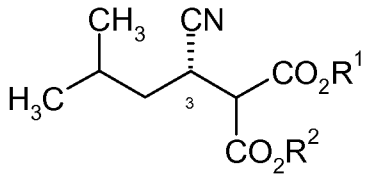
$$100 \times (er-1) / (er+1)$$

where "er'' is the ratio of the more abundant enantiomer to the less abundant enantiomer.

The term "optionally substituted" with reference to an alkyl or aryl group means that a hydrogen atom of the alkyl or aryl group may be replaced by one of the groups listed. The substitution may be made at any position within the alkyl or aryl group. When the optional substitution is with "one or more groups" then any number of hydrogen atoms of the alkyl or aryl group, up to a maximum equal to the number of hydrogens present in the alkyl or aryl group, may be replaced, and each replacement is independent of the others.

The term "perfluoroalkyl" means an alkyl group as defined above wherein all the hydrogen atoms have been replaced by fluorine. Examples of perfluoroalkyl radicals include trifluoromethyl, pentafluoroethyl and heptafluoroisopropyl.

As set out above, in a first aspect the present invention provides compounds of formula (I)



(I)

in enantiomerically enriched form, wherein the 3*S*-enantiomer is present in excess. In general it is preferred that the enantiomeric excess be as high as possible. Compounds of formula (I) in the form of substantially pure single enantiomers (i.e. with an e.e. of at least 95% or at least 99%) are especially preferred.

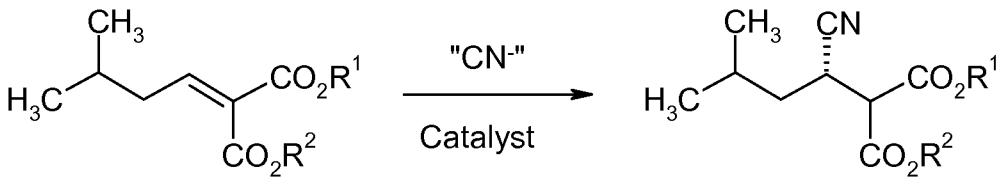
It will be noted that when R^1 and R^2 are different then the compounds of formula (I) have a second chiral centre. Furthermore, some embodiments of R^1 and R^2 may include additional chiral centres. Reference herein to compounds of formula (I) being in enantiomerically enriched form is intended to relate only to the stereochemistry at the 3-position (as indicted in the formula above). The compounds of formula (I) may thus include single diasteroisomers and mixtures thereof. However, it will generally be preferred that these additional chiral centres be avoided. Thus it is generally preferable for R^1 and R^2 to be the same, and to be achiral groups.

Compounds of formula (I) of particular interest include:

dimethyl 2-((1*S*)-1-cyano-3-methylbutyl)-malonate,
diethyl 2-((1*S*)-1-cyano-3-methylbutyl)-malonate, and
(2*S*)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4-methylpentanenitrile.

The compounds of formula (I) may be prepared according to the methods described herein.

As noted above, in one method for the preparation of a compound of formula (I) a compound of formula (II) is allowed to react with a cyanide source in the presence of a chiral catalyst.



(II) (I)

Preferably the chiral catalyst is a chiral phase transfer catalyst and the reaction is carried out in a two-phase system comprising water and a water-immiscible solvent.

A number of chiral phase transfer catalysts are commercially available whilst the syntheses of others have been described in the literature. (For a recent review, see Hashimoto and Maruoka, *Chem. Rev.*, 2007, 107, 5656-5682). Chiral phase transfer catalysts may be ephedrine, quinine, quinidine, cinchonidine, cinchonine, crown ether or tartrate derivatives. They may be chiral tetraalkylammonium salts, chiral crown ethers, chiral phosphonium salts, chiral cinchonidinium salts, chiral cinchoninium salts, chiral quininium salts, chiral azepinium salts.

The chiral phase transfer catalysts may also be non-racemic chiral quaternary ammonium ions, i.e., nitrogen bonded to four carbons, which present an asymmetric environment, causing differentiation between the two enantiotopic faces of a prochiral carbon atom, typically an sp^2-hydbridised carbon atom. The quaternary ammonium moiety may be embedded in an asymmetric bicyclic or polycyclic

scaffold which provides a rigid or semi-rigid environment. Furthermore, the catalyst may bear substituents which may also affect catalyst reactivity and which may provide enhanced enantioselectivities.

It is preferred that the chiral phase transfer catalyst is selected from:
(-)-*N*-Benzyl-*N*-methylephedrinium halide;
(-)-*N*-Dodecyl-*N*-methylephedrinium halide;
(-)-*N,N*-Dimethylephedrinium halide;
N-Benzylcinchonidinium halide;
O-Allyl-*N*-benzylcinchonidinium halide;
N-(9-Anthracenylmethyl)cinchonidinium halide;
O-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium halide;
N-Benzylquininium halide;
N-(4-Trifluoromethylbenzyl)cinchoninium halide;
O,O'-Diallyl-*N,N'*-(2,7-naphthalenediyldimethyl)bis(hydrocinchonidinium) dihalide;
(11b*S*)-4,4-Dibutyl-4,5-dihydro-2,6-bis-(3,4,5-trifluorophenyl)-3*H*-dinaphth[2,1-*c*:1',2'-e]azepinium halide;
Nα-BOC-*Nε*–(2-chloro-Z)-D-lysine;
(2*R*,3*R*)-2,3-Dimethyl-1,4,7,10,13,16-hexoxacyclooctane ;
(2*R*,3*R*,11*R*,12*R*)-2,3,11,12-Tetramethyl-1,4,7,10,13,16-hexoxacyclooctane;
(4*S*,5*S*)-N,N,N',N'-tetrakis[(4-m4thoxyphenyl)methyl]2,2-dimethyl1,3-dioxolane-4,5-dimethanine;
N-(3,5-Bis(trifluoromethyl)benzyl)cinchoninium halide;
N-(3,4,5-tifluorobenzyl)cinchoninium halide and
N-(2,3,4,5,6-pentafluorobenzyl)cinchoninium halide.

Where the halide salt has been specified in the list above, the following salts are preferred:
(-)-*N*-Benzyl-*N*-methylephedrinium bromide;
(-)-*N*-Dodecyl-*N*-methylephedrinium bromide;
(-)-*N,N*-Dimethylephedrinium bromide;

N-Benzylcinchonidinium chloride;
N-Benzylcinchonidinium bromide;
O-Allyl-*N*-benzylcinchonidinium bromide;
N-(9-Anthracenylmethyl)cinchonidinium chloride;
O-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide;
N-Benzylquininium chloride;
N-(4-Trifluoromethylbenzyl)cinchoninium bromide;
N-3,5-bis(trifluoromethyl)benzyl cinchoninium bromide;
O,O'-Diallyl-*N,N'*-(2,7-naphthalenediyldimethyl)bis(hydrocinchonidinium) dibromide;
(11b*S*)-4,4-Dibutyl-4,5-dihydro-2,6-bis-(3,4,5-trifluorophenyl)-3*H*-dinaphth[2,1-*c*:1',2'-e]azepinium bromide;
N-(3,5-Bis(trifluoromethyl)benzyl)cinchoninium bromide;
N-(3,4,5-tifluorobenzyl)cinchoninium bromide and
N-(2,3,4,5,6-pentafluorobenzyl)cinchoninium bromide.

Catalysts such as (trifluoromethylbenzyl)cinchoninium halide and 3,5-bis(trifluoromethyl)benzyl cinchoninium halide, are especially preferred. More preferably, the chiral phase transfer catalyst is (trifluoromethylbenzyl)cinchoninium bromide or 3,5-bis(trifluoromethyl)benzyl cinchoninium bromide.

The catalyst may be used in an amount ranging from 0.05 to 1.1 equivalents per molar equivalent of the compound of formula (II) without negatively affecting the e.e. Preferably a 0.05-0.20 molar equivalent is used. This may be especially advantageous as the catalyst may be expensive and/or not readily available. In addition, the present invention envisages that the catalyst may be recovered and re-used.

When a chiral phase transfer catalyst is used, the reaction of the compound of formula (II) with a cyanide source is carried out in a two-phase system. It is possible that the compound of formula (II) may itself provide one of the phases and may be used neat, i.e. undissolved in an additional solvent. More typically, the reaction is carried out in a two-phase system comprising water and a water-

immiscible solvent. A suitable amount of a compound, e.g. a glycol, which lowers the freezing point of the aqueous phase of the reaction mixture may be added. Preferably the water-immiscible solvent is a solvent which provides good recoveries of the organic materials. It is also preferred that a solvent with medium polarity is used. In some embodiments, it may be advantageous to use a solvent which is not inert under the reaction conditions. For example, a water-immiscible ketone may also be used to bring the cyanide anion into the organic phase as a cyanohydrin. Examples of suitable solvents include hydrocarbons such as toluene, xylene and mesitylene, ethers such as methyl-*t*-butyl ether, 2-methyltetrahydrofuran, chlorinated solvents such as dichloromethane and chlorobenzene, water-immiscible ketones such as methyl ethyl ketone, diethyl ketone and alcohols such as *t*-amyl alcohol, 3-pentanol, n-butanol, isobutanol. More preferably the water-immiscible solvent is selected from methyl-*t*-butyl ether and *t*-amyl alcohol. Most preferably, the solvent is methyl-*t*-butyl ether.

When the invention is used to prepare a compound of formula (I) wherein R^1 and R^2 together are $-C(R^3)(R^4)-$, the solvent is preferably toluene or dichloromethane.

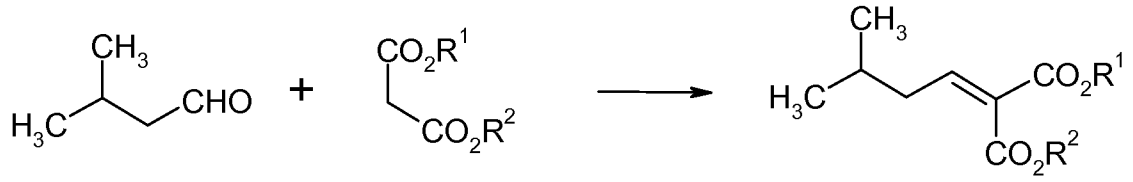
A number of cyanide sources may be used to provide the cyanide anion required for the reaction. They include acetone cyanohydrin and TMSCN. More usually, the cyanide source is a cyanide salt of an alkali metal, preferably sodium or potassium.

The reaction may be carried out at a temperature in the range of -78 to 80°C, more preferably in the range -20 to 40°C, and still more preferably in the range 0-30°C.

Optionally, a lipophilic proton source to the reaction mixture. In this way, the basicity of the cyanide ions may be modulated to some extent by the partial conversion of cyanide ions to hydrogen cyanide. The proton source may be added in any quantity, a stoichiometric quantity being the typical amount. Typical lipophilic proton sources are long-chain alcohols, such as 1-octanol.

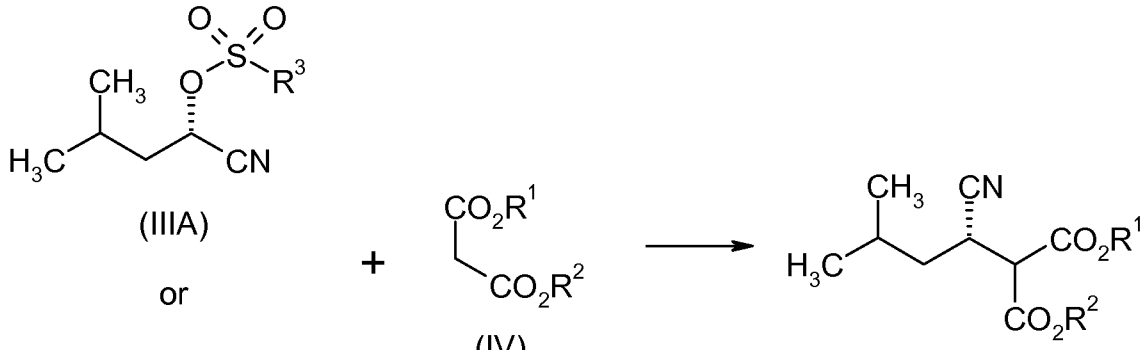
The reaction of the compound of formula (II) with a cyanide source may be carried out in continuous, semi-continuous or batch fashion.

The compounds of formula (II) may be prepared from isovaleraldehyde and a malonate of formula (IV), for example as described in U.S. Patents US 6046353, US 5840956, and US 5637767.



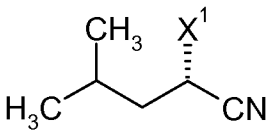
(IV) (II)

In an alternative method, the compounds of formula (I) may be prepared by reacting a compound of formula (III*A*) or (III*B*) with a malonate derivative of formula (IV) in the presence of a base.



(IIIA)

or



(III*B*)

R^3 is selected from C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, and phenyl optionally substituted with C_1-C_4 alkyl, halo or NO_2. Preferred embodiments of R^3 include methyl, trifluoromethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl and 2-, 3- and4-nitrophenyl. X^1 is selected from Cl and Br.

The base may be any suitable base. Suitable bases are those that deprotonate the malonate to a sufficient degree to allow the reaction to proceed, but which do not react with the various functional groups present in the starting materials and the product. Examples of suitable bases include alkali metal carbonates (such as caesium carbonate) and alkali metal hydrides (such as sodium hydride). Alkali

metal alkoxides (such as sodium ethoxide and potassium t-butoxide) may also be suitable provided that they do not lead to transesterification products.

The reaction will generally be carried out in a suitable solvent. Suitable solvents are those in which the stating materials and the base have sufficient solubility to allow the reaction to proceed, but which do not adversely react with the reactants. Examples of suitable solvents include nitriles (such as acetonitrile) and ethers (such as tetrahydrofuran, 2-methyltetrahydrofuran and 1,2-dimethoxyethane). Alcohols (such as ethanol) may also be suitable solvents provided that they do not lead to transesterification products. Solvent mixtures are also contemplated.

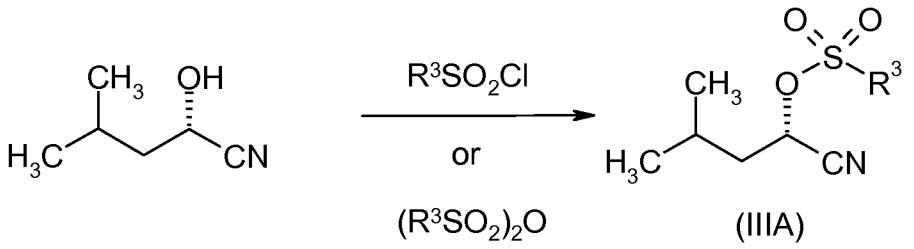
The reaction may be carried out at any temperature between the freezing point and the boiling point of the solvent. Preferred temperatures are in the range of 20°C to 80°C, and particularly 40°C to 60°C.

In some cases it may be advantageous to allow the base to react with the malonate before the compound of formula (III*A*) or (III*B*) is added.

In a particularly preferred embodiment, a compound of formula (III*A*) wherein R^3 is phenyl or substituted phenyl is reacted with the sodium salt of diethyl malonate in a polar solvent at about 50°C to provide the compound of formula (I) wherein R^1 and R^2 are both ethyl.

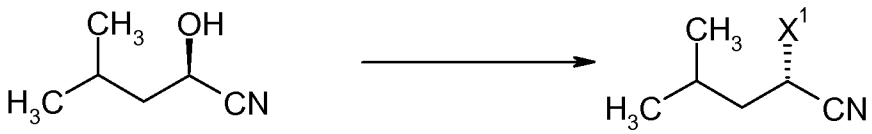
The compounds of formula (III*A*) and (III*B*) should be enantiomerically enriched, with the (*S*)-enantiomer present in excess. Preferably the compounds of formula (III*A*) and (III*B*) should be in the form of the substantially pure (*S*)-enantiomer.

The compounds of formula (III*A*) can be prepared according to the published methods (*supra*) from (*S*)-2-hydroxy-4-methylpentanenitrile ((*S*)-isovaleraldehyde cyanohydrin) by reaction with an appropriate sulfonyl chloride or sulfonic acid anhydride.



(IIIA)

The compounds of formula (III*B*) can be prepared according to the published methods (*supra*) from (*R*)-2-hydroxy-4-methylpentanenitrile ((*R*)-isovaleraldehyde cyanohydrin) by reaction with an appropriate halogenating agent (for example thionyl chloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus oxybromide and triphenylphosphine/carbon tetrabromide).



(III*B*)

Both the (*R*)- and (*S*)-enantiomers of isovaleraldehyde cyanohydrin are known and may be prepared by a number of methods. A preferred method is to react isovaleraldehyde with a cyanide source (such as an alkali metal cyanide or acetone cyanohydrin) in the presence of a hydroxynitrile lyase enzyme. Examples of suitable enzymes include (*S*)-hydroxynitrile lyases from *Hevea brasiliensis*, *Manihot esculenta*, and *Sorghum bicolor* and (*R*)-hydroxynitrile lyase from *Prunus amygdalus*.

The enantiomerically enriched compounds of formula (I) are useful intermediates for the manufacture of pregabalin. Starting from the compounds of formula (I) it is necessary to perform three transformations in order to get to pregabalin:

- Hydrolysis of the one (or both)of the ester groups to liberate the free carboxylic acid group, and
- Decarboxylation to remove the second carboxylate group.
- Hydrolysis of the second ester group (if present) and
- Reduction of the nitrile to give $-CH_2NH_2$

These steps may be performed in any order, following methods already known in the art. A number of methods for the preparation of pregabalin from a racemic mixture of a compound of formula (I) and its 3R-enantiomer have been described in the prior art, e.g. in US 5637767. In addition, a process whereby a chiral β-cyanodiacid intermediate is reduced, followed by a decarboxylation step to give enantiopure pregabalin, has been described in WO 2006/000904. WO 2006/000904 also describes the reduction of the monoester of the β-cyanodiacid intermediate, to form a lactam which is subsequently hydrolysed to give enantiopure pregabalin. Other approaches from the monoester of the the β-cyanodiacid intermediate are discussed in *Organic Process Research and Development*, Vol. 12 (3), 2008, 392-398. The skilled reader will be able to modify the methods described in the art as necessary.

Advantageously, in one aspect of the invention, yield losses associated with the production of an undesired enantiomer may be substantially reduced or even be eliminated altogether.

Examples

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

bp	Boiling point
$BzEt_3NCl$	Benzyltriethylammonium chloride
CNDE	2-(1-cyano-3-methylbutyl)malonate diethyl ester
CyH	Cyclohexane
d	Doublet
DCM	Dichloromethane
DEK	Diethyl ketone
DIW	De-ionised water
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dt	Doublet of triplets

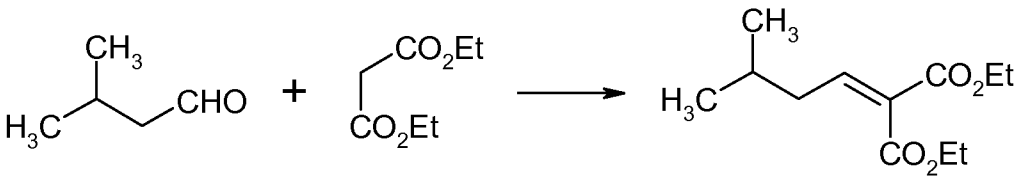
eq or eq.	Equivalent
e.e. or ee	Enantiomeric excess
EtOAc	Ethyl Acetate
HPLC	High Performance Liquid Chromatography
Hr or h	Hour
^{1}H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
IPA	Iso-propyl Alcohol
L	Litre
m	Multiplet
mbar	Millibar
MEK	Methyl Ethyl Ketone
2-MeTHF	2-Methyl tetrahydrofuran
min	Minute
mL	Millilitre
mmol	Millimole
Mp	Melting point
MTBE	Methyl tert-butyl Ether
PhCl	Chlorobenzene
PhMe	Toluene
ppm	Parts per million
PTC	Phase Transfer Catalyst
q	Quartet
R_f	Retention factor
RT	Room temperature
s	Singlet
t	Triplet
^{t}amylOH	Tert-amyl alcohol
δ	Chemical shift

Commercial chemicals were purchased from Aldrich and were used as received unless stated otherwise. Thin layer chromatography was performed on pre-coated plastic plates (Merck silica 60F254), and visualised using UV light and $KMnO_4$ dip. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian INOVA 300

MHz spectrometer. Chemical shifts are quoted relative to tetramethylsilane and referenced to residual solvent peaks as appropriate. Unless otherwise indicated, chiral HPLC analysis was performed using an Agilent 1200 HPLC system and data was processed using the Chemstation software or with a Varian semiprep/analytical HPLC using Galaxie software. In some cases, hydrolysis of the cyano-adduct, in particular, CNDE, occurs under the reaction conditions. As a result, the enantiomeric excess quoted was normalised to 100%, based on the values obtained for the HPLC area%.

Preparation 1

Diethyl 2-(3-methylbutylidene)malonate (Et-ene-malonate)



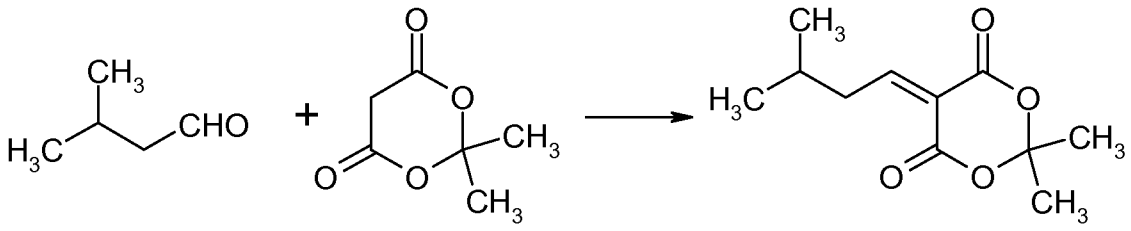
Et-ene-malonate

A mixture of isovaleraldehyde (12.5 mL, 116 mmol, 1.0 eq.), diethyl malonate (16.7 mL, 110 mmol, 0.95 eq.), dipropylamine (0.8 mL, 5.8 mmol, 0.05 eq.), glacial acetic acid (0.65 mL, 11.4 mmol, 0.1 eq.) and cyclohexane (28 mL) was stirred at reflux with azeotropic removal of water using a Dean-Stark condenser. After 3 hours removal of water was complete and the mixture was allowed to cool to room temperature. Water (20 mL) was added and the mixture stirred for 10 min. The organic layer was separated, washed with further water (20 mL), dried over $MgSO_4$, filtered and the solvent evaporated leaving a colourless oil which was purified by vacuum distillation. Yield 21.5 g (85%), bp 66 °C/0.1 mbar.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01 (t, 1H, CH=), 4.30 (q, 2H, $OC\underline{H}_2Me$), 4.24 (q, 2H, $C\underline{H}_2Me$), 2.19 (dd, 2H, $C\underline{H}_2CHMe_2$), 1.82 (m, 1H, $C\underline{H}Me_2$), 1.33 (t, 3H, $OCH_2C\underline{H}_3$), 1.29 (t, 3H, $OCH_2C\underline{H}_3$), 0.94 (d, 6H, $CH(C\underline{H}_3)_2$).

Preparation 2

2,2-Dimethyl-5-(3-methylbutylidene)-1,3-dioxane-4,6-dione (MA-ene-malonate).

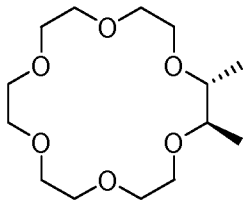


MA-ene-malonate

MA-ene-malonate was prepared using the procedure described in: Tsuno, K. Sugiyama, H. Ago, *Heterocycles* **1994**, *38*, 2631. Isovaleraldehyde (11.2 ml, 104.5 mmol, 1.05 eq) and Meldrum's acid (14.4 g, 99.9 mmol, 1 eq) were dissolved in MTBE (500 ml). Piperidine (0.2g) and glacial acetic acid (0.2 g) were added. The mixture was heated to reflux temperature and water was removed using a Dean-Stark collector. After about 3 h, 1.5 ml of water had collected and overnight distillation did not increase this amount. The mixture was cooled to ambient temperature and then was poured into a separating funnel containing 1M aq. HCl (200 ml). After vigorous shaking, the aqueous layer was discarded and the organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo.* The residues were purified *via* filtration through a dry-flash silica plug eluted with 9:1 with a gradient to 1:1 CyH/EtOAc. The product eluted as a yellow band (TLC: 8:2 CyH/EtOAc R_f =0.45, UV, $KMnO_4$) and 16.26 g (77%) of product was obtained as a yellow oil.

Preparation 3

(-)-(2*R*,3*R*)-2,3-Dimethyl-1,4,7,10,13,16-hexaoxacyclooctadecane (catalyst 14, see Table 1)



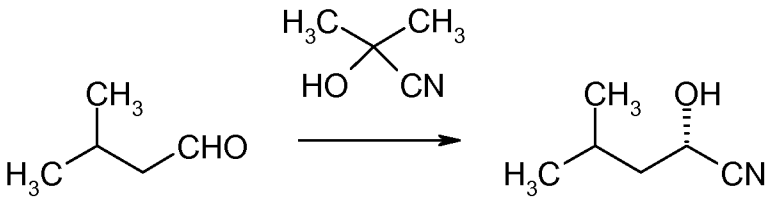
The crown ether PTC catalyst was prepared according to the procedure described in: K. Naemura, M. Ueno, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3695. A solution of

(2*R*,3*R*)-butane-2,3-diol (0.27 mL, 3.0 mmol, 1.0 eq.) and pentaethylene glycol bis(*p*-toluenesulfonate) (1.8 g, 3.3 mmol, 1.1 eq) in THF (160 mL) was added dropwise over 10 hours to a suspension of sodium hydride (180 mg, 7.5 mmol, 2.5 eq.) and potassium tetrafluoroborate (425 mg, 3.3 mmol, 1.1 eq.) in refluxing THF (160 mL). Once the addition was complete the mixture was refluxed for a further 36 hours then allowed to cool to room temperature. The mixture was filtered and the filtrate concentrated in vacuo. The residue was taken up in chloroform. The resulting solution was washed with water and brine, dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by flash chromatography on neutral alumina (EtOAc eluent) to give 533 mg yellow oil. $[\alpha]_D^{20}$ -7.69° (c 1.04, $CHCl_3$) (lit. -7.36°), MS: *m/z* 315 $[M+Na]^{+.}$.

^1H NMR ($CDCl_3$, 300 MHz): δ 3.67 (m, 20H, 10 x CH_2), 3.49 (m, 2H, 2 x CH), 1.08 (d, 2 x CH_3).

Preparation 4

(*S*)-2-Hydroxy-4-methylpentanenitrile



Cassava S-Hydroxynitrile Lyase (Julich Chemicals: 1350ml, 2.355U/mL) and citric acid (500mL, 0.1M) were stirred together for 5 minutes and the pH checked (pH=5). MTBE (10L) and 3-methylbutanal (1000g, 11.61moles, 1.06eq) were then charged followed by acetone cyanohydrin (1L, 929.4g, 10.92moles). The resultant two phase mixture was stirred at 400rpm at 25ºC for 21h. The stirring was then stopped and the two phases allowed to separate. The upper organic phase was decanted off and the remaining enzyme mixture was stirred with further MTBE for 30 minutes before settling and decanting as before. The two organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give pale yellow oils.

Wt Yield 1200g, 92%, w/w ^1H NMR gave 81.6% contained weight hence yield 979.3g, 79%.

MTBE extract: Wt yield 90g, 7%, w/w ^{1}H NMR gave 82.8% contained weight hence yield 74.5g, 6%.

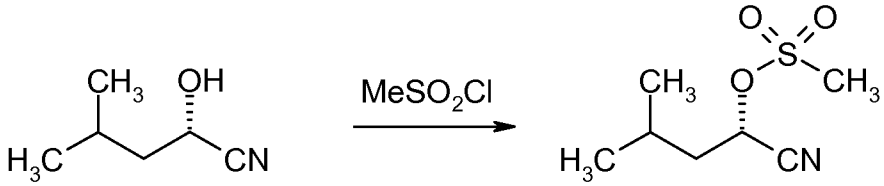
Overall yield 1053.8g, 85%.

^{1}H NMR: δ 4.50 (1H, m), 1.90-1.60 (3H, m), 0.90 (6H, 2d, J=6.59 Hz).

Chiral GC analysis gave a chiral purity of 94.6%ee.

Preparation 5

(1*S*)-1-Cyano-3-methylbutyl methanesulfonate (mesylate)



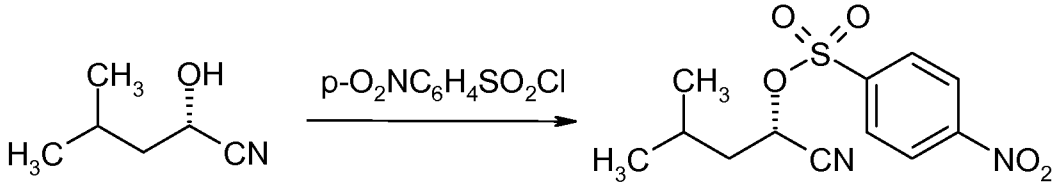
Methanesulfonyl chloride (18.1mL, 0.234moles, 1.06eq) in MTBE (125mL) was added in portions over 10mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (25g, 0.221moles, 1.0eq), triethylamine (23.5g, 0.232moles, 1.05eq) and MTBE (125mL) at 0-10ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight, water was added and the two phases separated off, washing the organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to a pale yellow oil. The crude product was dissolved in 50/50 dichloromethane/heptane and passed through a short silica gel column eluting with 50/50 dichloromethane/heptane, and the resultant fraction was evaporated under reduced pressure to give a pale yellow oil.

Yield 30.5g, 72%, 94.5% ee by chiral HPLC.

^{1}H NMR ($CDCl_3$) δ 5.19 (1H, m), 3.19 (3H, s), 1.95-1.80 (3H, m), 1.00 (6H, d, J=6.22).

Preparation 6

(1*S*)-1-Cyano-3-methylbutyl 4-nitrobenzenesulfonate (4-nosylate)



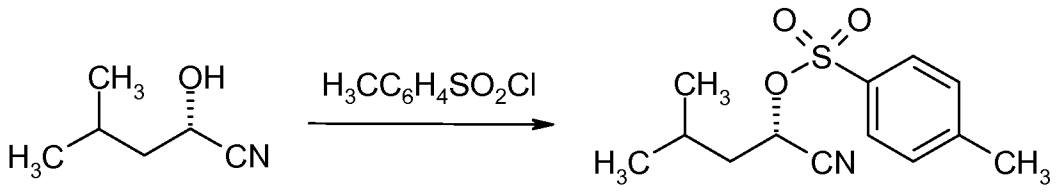
4-Nitrobenzenesulfonyl chloride (20.8g, 0.094moles, 1.06eq) was added in portions over 10mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (10g, 0.088moles, 1.0eq), triethylamine (9.4g, 0.093moles, 1.05eq) and MTBE (100mL) at 0-10ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight, water was added and the two phases separated off, washing the organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to a pale orange oil which solidified on standing. The crude product was dissolved in 50/50 dichloromethane/heptane and passed through a short silica gel column eluting with 50/50 dichloromethane/heptane, the resultant fraction was evaporated under reduced pressure to give a pale yellow oil which solidified on standing.

Yield 24.2g, 92%, 94% ee by chiral HPLC.

^{1}H NMR ($CDCl_3$) δ 8.45 (2H, d, J=8.79), 8.15 (2H, d, J=8.79), 5.20 (1H, m), 1.95-1.80(3H, m), 0.95 (6H, 2d, J=6.59).

Preparation 7

(1*S*)-1-Cyano-3-methylbutyl 4-toluenesulfonate (tosylate)



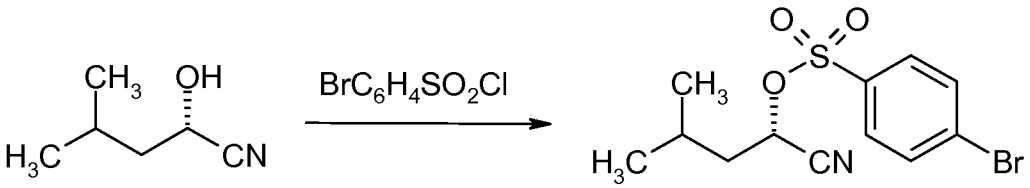
Toluenesulfonyl chloride (17.9g, 0.094moles, 1.06eq) was added in portions over 10mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (10g, 0.088moles, 1.0eq), triethylamine (9.4g, 0.093moles, 1.05eq) and MTBE (100mL) at 0-10ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight, water was added and the two phases separated off, washing the organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to a colourless oil which was purified as described for the 4-nosylate to give a colourless oil.

Yield 22.6g, 96%, 92.7% ee by chiral HPLC.

^{1}H NMR ($CDCl_3$) δ 7.80 (2H, d, J=8.42), 7.40 (2H, d, J=8.06), 5.05 (1H, m), 2.45 (3H, s), 1.90-1.70 (3H, m), 0.90 (6H, 2d, J=6.59, 6.22).

Preparation 8

(1*S*)-1-Cyano-3-methylbutyl 4-bromobenzenesulfonate



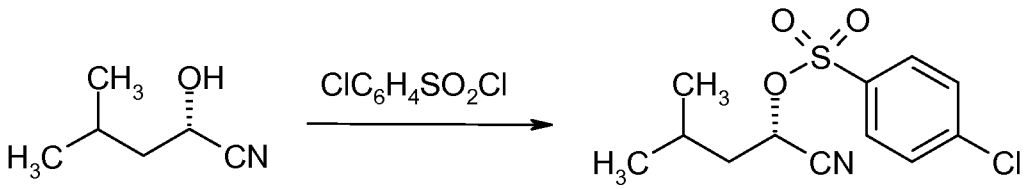
4-Bromobenzenesulfonyl chloride (23.9g, 0.094moles, 1.06eq) was added in portions over 10mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (10g, 0.088moles, 1.0eq), triethylamine (9.4g, 0.093moles, 1.05eq) and MTBE (100mL) at 0-10ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight, water was added and the two phases separated off, washing the organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to a colourless solid which was purified as described for the 4-nosylate to give a colourless solid.

Yield 24.7g, 84%.

^{1}H NMR ($CDCl_3$) δ 7.80 (2H, d, J=8.79), 7.75 (2H, d, J=8.42), 5.10 (1H, m), 1.90-1.70 (3H, m), 0.95 (6H, 2d, J=6.22, 6.59).

Preparation 9

(1*S*)-1-Cyano-3-methylbutyl 4-chlorobenzenesulfonate



4-Chlorobenzenesulfonyl chloride (19.8g, 0.094moles, 1.06eq) was added in portions over 10mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (10g, 0.088moles, 1.0eq), triethylamine (9.4g, 0.093moles, 1.05eq) and MTBE (100mL) at 0-10ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight, water was added and the two phases separated off, washing the

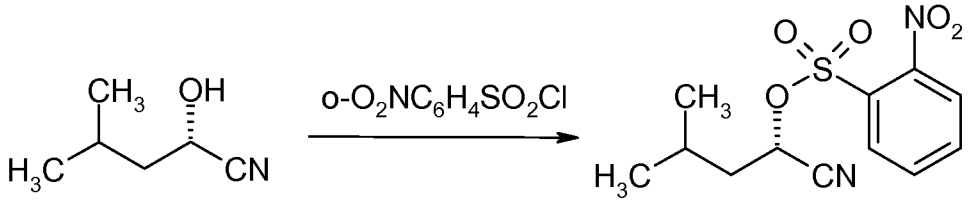
organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to a colourless oil which solidified on standing. The crude product was purified as described for the 4-nosylate to give a colourless solid.

Yield 22.6g, 89%, 93.6% ee by chiral HPLC.

^1H NMR ($CDCl_3$) δ 7.90 (2H, d, J=8.79), 7.60 (2H, d, J=8.79), 5.10 (1H, m), 1.95-1.75 (3H, m), 0.95 (6H, 2d, J=6.22).

Preparation 10

(1*S*)-1-Cyano-3-methylbutyl 2-nitrobenzenesulfonate (2-nosylate)



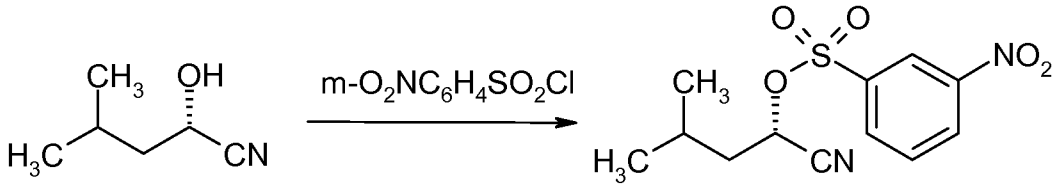
2-Nitrobenzenesulfonyl chloride (20.8g, 0.094moles, 1.06eq) was added in portions over 10mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (10g, 0.088moles, 1.0eq), triethylamine (9.4g, 0.093moles, 1.05eq) and MTBE (100mL) at 0-10ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight, water was added and the two phases separated off, washing the organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to an orange oil which was purified as described for the 4-nosylate to give a yellow oil.

Yield 18.9g, 72%, 93% ee by chiral HPLC.

^1H NMR ($CDCl_3$) δ 8.20 (1H, d, J=8.42), 8.00-7.80 (3H, m, J=8.06), 5.30 (1H, m), 2.00-1.80 (3H, m), 1.00 (6H, 2d, J=6.59, 6.22).

Preparation 11

(1*S*)-1-Cyano-3-methylbutyl 3-nitrobenzenesulfonate (3-nosylate)



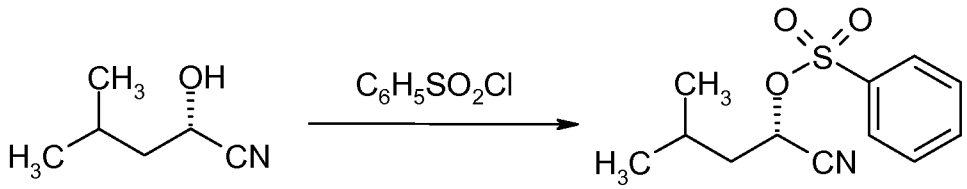
3-Nitrobenzenesulfonyl chloride (20.8g, 0.094moles, 1.06eq) was added in portions over 10mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (10g, 0.088moles, 1.0eq), triethylamine (9.4g, 0.093moles, 1.05eq) and MTBE (100mL) at 0-10ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight, water was added and the two phases separated off, washing the organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to a pale yellow oil which was purified as described for the 4-nosylate to give a very pale yellow oil.

Yield 20.5g, 78%.

^{1}H NMR ($CDCl_3$) δ 8.80 (1H, d, J=8.42), 8.55 (1H, d, J=), 8.30 (1H, d, J=8.06), 7.85 (1H, m, J =), 5.20 (1H, m), 2.00-1.75 (3H, m), 1.00 (6H, 2d, J=6.59, 6.22).

Preparation 12

(1*S*)-1-Cyano-3-methylbutyl benzenesulfonate (besylate)



Benzenesulfonyl chloride (33.1g, 0.187moles, 1.06eq) was added in portions over 15mins to a solution of (S)-2-hydroxy-4-methylpentanenitrile (20g, 0.177moles, 1.0eq), triethylamine (18.8g, 0.186moles, 1.05eq) and MTBE (100mL) at 0-5ºC. The resultant mixture was allowed to warm to room temperature (15-20ºC) and then stirred overnight. Water was added and the two phases separated off, washing the organic phase with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to a pale yellow oil (44.9g, 100% wt. yield) which was purified as described for the 4-nosylate to give a very pale yellow oil.

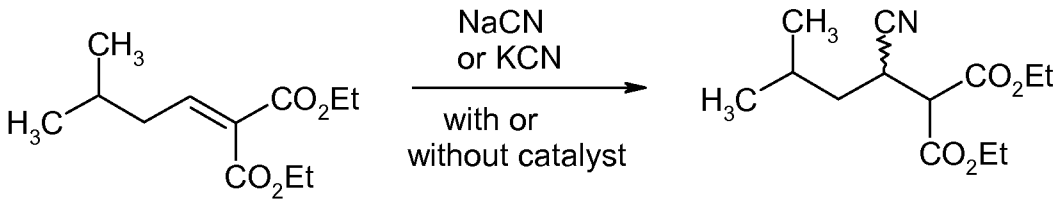
Yield 40.9g, 91.3% weight yield, 93.2% ee by chiral HPLC.

Assay by ^{1}H NMR 81.7% w/w, 75% contained yield. Structure was confirmed by ^{1}H NMR.

Examples 1 to 20 relate to the phase-transfer catalysis method.

Example 1

General procedure for the hydrocyanation of Et-ene-malonate, with or without catalyst



Et-ene-malonate CNDE

Et-ene-malonate (Preparation 1: 20 mg, 0.09 mmol, 1.0 eq.), a catalyst, if used, (0.018 mmol, 0.2 eq.), 1.2 mL water and 0.4 mL organic solvent were mixed in a small vial. Aqueous NaCN or KCN (0.05 mL of a 2M solution, 0.1 mmol, 1.1 eq.) was added and the vial sealed. The mixture was stirred rapidly at room temperature overnight, then allowed to settle and the organic layer was sampled by HPLC. Alternatively, the reaction may be carried out at 0 °C but no difference in the enantiomeric excess obtained was observed.

The following chiral HPLC assay was used.
Column: Chiralpak AS-H
Eluent: 98/2 heptane/ethanol
Flowrate: 1 mL/min
UV detection: 230 nm
Column temperature: ambient

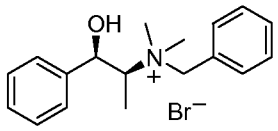
Retention times (see Figures 1, 2 and 3)
Et-ene-malonate 4.3 min

R-CNDE	9.5 min
S-CNDE	11.0 min

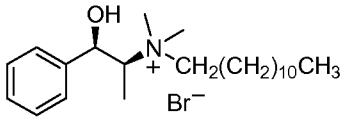
The HPLC traces for Et-ene-malonate, racemic CNDE and *R*-CNDE obtained using the HPLC protocol described above are shown in Figures 1, 2 and 3 respectively. The peak at about 3.8 min in Figure 3 is due to toluene.

For ease of reference, the catalysts used are referred to by various numbers which correspond to the following table. The same numbering is used to refer to the catalysts in subsequent tables.

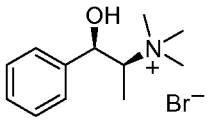
Table 1: Catalysts used for the hydrocyanation reaction



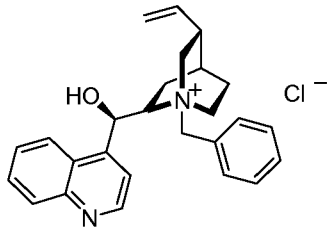
1 (-)-*N*-Benzyl-*N*-methylephedrinium bromide



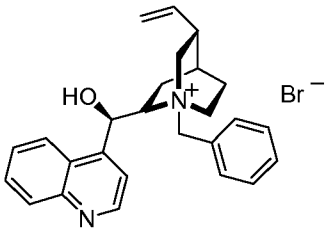
2 (-)-*N*-Dodecyl-*N*-methylephedrinium bromide



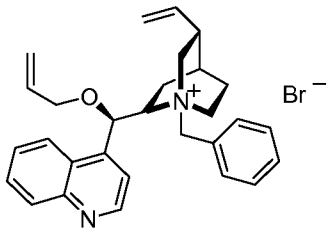
3 (-)-*N*,*N*-Dimethylephedrinium bromide



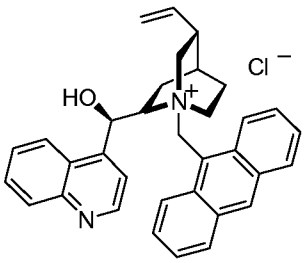
4 *N*-Benzylcinchonidinium chloride



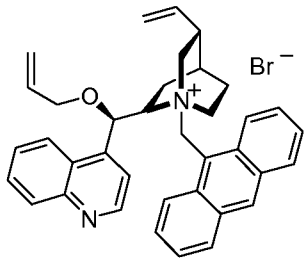
5 *N*-Benzylcinchonidinium bromide



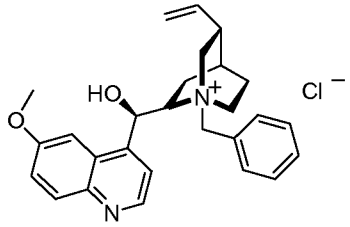
6 *O*-Allyl-*N*-benzylcinchonidinium bromide



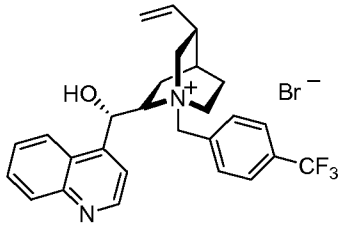
7 *N*-(9-Anthracenylmethyl)cinchonidinium chloride



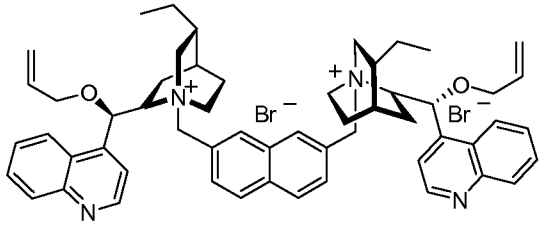
8 *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide



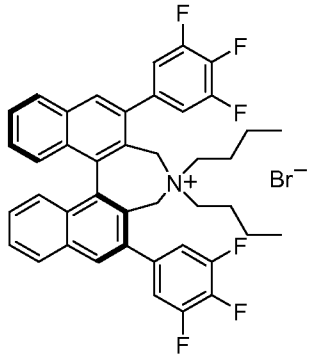
9 *N*-Benzylquininium chloride



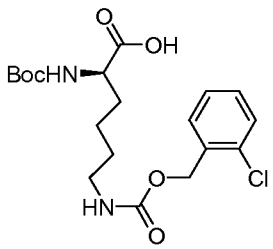
10 *N*-(4-Trifluoromethylbenzyl)cinchoninium bromide



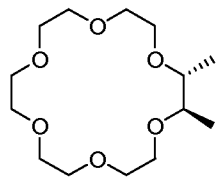
11 *O*,*O'*-Diallyl-*N*,*N'*-(2,7-naphthalenediyldimethyl) bis(hydrocinchonidinium) dibromide



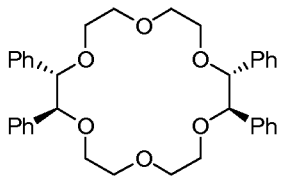
12 (11b*S*)-4,4-Dibutyl-4,5-dihydro-2,6-bis-(3,4,5-trifluorophenyl)-3*H*-dinaphth[2,1-*c*:1',2'-*e*]azepinium bromide



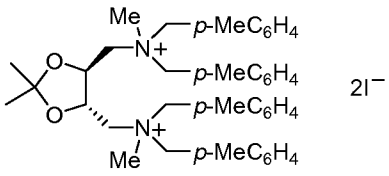
13 *Nα*-BOC-*Nε*-(2-chloro-Z)-D-lysine



14 (2*R*,3*R*)-2,3-Dimethyl-1,4,7,10,13,16-hexoxacyclooctane



15 (2*R*,3*R*,11*R*,12*R*)-2,3,11,12-Tetraphenyl-1,4,7,10,13,16-hexoxacyclooctane



16 (4*S*,5*S*)-*N*,*N*,*N'*,*N'*-tetrakis[(4-m4thoxyphenyl)methyl]2,2-dimethyl1,3-dioxolane-4,5-dimethanine

Table 2: Results obtained for the reaction of Et-ene-malonate with NaCN or KCN in a two-phase solvent system of water and toluene or dichloromethane.

	% ee *R* or *S*			
Catalyst	**PhMe/NaCN**	**PhMe/KCN**	**DCM/NaCN**	**DCM/KCN**
1	4 *S*	12 *S*	2 *S*	5 *S*
2	4 *R*	4 *S*	8 *S*	4 *S*
3	14 *R*	14 *S*	No reaction	No reaction
4	10 *R*	2 *S*	2 *R*	10 *R*
5	14 *R*	6 *S*	14 *S*	10 *S*
6	10 *S*	14 *S*	6 *S*	6 *R*
7	10 *R*	8 *R*	14 *S*	5 *S*
8	2 *R*	4 *S*	4 *S*	8 *S*
9	0 -	12 *R*	12 *R*	13 *S*
10	4 *S*	2 *R*	13 *S*	12 *S*
11	4 *R*	0 -	8 *R*	8 *R*
12	6 *S*	4 *S*	2 *S*	0 -
13	2 *S*	16 *S*	4 *S*	0 -
14	4 *S*	2 *S*	No reaction	1 *S*
No catalyst			No reaction	No reaction
$BzEt_3NCl$			No reaction	No reaction

Except where noted, full conversion of Et-ene-malonate to CNDE was observed.

Example 2

Effect of stoichiometric quantities of catalyst

The procedure of Example 1 was used, except that KCN was used as the cyanide source, the catalyst was used in stoichiometric quantities and dichloromethane was used as the organic solvent. The conversion of Et-ene-malonate to CNDE was determined by ^1H NMR and the ee of CNDE was measured by chiral HPLC.

Table 3: Effect of using a stoichiometric quantity of catalyst on the extent of conversion of Et-ene-malonate and enantiomeric excess of the *R* or *S* enantiomer obtained

Catalyst	% conversion	% ee *R* or *S*
1	96	10 *R*
2	100	13 *S*
3	12	-
4	100	8 *S*
5	100	4 *S*
6	100	14 *R*
7	100	3 *S*
8	100	9 *R*
9	100	10 *S*
10	100	26 *S*
13	trace	-
14	0	-

Example 3

Effect of solvent on the enantiomeric excess of the *R* or *S* enantiomer obtained

The procedure of Example 1 was used, except that KCN was used as the cyanide source and the organic solvent was varied according to the table below. The ee of CNDE was measured by chiral HPLC.

Table 4: Effect of solvent on the enantiomeric excess of the *R* or *S* enantiomer obtained

	% ee *R* or *S*				
Catalyst	**MTBE**	**2-Me-THF**	**PhCl**	**^{t}amylOH**	**Diethyl ketone**
1	10 *R*	2 *R*	7 *R*	6 *R*	4 *R*
2	14 *S*	9 *S*	11 *S*	8 *S*	18 *S*

4	14 *S*	4 *R*	16 *R*	12 *S*	5 *R*
5	7 *R*	7 *R*	10 *R*	10 *S*	4 *R*
6	6 *R*	3 *R*	8 *R*	3 *R*	5 *R*
7	4 *S*	3 *R*	10 *R*	12 *S*	8 *R*
8	12 *R*	6 *R*	4 *R*	4 *R*	5 *R*
9	10 *S*	3 *S*	8 *R*	14 *S*	11 *S*
10	11-28 *S*	3 *S*	14 *S*	19-26 *S*	15 *S*
11	12-20 *R*	6 *R*	9 *R*	-	-
12	2 *S*	2 *S*	-	-	-

Example 4

Effect of solvent on reactions catalysed by catalyst 10

The procedure of Example 3 was used on a scale of 200 mg Et-ene-malonate. NaCN was used as the cyanide source and the catalyst used was *N*-(4-trifluoromethylbenzyl)cinchonininium bromide (catalyst **10**, 0.2 eq).

Table 5: Effect of solvent on the enantiomeric excess of the *R* or *S* enantiomer obtained with catalyst **10**

Solvent	% yield of R-CNDE	% yield of S-CNDE	% ee *S*
No organic solvent added	12.9	25.7	11-20
t-Amyl Alcohol	22.7	25.3	6
3-Pentanol	29.2	33.6	7
MEK	18.6	24.6	10-14
DEK	24.1	29.7	11-18
n-Butanol	18.6	24.6	9-13
isobutanol	15.3	16.9	4

Example 5

Addition of proton source

The procedure of Example 1 was used, except that KCN was used as the cyanide source, and the organic solvent was varied according to the table below. The catalyst used was *N*-(4-trifluoromethylbenzyl)cinchonininium bromide (catalyst **10**,

0.2 eq). A stoichiometric quantity of 1-octanol was also added to the reaction mixture. The reactions were repeated several times on a scale of 20 mg of Et-ene-malonate, also carried out in duplicate on 200 mg Et-ene-malonate, giving S-CNDE of 23% and 33% ee. The ee of CNDE was measured by chiral HPLC.

Table 6A: Effect of addition of 1-octanol on the enantiomeric excess of the *R* or *S* enantiomer obtained

	% ee *S*	
Solvent	**20 mg Scale**	**200 mg Scale**
CH_2Cl_2	38	Reaction not carried out
MTBE	27-47	23-33
2-Me-THF	26-39	Reaction not carried out
PhCl	no product	Reaction not carried out

Example 6

Effect of catalyst loading when 2-octanol is added as a proton source

The procedure of Example 1 was used, with 0.2 g Et-ene-malonate, 1.1 eq of NaCN, 4 mL of MTBE, 12 mL H_2O, 1 eq of 2-octanol being employed. The mol% of catalyst, *N*-(4-trifluoromethylbenzyl)cinchonininium bromide (catalyst **10**) was varied according to the Table below.

Table 6B: Effect of addition of 2-octanol on the enantiomeric excess of the *S* enantiomer obtained

Catalyst loading (mol%)	% yield of *R*-CNDE	% yield of *S*-CNDE	% ee *S*
5	29.1	40.2	16
5	29.3	39.1	16
10	30.3	41.6	16
10	30.0	41.9	16
20	25.4	36.5	18
20	21.8	31.3	17

20	26.4	36.5	16

Example 7

Effect of water content

The procedure of Example 1 was used on a scale of 200mg of Et-ene-malonate. NaCN (1.1 eq.) was used as the cyanide source, and MTBE (4 mL) was used as the solvent. The catalyst used was *N*-(4-Trifluoromethylbenzyl)cinchonininium bromide (0.2 eq.). The level of water was varied according to the table below.

Table 7: Effect of water content

H_2O content	% yield of R-CNDE	% yield of S-CNDE	% ee *R*/*S*
1000 ppm	38.0	36.6	0
53 eq	34.8	47.2	15 *S*
127 eq	34.2	47.1	16 *S*
173 eq	31.1	44.7	18 *S*
667 eq	27.6	40.1	18 *S*
1132 eq	23.3	32.3	16 *S*
30 wt%*	46.4	42.7	0
100 wt%*	40.8	38.2	0
25 wt % aqeous NaCN	38.2	38.8	0
Saturated NaCN	48.1	45.6	0

* weight% based on weight of NaCN

As Table 7 indicates, the e.e. increases to a maximum of ~18% with increasing water level.

More concentrated cyanide solutions and solid sodium cyanide appear to give racemic product. R-CNDE was exposed to conditions simulating 50% reaction with 1000 ppm water (i.e. 0.6 eq of NaOH and 0.6 eq of NaCN). After 22 h GC analysis showed no erosion of e.e.

Example 8

Effect of temperature

The procedure of Example 1 was used to investigate the effect of temperature. The catalyst used was *N*-(4-trifluoromethylbenzyl)cinchonininium bromide (catalyst **10**, 0.2 eq.). The temperature at which the reaction was carried out varied according to the table below. Each reaction was carried out in duplicate using 200mg Et-ene-malonate, 1.1 eq of NaCN and 20 mol% catalyst, 12mL water and 4mL MTBE.

Table 8: Effect of temperature

Run	T (ºC)	% yield of R-CNDE	% yield of S-CNDE	% ee *S*
1	22	27.6	39.4	17
2	22	27.6	39.7	18
3	10	27.4	38.5	16
4	10	27.6	38.8	16
5	0	24.1	33.3	16
6	0	28.6	38.6	15.5

Example 9

Effect of increasing the amount of NaCN

The procedure of Example 1 was used to investigate the effect of using 1.5 eq NaCN. The catalyst used was *N*-(4-trifluoromethylbenzyl)cinchonininium bromide (catalyst **10**, 0.1 eq.). The reaction was carried out using 200 mg Et-ene-malonate and MTBE (4 mL) as the organic solvent.

The above experiment was repeated, using identical conditions, with the exception that 1 eq. of 1-octanol is used as a proton source.

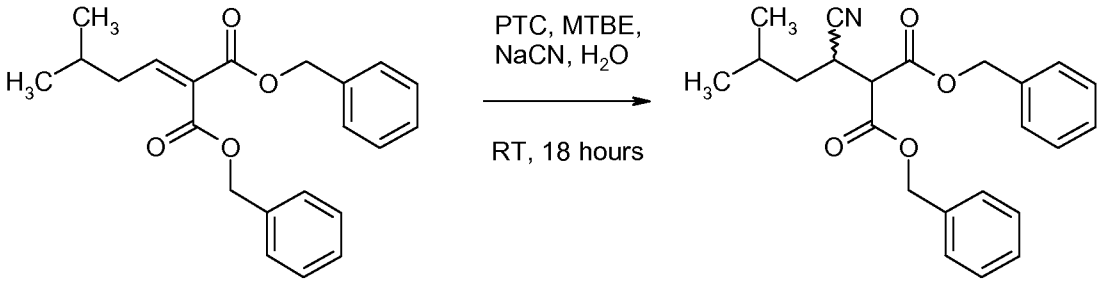
Table 9: Effect of using 1.5 eq of NaCN

Number of eq. of 1-octanol used	% yield of *R*-CNDE	% yield of *S*-CNDE	% ee *S*
1.0	31.8	44.2	16
1.0	33.5	45.4	15
0	36.0	51.0	16
0	37.1	51.1	16

An increase in the number of equivalents of NaCN resulted in higher conversion to both the *R* and *S*-enantiomers of CNDE.

Example 10

General procedure for the hydrocyanation of dibenzyl 2-(3-methylbutylidene)-malonate (Bn-ene-malonate)



Bn-ene-malonate Bn-CN-malonate

Dibenzyl 2-(3-methylbutylidene)malonate (Bn-ene-malonate) (0.15 g, 0.426 mmol, 1 eq) and the PTC (0.021 mmol, 0.05 eq) were weighed out into a vial and were slurried with MTBE (1.8 ml). NaCN (0.031 g, 0.638 mmol, 1.5 eq) was dissolved in water (5.4 mL) and was added. The mixture was vigorously stirred overnight. The layers were allowed to stand and separate. 50 µL of the organic layer was then removed and was diluted with 1.5 mL IPA for HPLC analysis. To obtain a clean reference sample of the product, the product was purified *via* column chromatography with a gradient from 9:1 to 8:2 CyH/ether (TLC: 8:2 CyH/EtOAc, R_f SM= 0.4, R_f Prod= 0.3, UV, $KMnO_4$).

The following chiral HPLC assay was used.

Column: Daicel OJ-H 4.6 mm x 25 cm column + guard
Solvent A: Heptane
Solvent B: Ethanol
Injection : 5 µl
Column temperature: ambient
Detection: 220 nm (bandwidth 8)
Program: Isocratic 85:15 A:B
Flow rate: 1 ml/min

Retention times	
Benzylalcohol	6.1 min
Bn-ene-malonate	13.5 min
Bn-CN-malonate peak 1	15.8 min
Bn-CN-malonate peak 2	17.8 min

Example 11 (for reference only)

Racemic dibenzyl 2-(1-cyano-3-methylbutyl)malonate (Bn-CN-malonate)

The procedure of Example 10 was used to obtain dibenzyl 2-(1-cyano-3-methyl-butyl)malonate as a racemate by using *n*Bu_4NBr as the catalyst. The reaction did not go to completion. However, the product was obtained clean after chromatography.

^{1}H-NMR ($CDCl_3$) 300 MHz: δ (ppm) 0.89 (6H, t, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$), 1.17 – 1.12 – 1.24 (1H, m, CH_2), 1.53 – 1.65 (1H, m, CH_2), 1.78 – 1.92 (1H, m, $C\underline{H}(CH_3)_2$), 3.26 – 3.36 (1H, m, CHCN), 3.64 (1H, d, *J* = 8.1 Hz, $C\underline{H}CHCN$), 5.15 – 5.24 (4H, m, CH_2Ph), 7.25 – 7.40 (10H, m, Ph).

^{13}C-NMR (CDCl3) 75 MHz: δ (ppm) 20.8 (CH_3), 23.0 (CH_3), 26.0 (CH), 29.4 (CH), 38.5 (CH_2), 53.8 (CH), 68.0 (CH_2), 68.1 (CH_2), 119.2 (CN), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.6 (CH), 128.7 (CH), 134.5 (C), 134.6 (C), 165.8 (CO), 165.9 (CO).

Example 12

Effect of dilution on the hydrocyanation of Bn-ene-malonate using PTC 10 (see Table 1)

The procedure of Example 10 was used, using *N*-(4-trifluoromethylbenzyl)-cinchonininium bromide (catalyst **10**, 0.051 eq.) as the phase transfer catalyst (PTC). The amounts of MTBE and water were varied according to Table 11.

Table 11: Dilution effects on conversion of Bn-ene-malonate and ee obtained with PTC 10

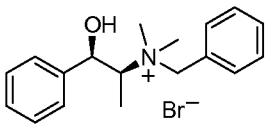
Entry	Volume of MTBE (ml/g substrate)	Volume of Water (ml/g substrate)	% ee	% Bn-ene-malonate remaining (calibrated at 220 nm)
A	12	36	13	53
B	5	36	13	45
C	5	12	9	34
D	12	12	10	56
E	12	60	14	61
F	36	36	11	69

Example 13

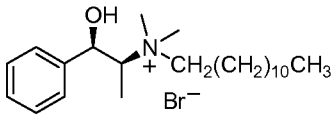
Hydrocyanation of Bn-ene-malonate using various phase transfer catalysts

The procedure of Example 12 was used. The PTC was varied according to Table 12, the numbering used for the various catalysts is the same as that used in Table 1, with the exception of PTC 17, 18 and 19, which do not appear in Table 1. Entry A in Table 11 gives details of the amounts of MTBE and water which were used.

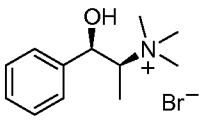
Table 13:Catalysts used in the hydrocyanation of Bn-ene-malonate



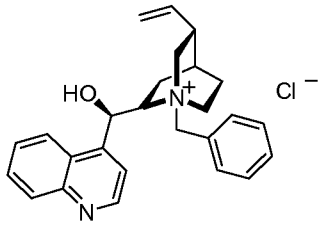
1 (-)-*N*-Benzyl-*N*-methylephedrinium bromide



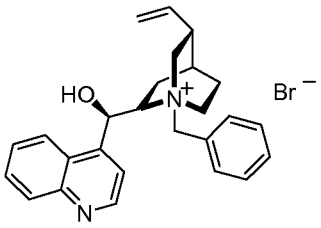
2 (-)-*N*-Dodecyl-*N*-methylephedrinium bromide



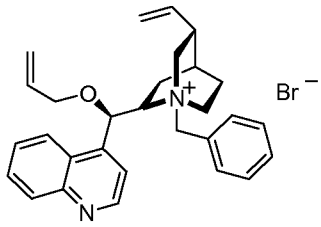
3 (-)-*N*,*N*-Dimethylephedrinium bromide



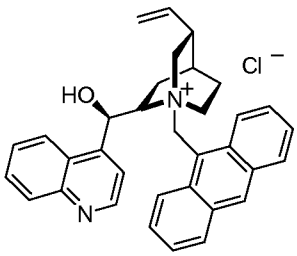
4 *N*-Benzylcinchonidinium chloride



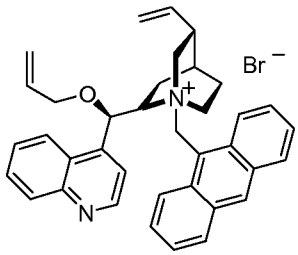
5 *N*-Benzylcinchonidinium bromide



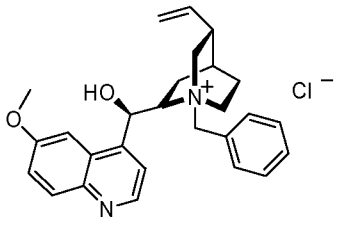
6 *O*-Allyl-*N*-benzylcinchonidinium bromide



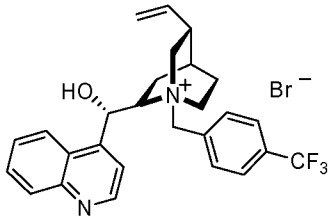
7 *N*-(9-Anthracenylmethyl)cinchonidinium chloride



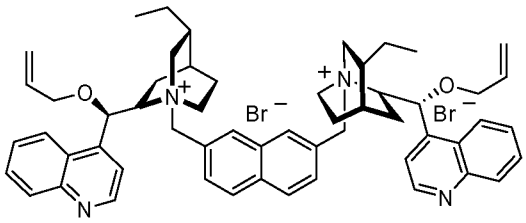
8 *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide



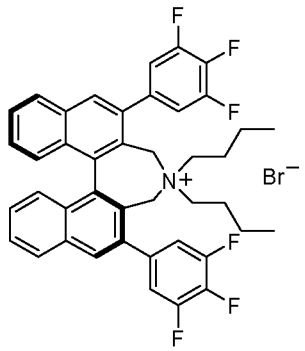
9 *N*-Benzylquininium chloride



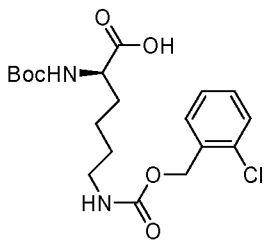
10 *N*-(4-Trifluoromethylbenzyl)cinchoninium bromide



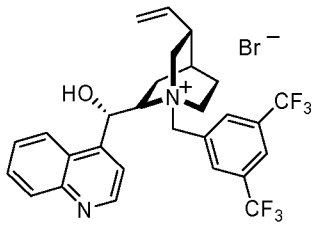
11 *O*,*O'*-Diallyl-*N*,*N'*-(2,7-naphthalenediyldimethyl) bis(hydrocinchonidinium) dibromide



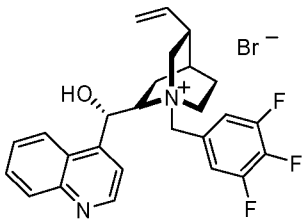
12 (11b*S*)-4,4-Dibutyl-4,5-dihydro-2,6-bis-(3,4,5-trifluorophenyl)-3*H*-dinaphth[2,1-*c*:1',2'-*e*]azepinium bromide



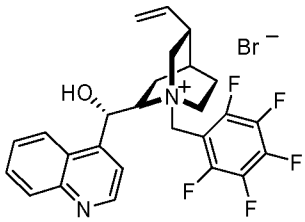
13 *Nα*-BOC-*Nε*-(2-chloro-Z)-D-lysine



17 *N*-(3,5-Bistrifluoromethylbenzyl)cinchoninium bromide



18 *N*-(3,4,5-trifluorobenzyl)cinchoninium bromide



19 *N*-(2,3,4,5,6-pentafluorobenzyl)cinchoninium bromide

Table 14: ee values obtained with various catalysts

PTC used (see Table 13 for reference)	% ee of Bn-CN malonate product
1	0
2	3
3	23
4	13
5	13
6	8
7	14
8	10
9	7
10	12
11	5
12	5
13	23
17	16
18	9
19	17

Overall, with the exception of PTC 11, none of the reactions went to completion and some hydrolysis, whereby benzyl alcohol was formed, was always observed. Figure 4 shows values obtained for the amounts of benzylalcohol, Bn-ene-malonate (the starting material) and Bn-CN-malonate obtained. These values are derived from three separate concentration calibrations for benzylalcohol, Bn-ene-malonate and Bn-CN-malonate. Consequently there is quite a margin for error in combining three calibrations as well as the fact that the phase separation in the reactions made sampling difficult, hence some % values will be overestimated. In cases where there was little conversion, the % ee may also not be an accurate reflection of the actual % ee obtained. As shown in Table 12 and Figure 4, the chinchonidinium catalysts were the slightly more selective set of PTC agents used.

Example 14

Hydrocyanation of Et-ene-malonate with PTCs 17, 18 and 19.

Et-ene-malonate (0.1 g, 0.438 mmol, 1 eq) and PTC 17, 18 or 19 (see Table 13) (0.024 mmol, 0.05 eq) were weighed out into a vial and were slurried with MTBE (2 mL). NaCN (0.032 g, 0.657 mmol, 1.5 eq) was dissolved in water (6 mL) and was added. The mixture was vigorously stirred overnight. The layers were allowed to stand and separate and then about 50 µL of the organic layer was removed and was diluted with about 1 mL IPA for HPLC analysis, which was carried out using the HPLC assay described in Example 1. The results obtained are summarised in Table 15.

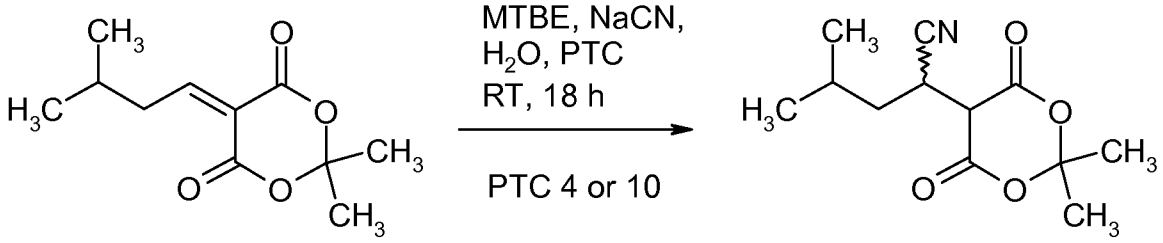
The conversions obtained from these reactions were not calibrated. In the cases of fluorobenzenes PTC 18 and PTC 19, white powder was clearly visible in the reaction mixture and these catalysts did not seem to be soluble. PTC17 was the most soluble catalyst.

Table 15: results obtained for hydrocyanation of Et-ene-malonate with PTCs 17, 18 and 19.

PTC	% ee *S*	% Et-ene-malonate remaining(uncalibrated at 220 nm)
17	23	83
18	17	92
19	17	96

Example 16

Hydrocyanation of MA-ene-malonate using PTC 4 or 10



MA-ene-malonate MA-CN-malonate

MA-ene-malonate (Preparation 2; 0.2 g, 0.94 mmol, 1 eq) and the PTC (0.094 mmol, 0.1 eq) were weighed out into a vial and were slurried with MTBE (4 mL). NaCN (0.07 g, 1.41 mmol, 1.5 eq) was dissolved in water (12 mL) and was added. The mixture was vigorously stirred overnight. The mixture was then acidified to pH 1 with 1M aqueous HCl and the product was extracted out with DCM (3 x 5 ml). The organic layer was dried over Na_2SO_4, filtered (a sample was removed for HPLC analysis) and the solvent was removed *in vacuo*.

The following chiral HPLC assay was used.

Column: Daicel AD-H 4.6 mm x 25 cm column + guard
Solvent A: Heptane (0.1% TFA)
Solvent B: Propan-2-ol (0.1% TFA)
Injection : 10 µl
Oven temperature: 20 °C
Detection: 220 nm (bandwidth 8)
Program: Isocratic 80:20 A:B
Flow rate: 1 ml/min

Retention times

MA-ene-malonate	4.68 min
MA-CN-malonate peak 1	5.76 min
MA-CN-malonate peak 2	6.46 min

HPLC analysis showed that the product isolated was racemic. No trace of the starting material was observed in the ^{1}H-NMR spectrum.

2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-4-methyl-pentanenitrile

^{1}H-NMR ($CDCl_3$) 300 MHz: δ (ppm) 0.99 (6H, dd, J = 6.6 Hz, J = 3.6 Hz, $CH(C\underline{H}_3)_2$), 1.17 – 1.28 (1H, m, CH_2), 1.78 (3H, s, $C(CH_3)_2$), 1.83 (3H, s, $C(CH_3)_2$), 1.80 – 1.96 (1H, m, $C\underline{H}(CH_3)_2$), 1.98 – 2.11 (1H, m, CH_2), 3.58 – 3.66 (1H, m, CHCN), 3.99 (1H, d, J = 2.6 Hz, $C\underline{H}CHCN$).

^{13}C-NMR ($CDCl_3$) 75 MHz: δ (ppm) 20.9 (CH_3), 22.9 (CH_3), 26.4 (CH), 26.6 (CH_3), 27.3 (CH), 28.2 (CH_3), 37.2 (CH_2), 48.0 (CH), 106.0 (C), 119.1 (CN), 162.2 (CO).

Example 17

Effect of buffering on the hydrocyanation of MA-ene-malonate using PTC 10

The procedure of Example 16 was used, with the exception that the aqueous layer was buffered. The reactions were also run in DCM instead of MTBE, as the poor solubility of the product makes it difficult to handle in MTBE. It is to be noted that since the product is very acidic and the reaction generates NaOH, the final pH differs form the pH of the buffer solution used as follows:

Table 16: Final pH obtained for the buffered hydrocyanation of MA-ene-malonate with PTC 10

Buffer used	Initial pH of buffer	Final pH of aqueous layer
Sodium phosphate	2.76	6.36
Ammonium acetate	5.14	8.61
Sodium phosphate	7.00	9.44
Sodium carbonate	9.32	9.35
Sodium phosphate	11.38	10.15

In each case the ee measured was <12%. NMR analysis indicated that the reactions went to completion.

Example 18

Hydrocyanation of MA-ene-malonate with solid NaCN in the absence of water, using PTC 10

The procedure of Example 16 was used. Water was not used; instead, amyl alcohol was used as a solvent. The NaCN was also used as a solid, rather than as an aqueous solution.

The product obtained was racemic.

Example 19

Solid phase NaCN reactions in various NMR solvents

The procedure of Example 18 was used. The reaction was run in various NMR solvents in the absence or presence of a PTC, as detailed in Table 17. After overnight stirring, NMR was used to determine whether conversion had occurred. The samples were acidified and a sample taken for HPLC analysis. The results are summarised in Table 17.

Table 17: Results obtained for the catalysed and uncatalysed hydrocyanation of MA-ene-malonate with solid NaCN

Entry	Solvent*	PTC	% conversion of starting material (as determined by NMR analysis)	% ee (as determined by HPLC analysis)
1	$CDCl_3$	None	0 (filtered)	N/A
2	$CDCl_3$	1	N/A	0
3	$CDCl_3$	2	N/A	0
4	$CDCl_3$	5	N/A	5
5	$CDCl_3$	6	N/A	4
6	$CDCl_3$	10	100 (filtered)	13
7	$CDCl_3$	17	N/A	9
8	MeCN-D_3	None	100	N/A
9	MeCN-D_3	10	100	13
10	Acetone-D_6	None	100	N/A
11	Acetone-D_6	10	100	0

* The reactions run in $CDCl_3$ had to be filtered before NMR analysis could take place.

Example 20

Effect of solvent on the enantiomeric excess obtained in the hydrocyanation of MA-ene-malonate with various chiral PTCs

To MA-ene-malonate (25mg) was added, the PTC (0.2 eq) and organic solvent (5mL/g), as detailed in Table 22. NaCN was added (1.1 eq in 15mL/g water). The reaction was stirred overnight at room temperature.

The organic phase was sampled, diluted with ethanol and analysed by chiral HPLC. A 12 min isocratic method using 80/20/0.1 heptane/IPA/TFA on a 250x4.6 Chiralpak AD-H column was used.

The enantiomeric excesses observed are tabulated below:

Table 22: Effect of solvent on the enantiomeric excess obtained in the hydrocyanation of MA-ene-malonate with various chiral PTCs

ee (%)[a]	DCM	Toluene	MIBK	TBME	nBuOAc	t-amyl-OH
PTC 1	3	Gum	2	n/a	7	2
2	2	4	6	3	4	1
3	1	n/a	4	n/a	0	2
4	3	Ppt	6	Gum	2	2
5	5	Ppt	5	Gum	4	1
6	2	-8	3	Gum	2	0
7	20	Gum	17	Gum	Gum	12
8	-4	Gum	-1	Gum	-4	-4
9	10	Gum	5	Gum	6	3
10	n/a	-29 (Gum)	n/a	Gum	n/a	n/a
none	n/a	n/a	n/a	n/a	n/a	3

[a] Enantiomeric excess of the product. Positive ee represents preference for the faster eluting enantiomer by HPLC. “n/a” indicates poor HPLC – either very weak or impurities overlapping product peaks

Gumming was seen in most reactions where toluene or TBME was used. As such the HPLC results were considered unrepresentative of the reaction, and in most

cases were poor. The precipitates formed in toluene/PTC4 and in toluene/PTC5 were isolated and also analysed, but did not show significant enrichment of either isomer.

Selectivity was generally low (<10%ee), although PTC 7 performed consistently well, with 12-20% ee in DCM, MIBK and t-amyl alcohol.

PTC 10 gave good selectivity (-29%) in toluene, although a gum also formed. Unfortunately due to a co-running peak, analysis in other solvents was not possible.

PTC 8 was the only other catalyst to give enrichment of the later running peak by HPLC – although this was only up to 4% ee.

Examples 21 to 23 relate to the cyanohydrin method.

Example 21

Conversion of sulfonate ester to S-CNDE

The following general method was used to investigate the effect of variations in the reaction conditions.

Base (1.5eq), solvent (4mL) and diethylmalonate (1.5eq) were stirred at rt for 5 mins. A solution of sulfonate (1.0eq) in solvent (1mL) was added and the reaction was heated to set temperature (jacket temp). The reaction was allowed to stir overnight. After 18hr the reaction was cooled to rt and analysed for formation of diethyl *S*-2-(1-cyano-3-methylbutyl)malonate.

Example 21(A)

Mesylate / Room Temperature

Following the general procedure outlined above, (1*S*)-1-cyano-3-methylbutyl methanesulfonate (Preparation 5) was reacted with diethyl malonate at room temperature using different bases and solvents. The reactions were sampled for gc analysis and were not worked-up. Consequently there is no yield data and the results obtained are qualitative.

Base: NaH

Solvent:

MeCN	16% conversion, 77.1%ee CNDE, 66.3%ee mesylate
DME	35.4% conversion, 88.0%ee CNDE, 75.9%ee mesylate
Me-THF	27.2% conversion, 92.8%ee CNDE, 89.0%ee mesylate
MTBE	11.7% conversion, 86.8%ee CNDE, 90.5%ee mesylate
DMF	0% conversion, 93.8%ee mesylate

Base: LiH

Solvent:

MeCN	4.5% conversion, 20.4%ee CNDE, 92.3%ee mesylate
DME	6.7% conversion, 20.0%ee CNDE, 92.7%ee mesylate
Me-THF	2.5% conversion, 20.0%ee CNDE, 95.3%ee mesylate

Base: Cs_2CO_3

Solvent:

MeCN	71.6% conversion, 24.0%ee CNDE, 9.5%ee mesylate
DME	71.0% conversion, 59.6%ee CNDE, 15.3%ee mesylate
Me-THF	23.0% conversion, 85.2%ee CNDE, 68.0%ee mesylate

Base: K_2CO_3

Solvent:

MeCN	0% conversion, no loss in ee of mesylate
DME	0% conversion, no loss in ee of mesylate
Me-THF	0% conversion, no loss in ee of mesylate

Base: $CaCO_3$

Solvent:

MeCN	0% conversion, no loss in ee of mesylate
DME	0% conversion, no loss in ee of mesylate
Me-THF	0% conversion, no loss in ee of mesylate

Example 21(B)

Mesylate / Reflux

Following the general procedure outlined above, (1*S*)-1-cyano-3-methylbutyl methanesulfonate (Preparation 5) was reacted with diethyl malonate at reflux using different bases and solvents.

Base: NaH

Solvent:

MeCN	Full conversion by NMR, 19.2% ee
DME	Full conversion by NMR, 49.9% ee
Me-THF	~90% conversion by NMR, 52.5% ee
MTBE	61.7% conversion, 71.5%ee CNDE, 68.7%ee mesylate
THF / Toluene	55.2% conversion, 70.7%ee CNDE, 68.9%ee mesylate
DMF	100% conversion, 29.1%ee CNDE

Base: Cs_2CO_3

Solvent:

MeCN	Full conversion by NMR, 19.1% ee
DME	Full conversion by NMR, 21.1% ee
Me-THF	Full conversion by NMR, 35.9% ee
EtOAc	Full conversion by NMR, 18.7% ee
MEK	Full conversion by NMR, 9.2% ee

Base: K_2CO_3

Solvent:

MeCN	7.0% conversion, 72.3%ee CNDE, 63.1%ee mesylate
DME	24.5% conversion, 80.2%ee CNDE, 77.1%ee mesylate
Me-THF	11.1% conversion, 86.8%ee CNDE, 87.9%ee mesylate

Base: $CaCO_3$

Solvent:

MeCN	0% conversion, no loss in ee of mesylate

DME	0% conversion, no loss in ee of mesylate
Me-THF	0% conversion, no loss in ee of mesylate

Base: LiH

Solvent:

MeCN	32.5% conversion, 54.0%ee CNDE, 84.0%ee mesylate
DME	58.5% conversion, 71.0%ee CNDE, 85.0%ee mesylate
Me-THF	35.0% conversion, 58.7%ee CNDE, 84.0%ee mesylate

Example 21(C)

4-Nosylate

Following the general procedure outlined above, (1*S*)-1-cyano-3-methylbutyl 4-nitrobenzenesulfonate (Preparation 6) was reacted with diethyl malonate at different temperatures using different bases and solvents.

Base: NaH

Solvent / Temperature:

DME / RT	~90% conversion, 94% ee
DME / 50°C	100% conversion, 94.6% ee
DME / 85°C	~80% conversion, 92.4% ee
Me-THF / RT	~90% conversion, 93.2% ee
Me-THF / 50°C	~99% conversion, 92.0% ee
THF / 50°C	~35% conversion, 94.0% ee
THF/toluene 50°C	~60% conversion, 91.2% ee

Base: Cs_2CO_3

Solvent / Temperature:

DME / 50°C	100% conversion, 91.8%
THF / 50°C	100% conversion, 92.0%

Due to the high chiral purity of the THF/NaH conditions the reaction was scaled up giving approximately an 80% conversion and a chiral purity of 94% over a two day reaction. There was no loss in chirality using the nosylate starting material.

Example 21(D)

4-Chlorobenzenesulfonate

Following the general procedure outlined above, (1*S*)-1-cyano-3-methylbutyl 4-chlorobenzenesulfonate (Preparation 9) was reacted with diethyl malonate at different temperatures using different bases and solvents.

Base: NaH

Solvent / Temperature:

MeCN / 50°C	~24% conversion, 93.1% ee
DME / 50°C	~57% conversion, 94.8% ee
THF / 50°C	~96% conversion, 90.0% ee
THF / reflux	92% conversion, 89.5% ee

Base: Cs_2CO_3

Solvent / Temperature:

MeCN / 50°C	~75% conversion, 70.5% ee
DME / 50°C	~81% conversion, 84.0% ee
THF / 50°C	~95% conversion, 88.3% ee
THF / reflux	100% conversion, 86.5% ee

Example 21(E)

4-Bromobenzenesulfonate

Following the general procedure outlined above, (1*S*)-1-cyano-3-methylbutyl 4-bromobenzenesulfonate (Preparation 8) was reacted with diethyl malonate at different temperatures using different bases and solvents.

Base: NaH

Solvent / Temperature:

MeCN / 50°C	~49% conversion, 92.6% ee
DME / 50°C	~56% conversion, 94.0% ee
THF / 50°C	~80% conversion, 92.7% ee
THF / reflux	100% conversion, 89.0% ee

Base: Cs_2CO_3

Solvent / Temperature:

MeCN / 50°C	~58% conversion, 80.0% ee
DME / 50°C	~83% conversion, 85.8% ee
THF / 50°C	~90% conversion, 91.1% ee
THF / reflux	100% conversion, 89.0% ee

Example 21(F)

Tosylate

Following the general procedure outlined above, (1*S*)-1-cyano-3-methylbutyl 4-toluenesulfonate (Preparation 7) was reacted with diethyl malonate at different temperatures using different bases and solvents.

Base: NaH

Solvent / Temperature:

DME / 50°C	~45% conversion, 89.5% ee
THF / 50°C	~55% conversion, 90.0% ee
THF / reflux	~70% conversion, 87.4% ee
Me-THF / 50°C	~33% conversion, 88.9% ee
MeCN / 50°C	~35% conversion, 92.0% ee
MTBE / 50°C	~21% conversion, 84.4% ee

THF/Toluene / 50°C	~44% conversion, 92.5% ee

Base: Cs_2CO_3

Solvent / Temperature:

DME / 50°C	~46% conversion, 84.5% ee
Me-THF / 50°C	~39% conversion, 89.9% ee
THF / reflux	~82% conversion, 81.0% ee

A further set of screening reactions was carried out using 2.5eq of sodium hydride and 2.6eq of diethyl malonate at 50°C.

Solvent:

DME	~95% conversion, 83.7% ee
THF	~81% conversion, 86.7% ee
Me-THF	~50% conversion, 90.5% ee
MeCN	~62% conversion, 60.0% ee
MTBE	~50% conversion, 61.0% ee
THF/Toluene	~59% conversion, 92.5% ee

A further set of screening reactions was carried out using increasing amounts of sodium hydride in THF at reflux.

Equivalents of NaH:

2.0	~85% conversion, 86.0% ee
2.5	~95% conversion, 83.2% ee
3.0	~96% conversion, 86.1% ee

Example 22

Diethyl (*S*)-2-(1-cyano-3-methylbutyl)malonate (Preparative scale)

Diethylmalonate (43.0g, 0.268moles, 1.6eq) was added to a slurry of sodium hydride (10.1g, 60% w/w, 0.251moles, 1.5eq) in dry THF (650mL) at ambient

temperature over a period of approximately 15 minutes. The slurry was stirred at ambient temperature for approximately 15 minutes. A solution of 2-nosylate cyanohydrin (50g, 0.168moles) in dry THF (50mL) was added and the reaction was heated to reflux and stirred for 3 hours. The reaction was allowed to stir to ambient temperature overnight. The reaction mixture was evaporated at <50°C and the orange residue was partitioned between MTBE (700mL) and water (700mL) and the two phases were separated. The organic phase was washed with water (700mL), dried over $MgSO_4$ and evaporated to give diethyl (S)-2-(1-cyano-3-methylbutyl)malonate as an orange oil.

Yield 57g, 133% weight yield, 95.4% ee by chiral GC.

Assay by ^{1}H NMR 50.6% w/w, 67% contained yield assuming 100% w/w 2-nosylate cyanohydrin. Structure was confirmed by ^{1}H NMR.

Example 23

Dimethyl (*S*)-2-(1-cyano-3-methylbutyl)malonate

Following the general method of example 21, (1*S*)-1-cyano-3-methylbutyl 4-toluenesulfonate (Preparation 7) was reacted with different amounts of dimethyl malonate in the presence of sodium hydride in THF.

Equivalents of dimethyl malonate:

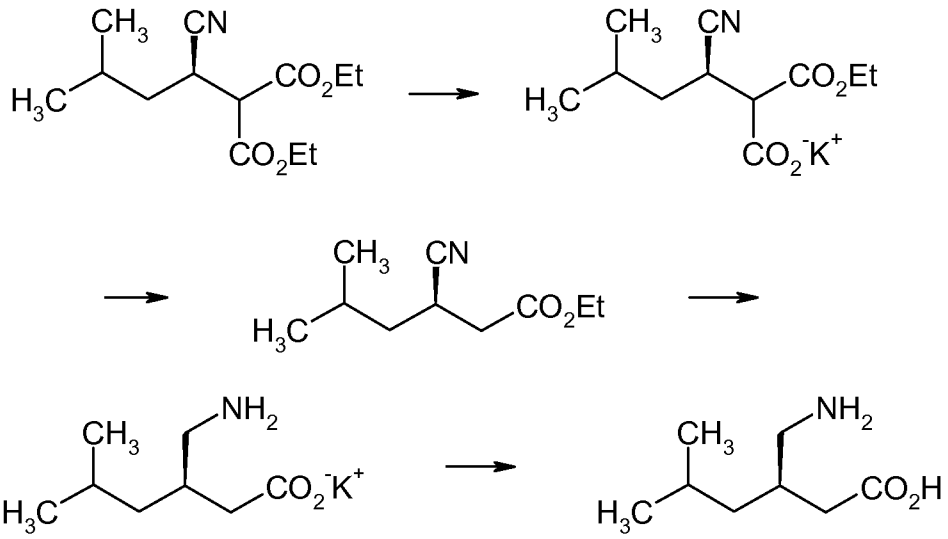
1.6	~41% conversion, 86.4% ee
2.1	~77% conversion, 82.2% ee
2.6	~95% conversion, 80.6% ee
3.1	~95% conversion, 82.0% ee

Example 24

Conversion of enantiomerically enriched CNDE into Pregabalin

Since *R*-CNDE was available in large quantities the process for converting enantiomerically enriched CNDE into Pregabalin was optimized using this material rather than *S*-CNDE. Accordingly, the procedure set out below provides the enantiomer of Pregabalin (*ent*-Pregabalin). It will be understood that results

obtained with one enantiomeric series are expected to be reproduced in the antipodal series.



a) Potassium (3*R*)-3-cyano-2-ethoxycarbonyl-5-methylhexanoate (CNDE-monoacid)

R-CNDE (85% ee, 88.02% w/w, 405.6g, 357g active, 1.4mol) was charged to a 3L 3-neck flask fitted with overhead stirring (600 rpm), pH probe and titrando dosing unit. Ethanol (420mL, 331.8g) was added and the solution was cooled to <2°C in an ice/water bath. Precooled aqueous KOH (8.8% w/w, 980g, 1.54 mol, 1.1 eq) was added dropwise to the solution (rate of addition = 15mL/min) over a period of 65 mins. During this period the temperature of the mixture rose from 1.4°C to 9.2 °C. The pH at end of the addition was 14.12. The reaction was allowed to stir overnight in an ice/water bath, warming slowly to room temperature. The pH profile of the reaction was recorded on a titrino data logger. Toluene (350mL) was added to the reaction mixture after 14 hr. The reaction was stirred for 15 minutes. Stirring was switched off and the reaction was allowed to settle for 15 minutes. The toluene layer was removed via siphon. This process was repeated for two more toluene extractions (350mL, 150mL). The remaining aqueous/ethanol phase was weighed and analysed by HPLC for w/w analysis of monoacid. This was then used as feedstock for the next step.

Weight reaction post toluene wash = 1690g. W/w CNDE-monoacid = 15.10%. Yield CNDE-monoacid = 255.2g, 1.124 mol, 80.3% soln yield.

b) Ethyl (3*R*)-3-cyano-5-methylhexanoate (CNE)

The solution of potassium (3*R*)-3-cyano-2-ethoxycarbonyl-5-methylhexanoate was charged to a 3L 3-neck flask fitted with overhead stirring (600 rpm), pH probe, distillation head, condenser and receiver and a titrando dosing unit. The pH of the stirring solution was adjusted to 7.0 via stat titrated addition of aqueous acetic acid (10% w/w). The reaction mixture was heated to reflux with overhead stirring to promote decarboxylation of the CNDE-monoacid to the desired CNE product. Approximately 500mL of ethanol was removed via distillation during the decarboxylation reaction. During the reaction the pH of the reaction mixture was maintained at 7.0 via stat titration of 10% acetic acid. The rate of addition of acetic acid was used to monitor the progress of the reaction. The reaction was complete within 10 hrs. The reaction was transferred to a separation funnel and the aqueous and organic layers were split while hot. The upper CNE layer was analysed via gc for w/w assay and chirality.

Yield CNE = 220.3g, 88.23% w/w, 194.4g, 1.062 mol, 94.5% yield from CNDE-monoacid. CNE ee = 87%.

c) Potassium (3*R*)-3-cyano-5-methylhexanoate (ent-Pregabalin potassium salt)

45% KOH (145 g, 99.6mL, 1.165mol) was charged slowly to a 1L round bottom flask containing yellow CNE oil (88.23% w/w, 218.3g, 192.6g active, 1.052mol) and DIW (87.7 mL) under N_2 with stirring at 300 rpm over 2 hrs ensuring the temperature was about 20°C. The reaction mixture was stirred at same temperature for 4hrs. The pH was checked (approx >12.5) and a sample of the aqueous was taken for analysis.

Raney Nickel catalyst slurry (9.5 g active) was transferred to a hydrogenator. Any residual catalyst in the weighing vessel was transferred to the hydrogenator with a further wash of DIW (55.13 mL). Finally the above cyanoacid potassium salt solution was transferred to the hydrogenator with DIW (97.56 mL). The mixture

was cooled to 22.5°C then hydrogenation was started at 35°C under a hydrogen pressure of 4.0 bar (gauge) until hydrogen uptake ceased. After hydrogenation, the batch was filtered and washed with DIW (87.20 mL). The solution was transferred for work up.

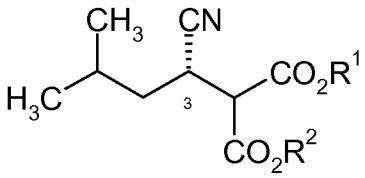
d) (3*R*)-3-Cyano-5-methylhexanoic acid (ent-Pregabalin)

The crude reaction mixture from the hydrogenation was transferred to a nitrogen inerted 2L jacketed reactor. A mixture of IPA (857.5mL) and DIW (173.2mL) was added and the mixture was heated to 53°C. Glacial acetic acid (expected 75.8g/72.2mL, 1.26mol) was added to bring the pH to 7.0. The mixture was cooled to 43°C over one hour before cooling to 25°C over at least 2hrs. The IPA was distilled off under vacuum to a batch volume of about 970mL while maintaining the pot temperature below 35°C and once distillation was complete the vacuum was broken at the same temperature with nitrogen. The pot temperature was reduced to 0°C over 2hrs and granulated at the same temperature for 3hrs. The product was isolated by filtration. The product was slurried twice on the filter with 12% water in IPA (205mL IPA: 21.9mL H_2O). The product was dried in a vacuum oven.

Yield *ent*-pregabalin = 51.6g, 95.91% w/w, 49.49g, 0.311 mol, 29.3% yield from CNE.

CLAIMS:

1. A compound of formula (I)



(I)

in an enantiomerically enriched form, wherein

R^1 and R^2 are the same or different and are each independently selected from C_1-C_{12}-alkyl, C_3-C_{12} cycloalkyl, aryl-C_1-C_6-alkyl and aryl, said alkyl, cycloalkyl and aryl being optionally substituted by one or more groups selected from halo, C_1-C_6-alkoxy and tri(C_1-C_3-alkyl)silyl; or

R^1 and R^2 together are –C(R^3)(R^4)–; and

R^3 and R^4 are the same or different and are each independently H or C_1-C_6-alkyl optionally substituted by one or more groups selected from halo, C_1-C_6-alkoxy and tri(C_1-C_3-alkyl)silyl; or

R^3 and R^4 together are –$(CH_2)_n$– where n is 2, 3, 4, 5 or 6;

wherein the 3*S*-enantiomer is present in excess and the enantiomeric excess is at least 10%.

2. The compound according to claim 1 wherein R^1 and R^2 are the same or different and are each independently selected from C_1-C_{12}-alkyl and benzyl.

3. The compound according to claim 2 wherein R^1 and R^2 are the same.

4. The compound according to claim 3 wherein R^1 and R^2 are selected from C_1-C_4-alkyl.

5. The compound according to claim 4 wherein R^1 and R^2 are both ethyl.

6. The compound according to claim 1 wherein:

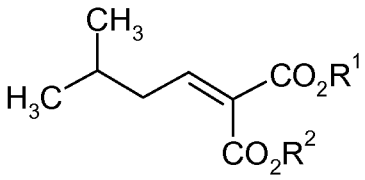
R^1 and R^2 together are –C(R^3)(R^4)–; and

R^3 and R^4 are the same or different and are each independently H or C_1-C_6-alkyl; or R^3 and R^4 together are $-(CH_2)_n-$ where n is 2, 3, 4, 5 or 6.

7. The compound according to claim 6 wherein R^3 and R^4 are both H or both methyl, or R^3 and R^4 together are $-(CH_2)_n-$ where n is 4 or 5.

8. The compound according to any one of claims 1 to 7 wherein the enantiomeric excess is at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99%.

9. A method for the preparation of a compound according to any one of claims 1 to 8 comprising reacting a compound of formula (II)

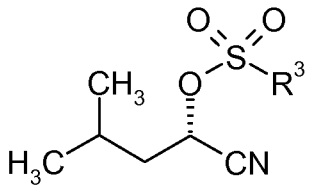


(II),

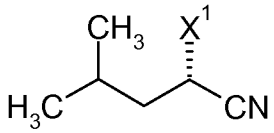
wherein R^1 and R^2 are as defined in formula (I);
with a cyanide source in the presence of a chiral catalyst.

10. The method according to claim 9 wherein the catalyst is a chiral phase transfer catalyst and wherein the reaction is carried out in a two-phase system comprising water and a water-immiscible solvent.

11. A method for the preparation of a compound according to any one of claims 1 to 8 comprising reacting a compound of formula (III*A*) or (III*B*)

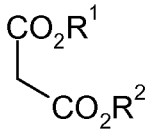


(III*A*)



(III*B*),

wherein R^3 is selected from C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, and phenyl optionally substituted with C_1-C_4 alkyl, halo or NO_2; and X^1 is selected from Cl and Br
with a compound of formula (IV)



(IV),

wherein R^1 and R^2 are as defined in formula (I);

in the presence of a base.

12. A method for the preparation of pregabalin, comprising the steps of:

(i) preparing an enantiomerically enriched compound of formula (I) as defined in any one of claims 1-8,

and

(ii) converting the enantiomerically enriched compound of formula (I) into pregabalin.

Figure 1: HPLC trace for Et-ene-malonate (see Example 1)

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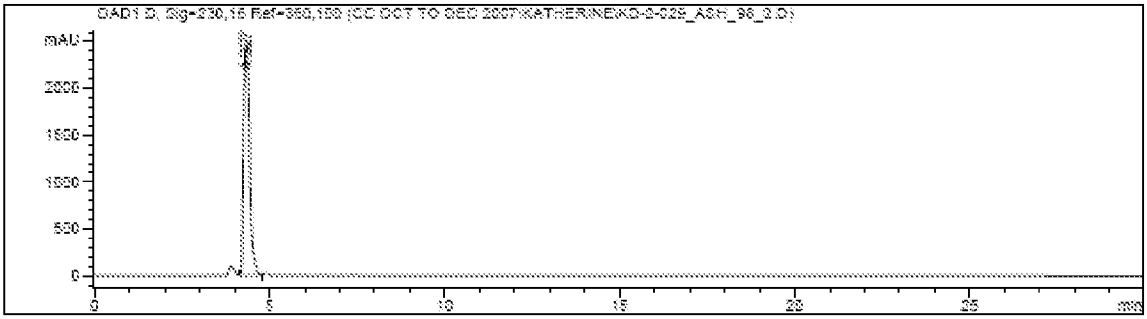

Figure 2: HPLC trace for racemic CNDE (see Example 1)

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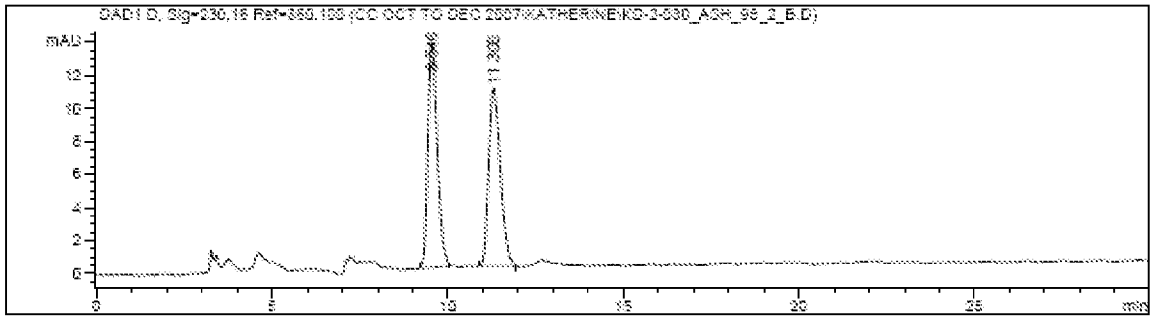

Figure 3: HPLC trace for *R*-CNDE (86% ee, for reference purposes) (see Example 1)

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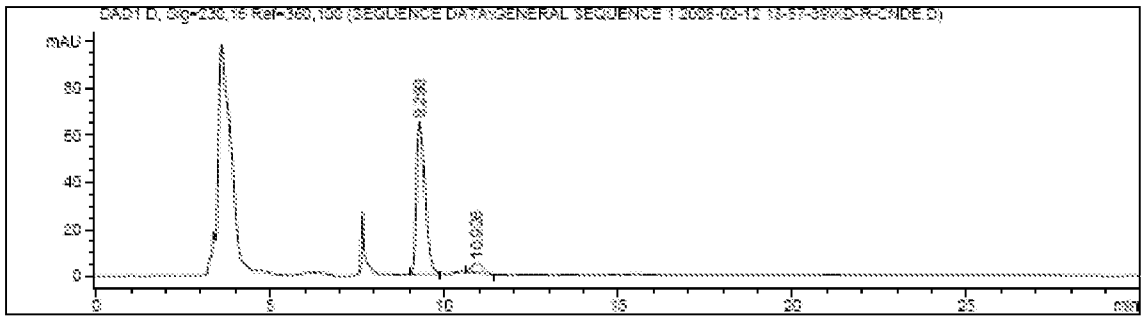

Figure 4: Extent of conversion of Bn-ene malonate with various PTCs.