



AFRICAN REGIONAL INDUSTRIAL PROPERTY ORGANISATION (ARIPO)

1215

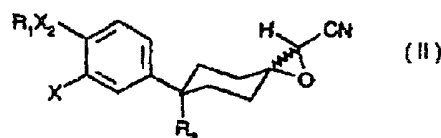
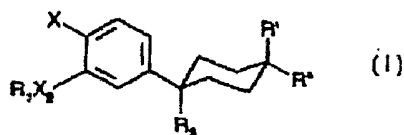
(11) (A)

(21) Application Number:	AP/P/1999/001618	(73) Applicant(s):	SMITHKLINE BEECHAM CORPORATION One Franklin Plaza Philadelphia PA 19103 United States Of America
(22) Filing Date:	19980212	(72) Inventors:	Allen ANDREW 121 Neyland Court Exton PA 19341 United States Of America
(24) Date of Grant & Publication	20031014	(74) Representative	Honey & Blanckenberg P O Box 85 Harare Zimbabwe
(30) Priority Data			
(33) Country:	US		
(31) Number:	60/037,608		
(32) Date:	19970212		
(84) Designated States:			
	GM GH KE LS MW SD		
	SL SZ UG ZW		

(51) International Patent Classification (Int.Cl.): C07C403/00

(54) Title: Compounds And Methods For Preparing Substituted 4-Phenyl-4-Cyanocyclohexanoic Acids.

(57) Abstract:



This invention relates to a method of preparing a compound of formula (I) by treating a compound of formula (II) with lithium bromide, magnesium bromide and the like.

Inventors' Cont.

2. Ann Marie DIEDERICH  
106 Kaiser Drive  
Downingtown  
PA 19335  
U.S.A.

3. Li LUI  
153 Hunsicker Drive  
Collegeville  
PA 19426  
U.S.A.

---

4. Wilford MENDELSON  
592 General Learoad Road  
King of Prussia  
PA 19406  
U.S.A.

5. Kevin WEBB  
1415 Powderhorn Drive  
Phoenixville  
PA 19460  
U.S.A.

## Compounds and Method for Preparing Substituted 4-Phenyl-4-cyanocyclohexanoic Acids

### Scope of the Invention

This invention covers intermediates and a synthetic route for making 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexanoic acid and its analogs. This acid and its named analogs are selective for inhibiting the catalytic site in the phosphodiesterase isoenzyme denominated IV (PDE IV hereafter) and as such the acids are useful in treating a number of diseases which can be moderated by affecting the PDE IV enzyme and its subtypes.

### 10 Area of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyper-reactivity of the respiratory tract to external stimuli.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated, which converts  $Mg^{+2}$ -ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by

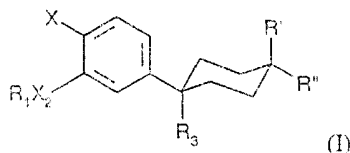
one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989]. Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case *in vivo*. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E<sub>2</sub> and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The process and intermediates of this invention provide a means for making certain 4-substituted-4-(3,4-disubstitutedphenyl)cyclohexanoic acids which are useful for treating asthma, and other diseases which can be moderated by affecting the PDE IV enzyme and its subtypes. The final products of particular interest are fully described in U.S. patent 5,552,483 issues 03 September 1996. The information and representations disclosed therein, in so far as that information and those representations are necessary to the understanding of this invention and in its practice, in total, are incorporated herein by reference.

### Summary of the Invention

This invention relates a method for making a compound of formula I



R<sub>1</sub> is -(CR<sub>4</sub>R<sub>5</sub>)<sub>n</sub>C(O)O(CR<sub>4</sub>R<sub>5</sub>)<sub>m</sub>R<sub>6</sub>, -(CR<sub>4</sub>R<sub>5</sub>)<sub>n</sub>C(O)NR<sub>4</sub>(CR<sub>4</sub>R<sub>5</sub>)<sub>m</sub>R<sub>6</sub>, -(CR<sub>4</sub>R<sub>5</sub>)<sub>n</sub>O(CR<sub>4</sub>R<sub>5</sub>)<sub>m</sub>R<sub>6</sub>, or -(CR<sub>4</sub>R<sub>5</sub>)<sub>r</sub>R<sub>6</sub> wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 0 to 6;

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;  
 R<sub>6</sub> is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC<sub>1-3</sub> alkyl,  
 halo substituted aryloxyC<sub>1-3</sub> alkyl, indanyl, indenyl, C<sub>7-11</sub> polycycloalkyl,  
 tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl,  
 5 tetrahydrothiopyranyl, thiopyranyl, C<sub>3-6</sub> cycloalkyl, or a C<sub>4-6</sub> cycloalkyl containing  
 one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be  
 optionally substituted by 1 to 3 methyl groups or one ethyl group:

provided that:

- a) when R<sub>6</sub> is hydroxyl, then m is 2; or
- 10 b) when R<sub>6</sub> is hydroxyl, then r is 2 to 6; or
- c) when R<sub>6</sub> is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl,  
 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
- d) when R<sub>6</sub> is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl,  
 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;
- 15 e) when n is 1 and m is 0, then R<sub>6</sub> is other than H in

$-(CR_4R_5)_nO(CR_4R_5)_mR_6$ ;

X is YR<sub>2</sub>, halogen, nitro, NH<sub>2</sub>, or formyl amine;

X<sub>2</sub> is O or NR<sub>8</sub>;

Y is O or S(O)<sub>m'</sub>;

20 m' is 0, 1, or 2;

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by  
 1 or more halogens;

R<sub>3</sub> is hydrogen, halogen, C<sub>1-4</sub> alkyl, CH<sub>2</sub>NHC(O)C(O)NH<sub>2</sub>, halo-substituted  
 C<sub>1-4</sub> alkyl, -CH=CR<sub>9</sub>R<sub>10</sub>, cyclopropyl optionally substituted with 1, 2, or 3 CN, OR<sub>8</sub>,

25 CH<sub>2</sub>OR<sub>8</sub>, NR<sub>8</sub>R<sub>10</sub>, CH<sub>2</sub>NR<sub>8</sub>R<sub>10</sub>, C(Z)H, C(O)OR<sub>8</sub>, C(O)NR<sub>8</sub>R<sub>10</sub>, or C≡CR<sub>8</sub>;

R<sub>8</sub> is hydrogen or C<sub>1-4</sub> alkyl optionally substituted by one to three fluorines;

R<sub>8</sub>' is R<sub>8</sub> or fluorine;

R<sub>10</sub> is OR<sub>8</sub> or R<sub>11</sub>;

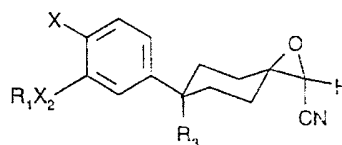
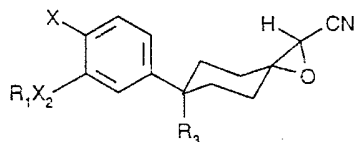
R<sub>11</sub> is hydrogen, or C<sub>1-4</sub> alkyl optionally substituted by one to three fluorines;

30 Z' is O, NR<sub>9</sub>, NOR<sub>8</sub>, NCN, C(-CN)<sub>2</sub>, CR<sub>8</sub>CN, CR<sub>8</sub>NO<sub>2</sub>, CR<sub>8</sub>C(O)OR<sub>8</sub>,

CR<sub>8</sub>C(O)NR<sub>8</sub>R<sub>8</sub>, C(-CN)NO<sub>2</sub>, C(-CN)C(O)OR<sub>9</sub>, or C(-CN)C(O)NR<sub>8</sub>R<sub>8</sub>;

R' and R'' are independently hydrogen or -C(O)OH;

which method comprises treating a compound of formula II(a) or II(b)



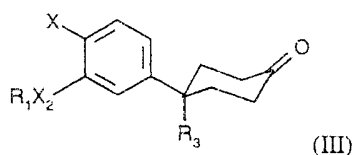
II(a)

II(b)

where R<sub>1</sub>, R<sub>3</sub>, X<sub>2</sub> and X are the same as for formula (I), with lithium bromide or magnesium bromide in a polar solvent at a temperature between about 60° and 100° C, optionally under an inert atmosphere for a time sufficient for the reaction to go to completion.

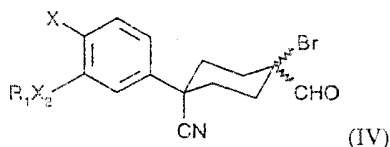
This invention also relates to compounds of formula II per se.

In another aspect this invention relates to a one-pot method for making the ketone of formula III starting with isovanillin,



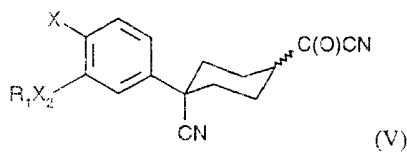
where R<sub>1</sub>, R<sub>3</sub>, X<sub>2</sub> and X are the same as for formula (I), as more fully described herein below.

In yet a third aspect this invention relates to a process for preparing a compound of formula I which process comprises treating a compound of formula (IV) using an alkali metal cyanide, for example LiCN, in a compatible solvent such as dimethylformamide which contains a small proportion of water



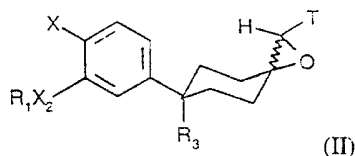
where, in formula III, R<sub>1</sub>, X and X<sub>2</sub> are the same as in formula I.

In a further embodiment this invention relates to a process for making a compound of formula I comprising treating an acyl nitrile of formula V with water.



The X, X<sub>2</sub> and R<sub>1</sub> groups in formula V are the same as those in formula I.

In yet a further embodiment this invention relates to compounds of formula II



R<sub>1</sub> is  $-(\text{CR}_4\text{R}_5)_n\text{C}(\text{O})\text{O}(\text{CR}_4\text{R}_5)_m\text{R}_6$ ,  $-(\text{CR}_4\text{R}_5)_n\text{C}(\text{O})\text{NR}_4(\text{CR}_4\text{R}_5)_m\text{R}_6$ ,  $-(\text{CR}_4\text{R}_5)_n\text{O}(\text{CR}_4\text{R}_5)_m\text{R}_6$ , or  $-(\text{CR}_4\text{R}_5)_r\text{R}_6$  wherein the alkyl moieties may be optionally substituted with one or more halogens;

5           m is 0 to 2;

          n is 1 to 4;

          r is 0 to 6;

          R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;

          R<sub>6</sub> is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC<sub>1-3</sub> alkyl,  
10 halo substituted aryloxyC<sub>1-3</sub> alkyl, indanyl, indenyl, C<sub>7-11</sub> polycycloalkyl,  
tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl,  
tetrahydrothiopyranal, thiopyranal, C<sub>3-6</sub> cycloalkyl, or a C<sub>4-6</sub> cycloalkyl containing  
one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be  
optionally substituted by 1 to 3 methyl groups or one ethyl group;

15           provided that:

          a) when R<sub>6</sub> is hydroxyl, then m is 2; or

          b) when R<sub>6</sub> is hydroxyl, then r is 2 to 6; or

          c) when R<sub>6</sub> is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal,  
2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

20           d) when R<sub>6</sub> is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal,  
2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

          e) when n is 1 and m is 0, then R<sub>6</sub> is other than H in

$-(\text{CR}_4\text{R}_5)_n\text{O}(\text{CR}_4\text{R}_5)_m\text{R}_6$ ;

          X is YR<sub>2</sub>, halogen, nitro, NH<sub>2</sub>, or formyl amine;

25           X<sub>2</sub> is O or NR<sub>8</sub>;

          Y is O or S(O)<sub>m'</sub>;

          m' is 0, 1, or 2;

          R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by  
1 or more halogens;

30           R<sub>3</sub> is hydrogen, halogen, C<sub>1-4</sub> alkyl, CH<sub>2</sub>NHC(O)C(O)NH<sub>2</sub>, halo-substituted  
C<sub>1-4</sub> alkyl, -CH=CR<sub>8</sub>R<sub>8</sub>', cyclopropyl optionally substituted by R<sub>8</sub>', CN, OR<sub>8</sub>,  
CH<sub>2</sub>OR<sub>8</sub>, NR<sub>8</sub>R<sub>10</sub>, CH<sub>2</sub>NR<sub>8</sub>R<sub>10</sub>, C(Z)H, C(O)OR<sub>8</sub>, C(O)NR<sub>8</sub>R<sub>10</sub>, or C≡CR<sub>8</sub>'

          R<sub>8</sub> is hydrogen or C<sub>1-4</sub> alkyl optionally substituted by one to three fluorines;

          R<sub>8</sub>' is R<sub>8</sub> or fluorine;

35           R<sub>10</sub> is OR<sub>8</sub> or R<sub>11</sub>;

R<sub>11</sub> is hydrogen, or C<sub>1-4</sub> alkyl optionally substituted by one to three fluorines;  
 Z' is O, NR<sub>9</sub>, NOR<sub>8</sub>, NCN, C(-CN)<sub>2</sub>, CR<sub>8</sub>CN, CR<sub>8</sub>NO<sub>2</sub>, CR<sub>8</sub>C(O)OR<sub>8</sub>,  
 CR<sub>8</sub>C(O)NR<sub>8</sub>R<sub>8</sub>, C(-CN)NO<sub>2</sub>, C(-CN)C(O)OR<sub>9</sub>, or C(-CN)C(O)NR<sub>8</sub>R<sub>8</sub>, and  
 T is CN or SO<sub>2</sub>R where R is C<sub>1-6</sub>alkyl or C<sub>0-3</sub>alkylphenyl.

## 5 Specific Embodiments of the Invention

This process involves a nine step synthesis for preparing certain 4-substituted-4-(3,4-disubstitutedphenyl)cyclohexanoic acids. The starting material is isovanillin, 3-hydroxy-4-methoxybenzaldehyde, or an analog thereof. "Analog" means another 3 and/or 4 position substituent conforming to the definitions of R<sub>1</sub>, R<sub>3</sub>, X<sub>2</sub> and X in the definition of formula (I).

The compounds which are made by this process are PDE IV inhibitors. They are useful for treating a number of diseases as described in U.S. patent 5,552,438 issued 3 September 1996.

The preferred compounds which can be made by this process are as follows:

Preferred R<sub>1</sub> substituents for the compounds of all named formulas are CH<sub>2</sub>-cyclopropyl, CH<sub>2</sub>-C<sub>5-6</sub> cycloalkyl, C<sub>4-6</sub> cycloalkyl unsubstituted or substituted with OHC<sub>7-11</sub> polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C<sub>1-2</sub> alkyl unsubstituted or substituted by 1 or more fluorines, -(CH<sub>2</sub>)<sub>1-3</sub>C(O)O(CH<sub>2</sub>)<sub>0-2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>1-3</sub>O(CH<sub>2</sub>)<sub>0-2</sub>CH<sub>3</sub>, and -(CH<sub>2</sub>)<sub>2-4</sub>OH.

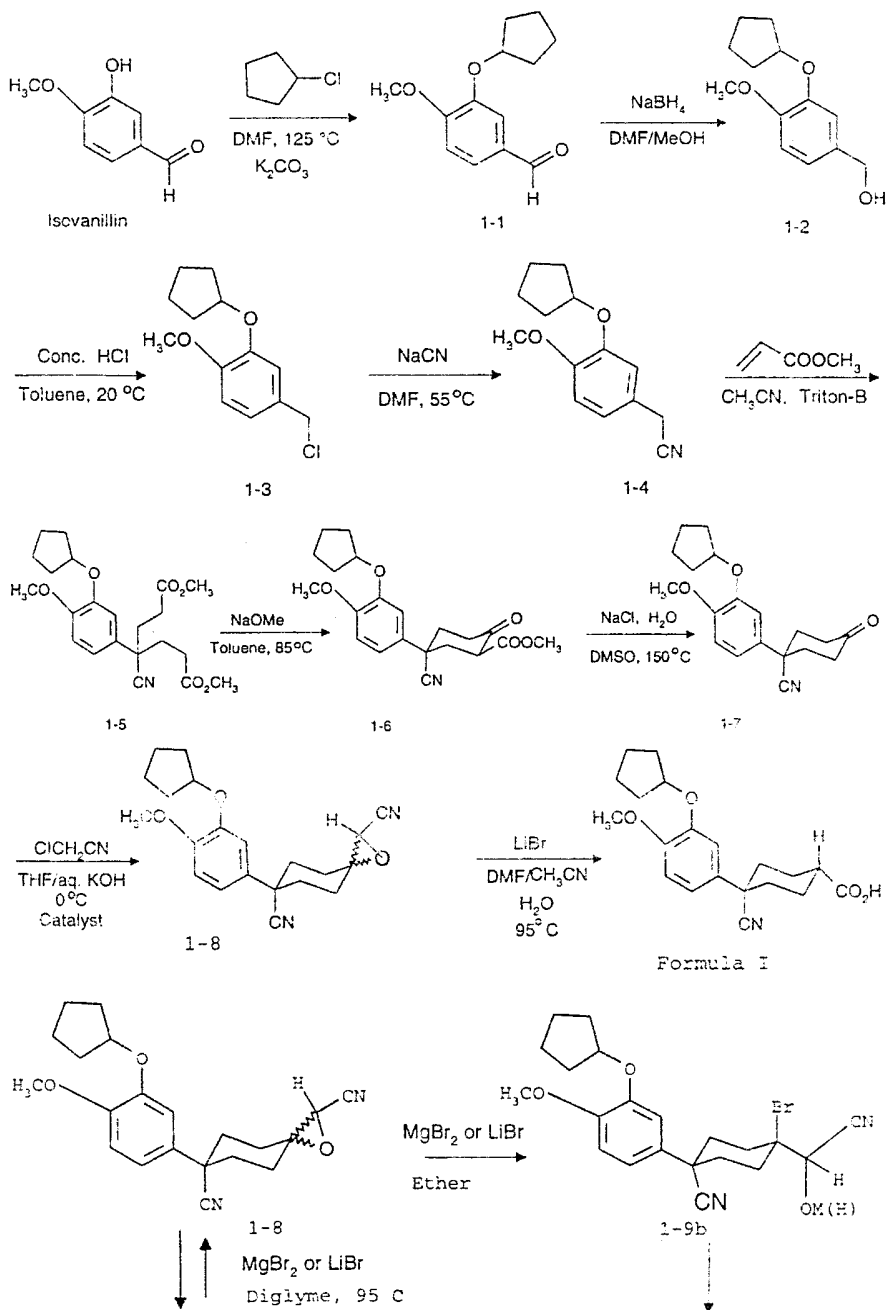
Preferred X groups for Formula (I), (II) or (III) are those wherein X is YR<sub>2</sub> and Y is oxygen. The preferred X<sub>2</sub> group for Formula (I) is that wherein X<sub>2</sub> is oxygen. Preferred R<sub>2</sub> groups are a C<sub>1-2</sub> alkyl unsubstituted or substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R<sub>2</sub> groups are those wherein R<sub>2</sub> is methyl, or the fluoro-substituted alkyls, specifically a C<sub>1-2</sub> alkyl, such as a -CF<sub>3</sub>, -CHF<sub>2</sub>, or -CH<sub>2</sub>CHF<sub>2</sub> moiety. Most preferred are the -CHF<sub>2</sub> and -CH<sub>3</sub> moieties.

Most preferred are those compounds wherein R<sub>1</sub> is -CH<sub>2</sub>-cyclopropyl, cyclopentyl, 3-hydroxycyclopentyl, methyl or CF<sub>2</sub>H; X is YR<sub>2</sub>; Y is oxygen; X<sub>2</sub> is oxygen; and R<sub>2</sub> is CF<sub>2</sub>H or methyl; and R<sub>3</sub> is CN.

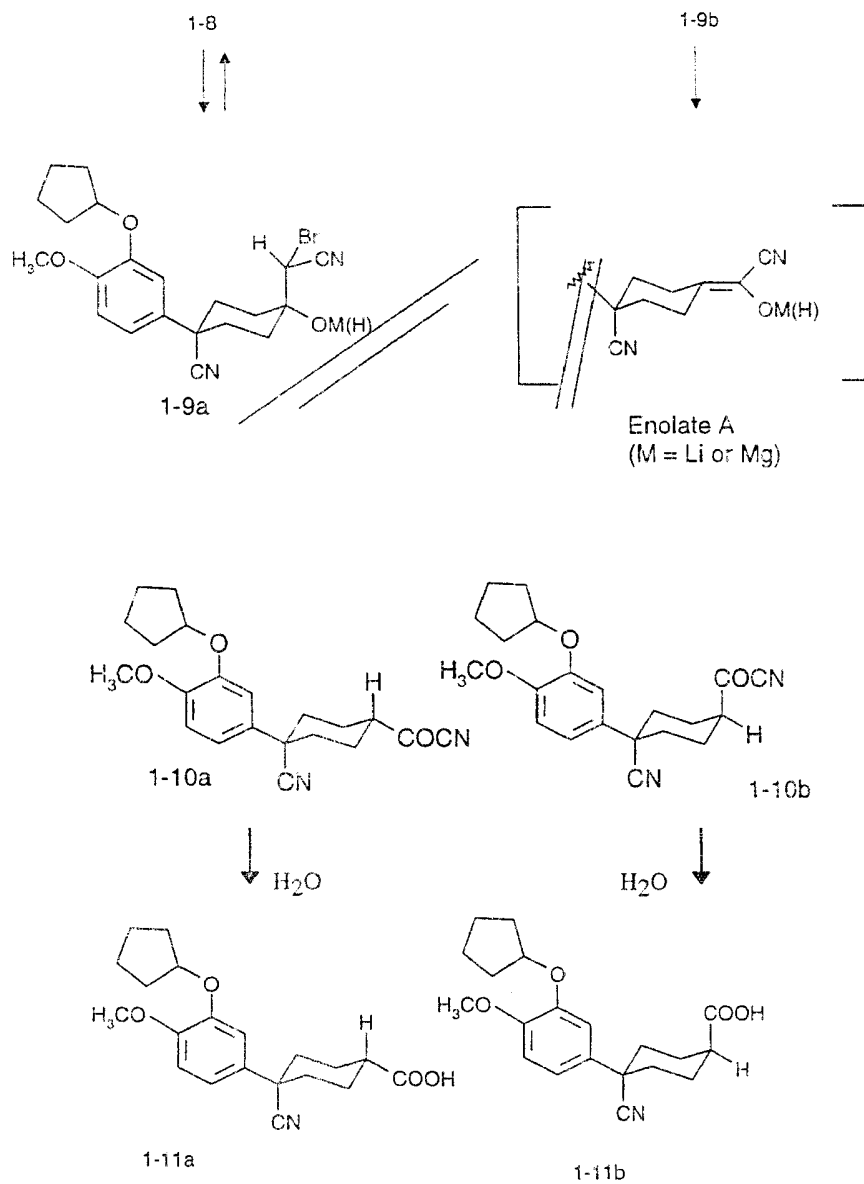
A representative schematic of this process is set out in Scheme I. This graphical representation uses specific examples to illustrate the general methodology used in this invention.



Scheme I



AP/199101018



Referring to Scheme I, isovanillin, 3-hydroxy-4-methoxybenzaldehyde, is a readily available starting material. It can be alkylated with an R<sub>1</sub>X moiety (X = Cl, Br, and I) as represented by cyclopentyl chloride. The reaction vessel is first flushed with an inert gas, for example nitrogen. A polar solvent such as DMF is then added to the

APC 01215

vessel, then the isovanillin, then the R<sub>1</sub>X adduct, and some base. About 2 equivalents of the R<sub>1</sub>X adduct versus the isovanillin are used. Likewise about 2 equivalents of base are used, again relative to the isovanillin. The base can be any inorganic base or a carbonate. Here it is illustrated by potassium carbonate. The vessel contents are heated  
5 to about 125° C for about 90 to 120 minutes in which time the reaction will have gone to completion. The vessel contents are cooled to ambient temperature, filtered to remove the inorganic salts, and washed with an alcohol such as methanol. This filtrate contains the aldehyde, labeled 1-1.

The aldehyde is then reduced to the alcohol using an inorganic reducing agent.  
10 To do this the filtrate from the foregoing reaction is treated with sodium borohydride and after workup affords the desired alcohol, 1-2 in 97% overall yield from isovanillin. This is achieved by cooling the filtrate to about 0° C after which a reducing agent, here sodium borohydride, is added. About 0.25 to 0.5 equivalents of this reducing agent is used. The temperature is kept at about 0° C during the addition of the reducing agent  
15 and for about 30 to 40 minutes thereafter. Then the temperature is allowed to rise to about room temperature after which about one-half an equivalent of HCl is added to the reaction vessel. The alcohol is then extracted into an organic solvent, toluene is illustrated, and washed with dilute sodium bicarbonate.

The top organic layer containing the alcohol is then treated with excess  
20 concentrated hydrochloric acid at ambient temperature to afford, after workup, the desired benzyl chloride 1-3. The chloride is isolated as a w/w solution in an amide solvent, DMF is illustrated, and treated with about a 50% molar excess of sodium cyanide at a mildly elevated temperature, here illustrated as 55° C. This affords the desired nitrile 1-4. The nitrile is isolated as a w/w solution in an appropriate solvent  
25 such as anhydrous acetonitrile and used directly in the next step.

The nitrile solution is charged with methyl acrylate. It is cooled to about -10° C, and slowly treated with a catalytic amount of Triton-B in the same solvent as used to dissolve the nitrile. The methyl acrylate is added in a 3 to 4-fold excess. The reaction is complete within 30 to 45 minutes after which the acrylate addition, the pimelate  
30 product, 1-5, is isolated as a w/w solution in toluene and treated with about 2 equivalents of sodium methoxide at about 75° C to give the β-keto-ester product, 1-6. The reaction solution is cooled and neutralized to pH 7 with mineral acid such as 6N

APC 01215

hydrochloric acid. The solution is charged with dimethyl sulfoxide, sodium chloride, water, and heated, for example to about 150° C, to effect the decarboxylation to give 1-7. The ketone, 1-7, is isolated from the solvent system as an off-white solid.

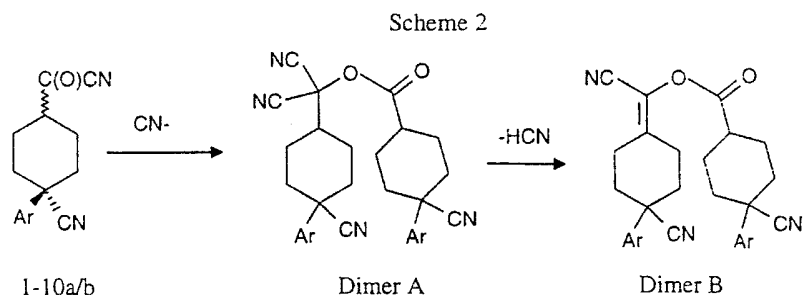
The dicyanonitrile 1-8 is prepared from the ketone by treating the ketone with chloroacetonitrile in the presence of an inorganic base and a catalytic amount of benzyltriethylammonium chloride (BTEAC). The ketone is charged into a mixture of strong base (aqueous potassium hydroxide) and a water miscible solvent such as tetrahydrofuran. A slight excess of chloroacetonitrile is added at reduced temperature, about 0° C or thereabouts. The reaction is maintained at about that temperature for the duration of the reaction, usually about 1 hour. The product is isolated and usually it is crystalline.

The dicyanonitrile is converted to the cyclohexanecarboxylic acid using a Lewis acid catalyst; water is also needed to drive the reaction to the acid. Without water intermediates 1-10a and 1-10b may dimerize. This reaction is carried out by charging a vessel with solvents, in this instance exemplified by DMF, acetonitrile and water, and the Lewis acid (about 1.5 equivalents), LiBr is illustrated, sweeping the vessel with an inert gas, adding the dicyanonitrile IIa or IIb, or a mixture of IIa and IIb and heating the vessel and its contents to about 100° C for a number of hours, 8 hours being an example. The acid is isolated by conventional means.

It should be noted that this reaction, that is the conversion of the epoxide to the acid, involves several intermediates which do not need to be isolated. It has been found that treating the epoxide with LiBr yields intermediates 1-9a and 1-9b. Intermediate 1-9a is formed when LiBr is added to the reaction pot. But intermediate 1-9a converts back to the epoxide under the recited reaction conditions. Intermediate 1-9b is also formed but apparently reacts rapidly to form intermediates such as enolate A, 1-10a and 1-10b etc leading to product. So it appears 1-9a and 1-9b are formed, but that 1-9a converts back to the epoxide which ultimately forms 1-9b which is then converted to other intermediates enroute to forming the acids of 1-11a and 1-11b. Parenthetically the designation "OM(H)" in 1-9a and 1-9b means the metal salt of the alcohol or the alcohol per se, depending on the reaction conditions. Intermediate 1-9b is believed to convert to the acyl nitriles of formulas 1-10a and 1-10b via the proposed bracketed intermediate. The existence of the proposed bracketed intermediate (enolate) has not

been fully confirmed. And while the acyl nitriles of 1-10a and 1-10b have not been directly observed, indirect evidence exists for these compounds by virtue of the fact the bis-condensation product dimer B was isolated and is analogous to reported compounds where a similar bis-condensate is the product of an acyl nitrile.

5



Dimers such as dimer A are known to form from the likes of acyl nitriles 1-10a/b in the presence of HCN (Thesing, J.; Witzel, D.; Brehm, A. *Angew Chem.* 1956, 68, 425; and Hunig, S.; Schaller, R. *Angew. Chem. Int. Ed. Engl.* 1982, 21,36).

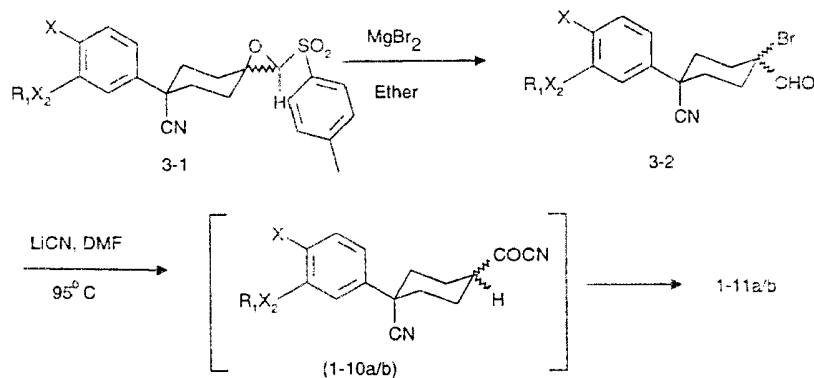
And in addition, authentic samples of intermediates 1-10a and 1-10b were prepared and found to convert to acids 1-11a and 1-11b when exposed to water. The equatorial isomer 1-10a converted to the acid in an equatorial/axial ratio of about 98:2 while the axial isomer 1-10a isomerized to a preponderance of the equatorial isomer 1-11a (77:23). It is believed the axial acyl nitrile converts to the equatorial acyl nitrile via the proposed bracketed enolate intermediate.

The second, following reaction scheme illustrates preparing the acids of formula (I) from the bromoaldehyde of formula (IV).

20

Scheme 3

AP/89/01018



The following examples are provided to illustrate specifics of the invention, not to limit it. What is reserved to the inventors is set forth in the claims appended hereto.

## 5 Specific Examples

### Example 1

#### Preparation of 3-cyclopentylloxy-4-methoxybenzaldehyde.

A 12 liter round bottom flask equipped with an overhead stirrer, internal thermometer, and a reflux condenser equipped with a nitrogen inlet was flushed with nitrogen. The flask was charged with dimethylformamide (2.4 L), isovanillin (350 g, 2.3 mol, 1 equivalent), cyclopentyl chloride (481 g, 4.6 mol, 2.0 equivalent) and potassium carbonate (634 g, 4.6 mol, 2.0 equivalents). The vigorously stirred suspension was heated to 125 °C for two hours or until the disappearance of isovanillin. The reaction was cooled to 20 -30 °C and filtered to remove the inorganic salts. The filter cake was rinsed with methanol (1.0 L).

The clear, light-brown filtrate (DMF and methanol) containing the product, 3-cyclopentylloxy-4-methoxybenzaldehyde, was used directly in the next step (100 % solution yield).

### Example 2

#### Preparation of 3-Cyclopentylloxy-4-methoxybenzyl alcohol.

A 12 liter round bottom flask equipped with an overhead stirrer, internal thermometer, and a reflux condenser equipped with a nitrogen inlet was flushed with nitrogen. The flask was charged with dimethylformamide (2.4 L), methanol (1.0 L), and 3-cyclopentylloxy-4-methoxybenzaldehyde (506 g, 2.3 mol, 1 equivalent). The contents of the flask were cooled to 0 to 5 °C followed by the addition of sodium borohydride (32.2 g, 0.85 mol, 0.37 equivalents). The reaction was maintained at 0 to 5 °C for 30 minutes, and warmed to 20 to 25 °C for an additional 2 hours or until the

disappearance of the aldehyde. A solution of 6N hydrochloric acid (195 mL, 1.17 mol, 0.51 equivalents) was added over 20 minutes. The reaction was concentrated under reduced pressure, and cooled to 20 to 25 °C.

The flask was charged with deionized water (1.9 L) and toluene (1.9 L). The layers were separated, the organic layer was isolated, and washed twice with deionized water (2 x 800 mL). The product, 3-cyclopentyloxy-4-methoxybenzyl alcohol was collected as a solution in toluene (97% solution yield) and used directly in the next step.

#### Example 3

##### Preparation of 4-Chloromethyl-2-cyclopentyloxy-1-methoxybenzene.

A 12 liter round bottom flask equipped with an overhead stirrer, internal thermometer, and a reflux condensor equipped with a nitrogen inlet was flushed with nitrogen. The flask was charged with 3-cyclopentyloxy-4-methoxybenzyl alcohol (495 g, 2.2 mol, 1 equivalent) in a solution of toluene. To the vigorously stirred reaction at 22 °C was added concentrated hydrochloric acid (600 g, 2.75 equivalents). The reaction was maintained at 20 to 25 °C for 30 minutes. The top organic layer was isolated and the bottom acidic layer was discarded. To the top organic layer was charged a solution of 10% sodium bicarbonate (550 g, 0.65 mol, 0.36 equivalents) and *t*-butyl methyl ether (814 g). The contents of the flask were vigorously stirred, and allowed to settle. The product, 4-chloromethyl-2-cyclopentyloxy-1-methoxybenzene, was isolated as a solution in toluene and *t*-butyl methyl ether (96.8% solution yield). This was used directly in the next step.

#### Example 4

##### Preparation of 4-Cyanomethyl-2-cyclopentyloxy-1-methoxybenzene.

A 12 liter round bottom flask equipped with an overhead stirrer, and a distillation apparatus was flushed with nitrogen. The flask was charged with 4-chloromethyl-2-cyclopentyloxy-1-methoxybenzene (519 g, 2.15 mol, 1.0 equivalents) in a solution of toluene and *t*-butyl methyl ether. The reaction was concentrated under reduce pressure to a residue. To the 12 liter flask was charged DMF (1.44 kg) and sodium cyanide (142 g, 2.9 mol, 1.35 equivalents). The reaction was heated to 55 °C for 6 hours or until deemed complete by the disappearance of the benzyl chloride. The reaction was concentrated under reduced pressure to a residue. To the flask was charged *t*-butyl methyl ether (2.30 kg) and deionized water (800 mL). The contents of the flask were vigorously stirred, and allowed to settle. The top organic layer was isolated, washed three times with deionized water (3 x 800 mL), and concentrated under atmospheric pressure to a residue. To the flask was added acetonitrile (1.26 kg) and the distillation was continued until an additional 400 mL of solvent was collected. The product, 4-cyanomethyl-2-cyclopentyloxy-1-methoxybenzene, was isolated as a solution in acetonitrile (92.2% yield). This was used directly in the next step.

Example 5Preparation of Dimethyl-4-cyano-4-(3-cyclopentyloxy-4-methoxy-phenyl) pimelate

A 12 liter round bottom flask equipped with an overhead stirrer, internal thermometer, and a reflux condensor equipped with a nitrogen inlet was flushed with nitrogen. The flask was charged with a solution of 4-cyanomethyl-2-cyclopentyloxy-1-methoxybenzene (460 g, 1.99 mol, 1.0 equivalent) in acetonitrile, and methyl acrylate (520 g, 6.0 mol, 3.0 equivalents). The contents of the flask was cooled to -10 °C. A pressure equalizing addition funnel was charged with acetonitrile (1.1 L) and benzyltrimethyl ammonium hydroxide (a 40% w/w solution in methanol, 25 g, 0.06 mol, 0.03 equivalents). The contents of the addition funnel was added to the flask. An exotherm was observed, and after stirring for 30 minutes the contents of the flask were cooled to 20 °C. The reaction was concentrated under reduced pressure to a residue. To the residue was added toluene (2.6 L). This solution of dimethyl-4-cyano-4-(3-cyclopentyloxy-4-methoxy-phenyl) pimelate (90% solution yield) was used directly in the next step.

Example 6Preparation of 4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one

A 12 liter round bottom flask equipped with an overhead stirrer, internal thermometer, and a reflux condensor equipped with a nitrogen inlet was flushed with nitrogen. The flask was charged with a solution of dimethyl-4-cyano-4-(3-cyclopentyloxy-4-methoxy-phenyl) pimelate (720 g, 1.78 mol, 1 equivalent) in toluene, and sodium methoxide (25 wt% in methanol, 545 g, 2.67 mol, 1.5 equivalents). The reaction was heated to 70 to 75 °C for 2 hours or until deemed complete by the disappearance of the pimelate. The reaction was cooled to 25 °C. A solution of 6N hydrochloric acid was added in order to adjust the pH to 6.8 - 7.2. The reaction was concentrated under vacuum to a residue. The flask was charged with dimethylsulfoxide (3.3 L), deionized water (250 mL) and sodium chloride (250 g).

The contents of the flask were heated to 145-155 °C, and held at this temperature for 2 hours. The reaction was cooled and concentrated under vacuum to a residue. To the residue was added water (1.9 L), ethyl acetate (1.25 L), and t-butyl methyl ether (620 mL). The solution was stirred and allowed to settle. The layers were separated, and the aqueous layer was re-extracted with ethyl acetate (1.25 L). The combined organic layers were washed twice with deionized water (2 X 2.5 L). The organic layer was isolated and concentrated under reduced pressure to a residue. To this residue was added isopropanol (1.66 L) and heated to produce a solution followed by the slow addition of hexanes (1.66 L). The suspension was cooled to 5 °C over 30 minutes, and held at 0 to 5 °C for two hours. The product was filtered and washed with



50-50 isopropanol-hexanes (840 mL) mixture at 0 °C. The product was dried to afford 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (315 g, 56 % from the pimelate).

Example 7

5            Preparation of cis-(+/-)-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxobicyclo[2.5]octane-2,6-dicarbonitrile.

A 5 liter round bottom flask equipped with an overhead stirrer, internal thermometer, and a nitrogen inlet was flushed with nitrogen. The flask was charged with 50% potassium hydroxide (220 g) and tetrahydrofuran (550 mL). While stirring at  
10 room temperature, benzyltriethylammonium chloride (8.1 g, 0.035 mol, 0.05 equivalent) was added. The solution was cooled to 0 °C. To a pressure equalizing addition funnel was charged a solution containing tetrahydrofuran (550 mL), 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl) cyclohexan-1-one (230 g, 0.73 mol, 1.0 equivalent), and chloroacetonitrile (59 g, 0.78 mol, 1.07 equivalent) at room  
15 temperature. While stirring the flask's contents at 0 °C, the solution in the pressure addition funnel was added over 15 minutes. The temperature was maintained between 0 and 5 °C, and stirred for one hour. The reaction was warmed to 25 °C, diluted with water (900 mL), and ethyl acetate (900 mL). The solution was stirred and allowed to settle for 30 minutes. The layers were separated, the organic layer was isolated, and  
20 concentrated by vacuum distillation to a residue. Methanol (540 mL) was added and the solution was heated to 40 °C. While cooling to 20 °C over 90 minutes, hexanes (540 mL) was added. Cooling was continued, and the product began to crystallize at 10 °C. The suspension was then cooled to -5 °C and held at -5-0 °C for two hours. The product was filtered and washed with a 50-50 methanol-hexanes mixture (300 mL) at 0  
25 °C. The product was dried to afford cis-(+/-)-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxobicyclo[2.5]octane-2,6-dicarbonitrile (190 g, 73 %) as a white crystalline solid.

Example 8

Preparation of 1-9a

In a stoppered 12 dram screw-top vial was added diglyme (5.92 g) and the  
30 epoxy nitrile (0.70 g, 1eq) of Example 7. This mixture was stirred with heating in an oil bath for 5 min. Then MgBr<sub>2</sub>·6H<sub>2</sub>O (0.906 g, 1.55 eq) was added. After 3 hr no starting material was detected. The reaction mixture was cooled, then mixed with 5% aqueous citric acid/ethyl acetate and the layers shaken and separated. The second extraction with ether/ethyl acetate gave some color extracted into organic layer; but the  
35 next extraction had no color. The organic fractions were combined and washed with water and brine and dried with MgSO<sub>4</sub>. The product was crystallized from hexane; mp 151-152 °C.

APT/99:01618

Elemental analysis: C - 58.20, H - 5.82, Br - 18.44, N - 6.46; found C - 58.32, H - 5.73, Br - 18.48, N - 6.34. The structure was confirmed by X-ray structure determination of a crystalline sample obtained from methyl alcohol.

Example 9

Preparation of 1-9b

5 To Mg (0.189 g, 2.02 eq) (polished with mortar and pestle) in ether was added 1,2-dibromoethane (1.55 g, 2.06 eq) in a small volume of ether to initiate the Grignard. When most of the magnesium was consumed and no more evolution of ethane was observed, the reaction was stirred for an additional 0.5 hr at room temperature after  
10 which was added the epoxide of Example 7 (1.41g; 1 eq) in a minimal amount of dry tetrahydrofuran at ambient temperature. After about 70 hr at room temperature there was obtained both the bromo cyanoalcohol (1-9b) and bromo cyanohydrin (1-9a) in a ratio of 6:1. The 1-9b product was isolated as an oil by preparative HPLC. The structure was confirmed by carbon and proton NMR.

Example 10

Preparation of Compound 3-1 - Epoxysulfone

15 To a 25ml round-bottom flask equipped with a magnetic stir bar and a rubber septum was charged 1.00 g of 4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexan-1-one, 0.70 g of chloromethyl *p*-tolylsulfone, and 7 ml of  
20 tetrahydrofuran. This was stirred, then 3 ml of 50% w/w aqueous NaOH and benzyltrimethyl ch (0.05g) was added. This suspension was vigorously stirred for 2 hours at room temperature. The reaction solution was transferred to a separatory funnel to which was added 50 ml of ethyl acetate and acidified with 6N HCl. The organic layer was retained, washed 2X with deionized water, dried with MgSO<sub>4</sub> and filtered to  
25 remove the salts.

Example 11

Preparation of Compound 3-2 - Bromoaldehyde

30 To magnesium (0.048g, 1.03 eq, 0.021 mol; polished with mortar and pestle) in ether was added 1,2-dibromoethane (0.40 g, 1.06 eq, 0.02 mol) under nitrogen. Two drops of iodine were added in ether to start the reaction, after which the reaction was heated gently. Once the Grignard had formed, the reaction flask was cooled to about 5 °C and the epoxysulfone of Example 10 (0.93 g, 1 eq, 0.002 mol) was added in ether/methylene chloride. The reaction was followed via TLC (conditions: silica gel with cyclohexane:toluene:acetonitrile:acetic acid 40:40:20:4). The reaction was stirred  
35 at 5° for 2 hours. The product was isolated by adding water and ether/TBME to the reaction mixture, and separating the organic layers. These were washed with water and brine and dried over MgSO<sub>4</sub>. Evaporation gave an oil which was flash chromatographed over 40 g of silica gel using a mixture of hexane and ethyl acetate (5-

AP/5/09/01018



AP001215

Preparation of Form 1-10a - 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexane acyl nitrile

In a flask a sample of the acid chloride (0.217 g, 0.006 mol, 1 eq) prepared in Example 12 was dissolved in CDCl<sub>3</sub> (2.34 mL). To this was solution (cooled to 5°C) was added trimethylsilyl cyanide (0.07g, 1.3 eq, 0.008 mol.) and a catalytic amount of ZnI<sub>2</sub> (0.004g). This solution was refluxed overnight. This yielded 0.211g of the captioned product. IR: COCN,  $\nu$  2220 cm<sup>-1</sup>; C=O,  $\nu$  1720cm<sup>-1</sup>. The isomeric purity of 1-10a was determined by hydrolyzing the acyl nitrile in warm water, the product being essentially pure compound 1-11a.

10

Example 15

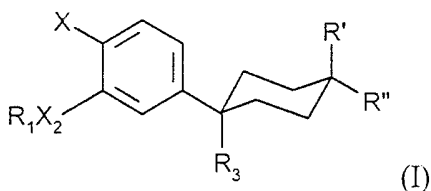
Preparation of Form 1-10b of 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexane acyl nitrile

In an experiment analogous to Example 14, the axial carboxylic acid was converted to the acid chloride using oxalyl chloride and catalytic amount of dimethyl formamide. This acid chloride was converted directly to the corresponding acyl nitrile, 1-10b, the isomer of the compound prepared in Example 14. The isomeric purity was assayed by hydrolyzing the acyl nitrile by stirring it in warm water for 20 hours. Analytical HPLC determination showed that > 96% of the product had the form of 1-10b.

15

AP/T/09/01618

1. A method for making a compound of formula I



$R_1$  is  $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$ ,

$-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$ ,  $-(CR_4R_5)_nO(CR_4R_5)_mR_6$ , or  $-(CR_4R_5)_rR_6$

wherein the alkyl moieties may be optionally substituted with one or more halogens;

$m$  is 0 to 2;

$n$  is 1 to 4;

$r$  is 0 to 6;

$R_4$  and  $R_5$  are independently selected from hydrogen or a  $C_{1-2}$  alkyl;

$R_6$  is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy $C_{1-3}$  alkyl, halo substituted aryloxy $C_{1-3}$  alkyl, indanyl, indenyl,  $C_{7-11}$  polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl,  $C_{3-6}$  cycloalkyl, or a  $C_{4-6}$  cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

a) when  $R_6$  is hydroxyl, then  $m$  is 2; or

b) when  $R_6$  is hydroxyl, then  $r$  is 2 to 6; or

c) when  $R_6$  is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then  $m$  is 1 or 2; or

d) when R<sub>6</sub> is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R<sub>6</sub> is other than H in  
-(CR<sub>4</sub>R<sub>5</sub>)<sub>n</sub>O(CR<sub>4</sub>R<sub>5</sub>)<sub>m</sub>R<sub>6</sub>;

X is YR<sub>2</sub>, halogen, nitro, NH<sub>2</sub>, or formyl amine;

X<sub>2</sub> is O or NR<sub>8</sub>;

Y is O or S(O)<sub>m'</sub>;

m' is 0, 1, or 2;

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

R<sub>3</sub> is hydrogen, halogen, C<sub>1-4</sub> alkyl, CH<sub>2</sub>NHC(O)C(O)NH<sub>2</sub>, halo-substituted C<sub>1-4</sub> alkyl, -CH=CR<sub>8</sub>'R<sub>8</sub>', cyclopropyl optionally substituted by R<sub>8</sub>', CN, OR<sub>8</sub>, CH<sub>2</sub>OR<sub>8</sub>, NR<sub>8</sub>R<sub>10</sub>, CH<sub>2</sub>NR<sub>8</sub>R<sub>10</sub>, C(Z')H, C(O)OR<sub>8</sub>, C(O)NR<sub>8</sub>R<sub>10</sub>, or C≡CR<sub>8</sub>'

R<sub>8</sub> is hydrogen or C<sub>1-4</sub> alkyl optionally substituted by one to three fluorines;

R<sub>8</sub>' is R<sub>8</sub> or fluorine;

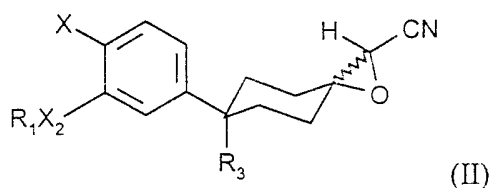
R<sub>10</sub> is OR<sub>8</sub> or R<sub>11</sub>;

R<sub>11</sub> is hydrogen, or C<sub>1-4</sub> alkyl optionally substituted by one to three fluorines;

Z' is O, NR<sub>9</sub>, NOR<sub>8</sub>, NCN, C(-CN)<sub>2</sub>, CR<sub>8</sub>CN, CR<sub>8</sub>NO<sub>2</sub>, CR<sub>8</sub>C(O)OR<sub>8</sub>, CR<sub>8</sub>C(O)NR<sub>8</sub>R<sub>8</sub>, C(-CN)NO<sub>2</sub>, C(-CN)C(O)OR<sub>9</sub>, or C(-CN)C(O)NR<sub>8</sub>R<sub>8</sub>;

R' and R'' are independently hydrogen or -C(O)OH;

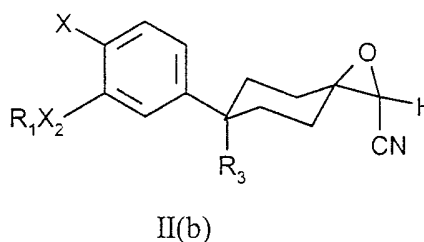
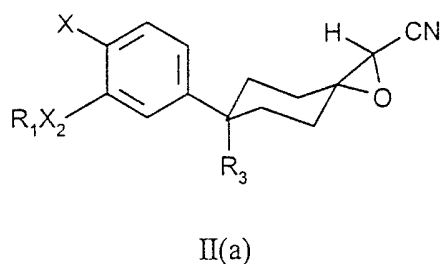
which method comprises treating a compound of formula II



where  $R_1$ ,  $R_3$ ,  $X_2$  and  $X$  are the same as for formula (I), with a Lewis acid in an aqueous solution at a temperature between about  $60^\circ$  and  $100^\circ$  C, optionally under an inert atmosphere for a time sufficient for the reaction to go to completion.

2. The method of claim 1 wherein  $R_1X_2$  is cyclopentyloxy and  $X$  is methoxy.

3. A compound of formula II(a) or II(b)



$R_1$  is  $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$ ,

$-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$ ,  $-(CR_4R_5)_nO(CR_4R_5)_mR_6$ , or  $-(CR_4R_5)_rR_6$

wherein the alkyl moieties may be optionally substituted with one or more halogens;

$m$  is 0 to 2;

$n$  is 1 to 4;

$r$  is 0 to 6;

$R_4$  and  $R_5$  are independently selected from hydrogen or a  $C_{1-2}$  alkyl;

$R_6$  is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy $C_{1-3}$  alkyl, halo substituted aryloxy $C_{1-3}$  alkyl, indanyl, indenyl,  $C_{7-11}$  polycycloalkyl,

tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranal, thiopyranal, C<sub>3-6</sub> cycloalkyl, or a C<sub>4-6</sub> cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group; provided that:

a) when R<sub>6</sub> is hydroxyl, then m is 2; or

b) when R<sub>6</sub> is hydroxyl, then r is 2 to 6; or

c) when R<sub>6</sub> is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R<sub>6</sub> is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R<sub>6</sub> is other than H in

$-(CR_4R_5)_nO(CR_4R_5)_mR_6$ ;

X is YR<sub>2</sub>, halogen, nitro, NH<sub>2</sub>, or formyl amine;

X<sub>2</sub> is O or NR<sub>8</sub>;

Y is O or S(O)<sub>m'</sub>;

m' is 0, 1, or 2;

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

R<sub>3</sub> is hydrogen, halogen, C<sub>1-4</sub> alkyl, CH<sub>2</sub>NHC(O)C(O)NH<sub>2</sub>, halo-substituted C<sub>1-4</sub> alkyl, -CH=CR<sub>8</sub>'R<sub>8</sub>', cyclopropyl optionally substituted by R<sub>8</sub>', CN, OR<sub>8</sub>', CH<sub>2</sub>OR<sub>8</sub>', NR<sub>8</sub>R<sub>10</sub>', CH<sub>2</sub>NR<sub>8</sub>R<sub>10</sub>', C(Z)'H, C(O)OR<sub>8</sub>', C(O)NR<sub>8</sub>R<sub>10</sub>', or C≡CR<sub>8</sub>'

R<sub>8</sub> is hydrogen or C<sub>1-4</sub> alkyl optionally substituted by one to three fluorines;

R<sub>8</sub>' is R<sub>8</sub> or fluorine;

R<sub>10</sub> is OR<sub>8</sub> or R<sub>11</sub>;

AP/F/99/01618



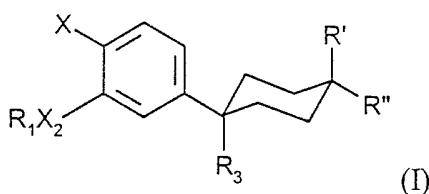
$R_{11}$  is hydrogen, or  $C_{1-4}$  alkyl optionally substituted by one to three fluorines; and

Z' is O,  $NR_9$ ,  $NOR_8$ ,  $NCN$ ,  $C(-CN)_2$ ,  $CR_8CN$ ,  $CR_8NO_2$ ,  $CR_8C(O)OR_8$ ,  $CR_8C(O)NR_8R_8$ ,  $C(-CN)NO_2$ ,  $C(-CN)C(O)OR_9$ , or  $C(-CN)C(O)NR_8R_8$ .

4. The compound of claim 3 wherein  $R_1X_2$  is cyclopentyloxy and X is methoxy.

5. The method of claim 1 or 2 wherein the Lewis acid is lithium bromide, water is present in at least 2 equivalents relative to the epoxide, and the reaction is heated to about 90-95 °C for up to about 8 hours.

6. A process for preparing a compound of formula (I)



$R_1$  is  $-(CR_4R_5)_rR_6$  wherein the alkyl moieties may be unsubstituted or substituted with one or more halogens;

r is 0 to 6;

$R_4$  and  $R_5$  are independently selected from hydrogen or a  $C_{1-2}$  alkyl;

$R_6$  is  $C_{3-6}$  cycloalkyl wherein the cycloalkyl group may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

X is  $YR_2$ ;

$X_2$  is O;

Y is O or  $S(O)_{m'}$ ;

$m'$  is 0, 1, or 2;

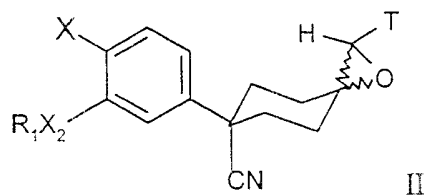
R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> unsubstituted or substituted by 1 or more halogens;

R<sub>3</sub> is CN; and

R' and R'' are independently hydrogen or -C(O)OH;

which process comprises

a) reacting a compound of formula II

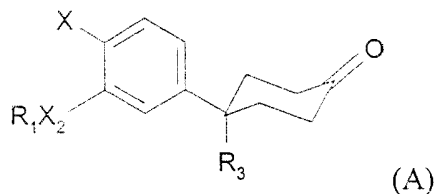


where R<sub>1</sub>, R<sub>3</sub>, X<sub>2</sub> and X are the same as in formula (I), and T is CN or SO<sub>2</sub>R where R is C<sub>1-6</sub>alkyl or C<sub>0-3</sub>alkylphenyl,

with at least about 1.5 equivalents of a Lewis acid at a temperature between about 60° and 100° C optionally under an inert atmosphere;

wherein the compound of formula (II) is prepared by

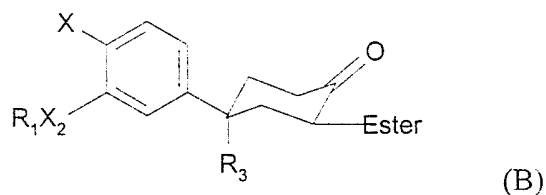
b) reacting a ketone of formula A



wherein R<sub>1</sub>, R<sub>3</sub>, X<sub>2</sub> and X are the same as in formula (I) with a molar excess of chloroacetonitrile, an inorganic base, and a catalytic amount of benzyltriethylammonium chloride in a water miscible solvent;

wherein the compound of formula (A) is prepared by

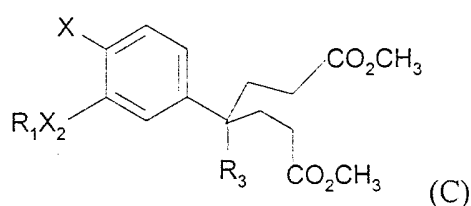
c) decarboxylating a beta-keto ester of formula B



wherein  $R_1$ ,  $R_3$ ,  $X_2$  and  $X$  are the same as in formula (I) by heating a solution of the the beta-keto ester with dimethylsulfoxide to about  $150^\circ\text{C}$ ;

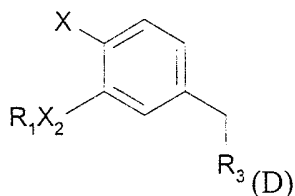
wherein the beta-keto ester of formula B is prepared by

d) cyclizing a pimelate of formula C



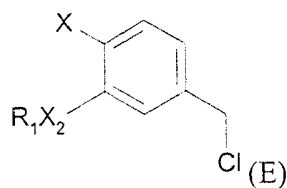
wherein  $R_1$ ,  $R_3$ ,  $X_2$  and  $X$  are the same as in formula (I) with about 2 equivalents of a strong base at about  $75^\circ\text{C}$ , wherein the compound of formula C is prepared by

e) reacting a nitrile of formula D



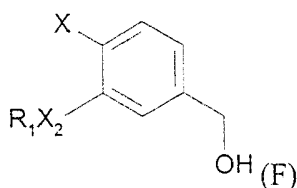
wherein  $R_1$ ,  $R_3$ ,  $X_2$  and  $X$  are the same as in formula (I) with an alkyl acrylate in a 3-4-fold molar excess in the presence of a catalytic amount of Triton-B, wherein formula (D) compounds are prepared by

f) reacting a compound of formula (E)



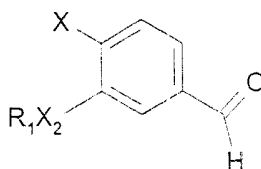
wherein  $R_1$ ,  $X_2$  and  $X$  are the same as in formula (I) with about a 50% molar excess of an alkali metal cyanide, wherein formula (E) compounds are prepared by;

g) reacting an alcohol of formula (F)



wherein  $R_1$ ,  $X_2$  and  $X$  are the same as in formula (I) with excess hydrochloric acid, wherein formula (F) compounds are prepared by;

h) reducing an aldehyde of formula (G)

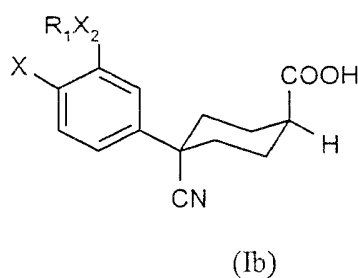
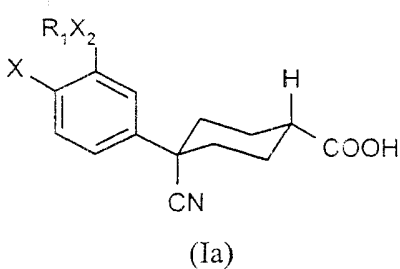


wherein  $R_1$ ,  $X_2$  and  $X$  are the same as in formula (I) wherein the reduction is carried out using an inorganic reducing agent.

7. The process of claim 6 wherein, in step a), the Lewis acid is lithium bromide, at least about 2 equivalents of water are present, and the reaction is heated to about 90-95 °C for up to about 8 hours.

8. The process of claim 6 wherein, in step b) the inorganic base is aqueous potassium hydroxide and the water-miscible solvent is tetrahydrofuran and the reaction is carried out at a temperature of about 0 °C.
9. The process of claim 6 wherein in step c) the strong base is sodium methoxide which is present in about 1.5 molar equivalents and the reaction is carried out at about 70 to 75 °C for up to 2 hours.
10. The process of claim 6 wherein steps c) and d) are combined by cyclizing the pimelate by reacting it with sodium methoxide decarboxylating the resulting beta-keto ester without isolating it by adding dimethylsulfoxide to the ester-containing solution and heating that solution to about 145 °C for up to 2 hours.
11. The process of claim 10 wherein after the cyclization reaction step is completed, the reaction mixture is cooled to about room temperature and the pH is adjusted to 6.8-7.2 before adding dimethylsulfoxide.
12. The process of claim 6, step e), wherein the alkyl acrylate is methyl acrylate.
13. The process of claim 6, step f), wherein the alkali metal cyanide is sodium cyanide and the reaction is carried out at about 55 °C.
14. The process of claim 6, step h), wherein the reducing agent is sodium borohydride.
15. The process of any one of claims 6 - 14 wherein, in formula I, R<sub>1</sub> is cyclopentyl; Y is oxygen; and R<sub>2</sub> is methyl.
16. A process for preparing a compound of formula I(a) or I(b) or a mixture thereof

AP/T/09:01618



wherein

r is 0 to 6;

X is OR<sub>2</sub>,

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

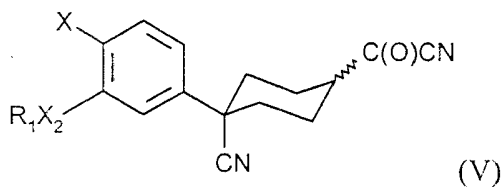
R<sub>1</sub> is -(CR<sub>4</sub>R<sub>5</sub>)<sub>r</sub>R<sub>6</sub>,

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;

R<sub>6</sub> is C<sub>3-6</sub> cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

X<sub>2</sub> is O;

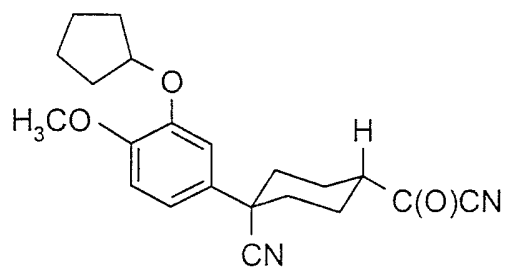
which process comprises treating an acyl nitrile of formula (V) with water



wherein X and R<sub>1</sub>X<sub>2</sub> are the same as in formula (Ia) and (Ib).

17. The process of claim 16 wherein the compound of formula (V) is that of formula (Va)

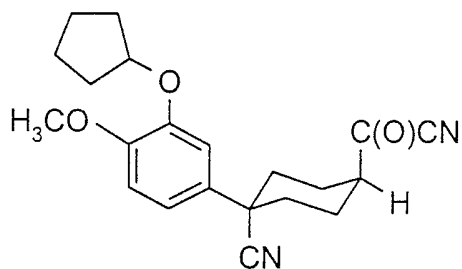
AP/T/99/01618



(Va)

and results in the formation of a compound of formula (Ia).

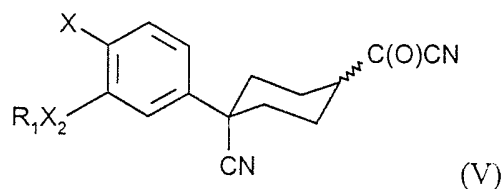
18. The process of claim 16 wherein the compound of formula (V) is that of formula (Vb)



(Vb)

and results in the formation of a compound of formula (Ib).

19. A process for preparing a compound of formula (V)



(V)

wherein

r is 0 to 6;

X is OR<sub>2</sub>,

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

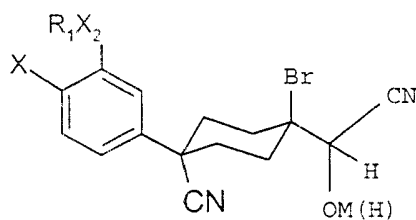
R<sub>1</sub> is -(CR<sub>4</sub>R<sub>5</sub>)<sub>r</sub>R<sub>6</sub>,

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;

R<sub>6</sub> is C<sub>3-6</sub> cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

X<sub>2</sub> is O;

which process comprises maintaining at about room temperature in solution for a time sufficient to effect the conversion, a compound of formula (Z)



(Z)

where X and R<sub>1</sub>X<sub>2</sub> are the same as in formula (V) and M is Li or Mg and the group (H) is hydrogen.

20. The process of claim 19 wherein formula (Z) is that of figure 1

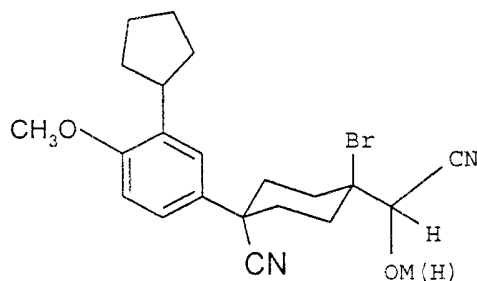


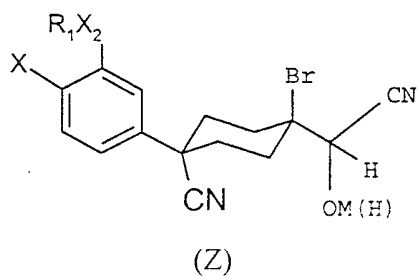
Figure 1

where M is Li or Mg and (H) is hydrogen.

21. A compound of formula (Z)

AP/99/01618





wherein

r is 0 to 6;

X is  $OR_2$ ,

$R_2$  is independently selected from  $-CH_3$  or  $-CH_2CH_3$  optionally substituted by 1 or more halogens;

$R_1$  is  $-(CR_4R_5)_rR_6$ ,

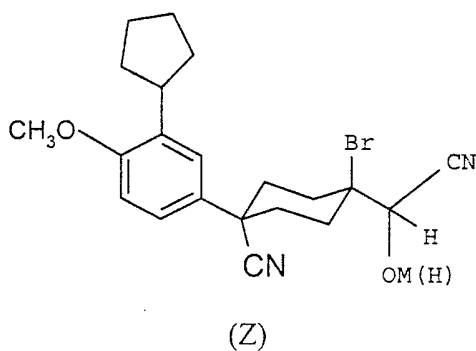
$R_4$  and  $R_5$  are independently selected from hydrogen or a  $C_{1-2}$  alkyl;

$R_6$  is  $C_{3-6}$  cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

$X_2$  is O; and

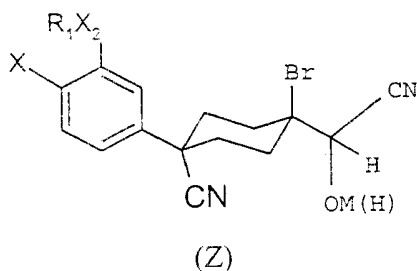
M is Li or Mg and (H) is hydrogen.

22. A compound of formula (Z) according to claim 21 which is



wherein M is Li or Mg and (H) is hydrogen.

23. A process for preparing a compound of formula (Z)



wherein

X is OR<sub>2</sub>,

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

R<sub>1</sub> is -(CR<sub>4</sub>R<sub>5</sub>)<sub>r</sub>R<sub>6</sub>,

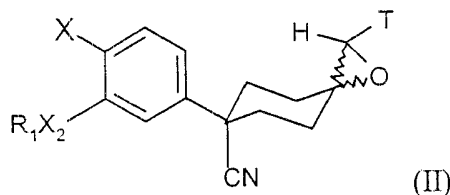
R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;

R<sub>6</sub> is C<sub>3-6</sub> cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

X<sub>2</sub> is O; and

M is Li or Mg and (H) is hydrogen;

which process comprises treating an epoxide of formula (II)



wherein X and R<sub>1</sub>X<sub>2</sub> are the same as in formula (Z) and T is CN or SO<sub>2</sub>R where R is C<sub>1-6</sub>alkyl or C<sub>0-3</sub>alkylphenyl with a Lewis acid under anhydrous conditions.

24. The process of claim 23 wherein the Lewis acid is LiBr.

25. The process of claim 22 or 23 wherein the epoxide of formula (II) has the structure represented by figure 2

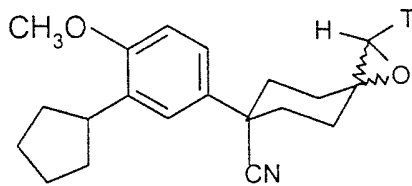
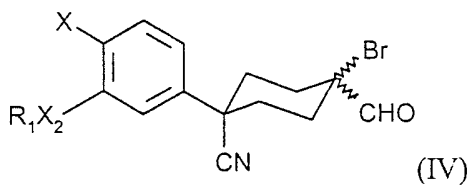


Figure 2

where T is CN or *p*-tolylsulfonyl.

26. A compound of formula (IV)



where

$r$  is 0 to 6;

$X$  is  $OR_2$ ,

$R_2$  is independently selected from  $-CH_3$  or  $-CH_2CH_3$  optionally substituted by 1 or more halogens;

$R_1$  is  $-(CR_4R_5)_rR_6$ ,

$R_4$  and  $R_5$  are independently selected from hydrogen or a  $C_{1-2}$  alkyl;

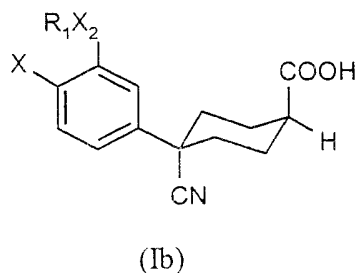
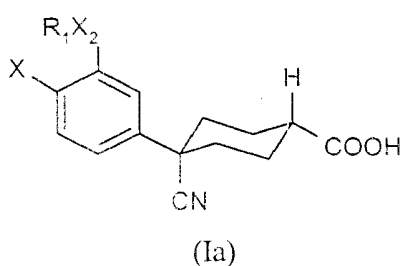
$R_6$  is  $C_{3-6}$  cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

$X_2$  is O.

27. A compound of formula (IV) according to claim 26 wherein  $X$  is methoxy,  $R_1$  is cyclopentyl and  $X_2$  is oxygen.

28. A process for preparing a compound of formula (Ia) or (Ib)

AP/T/99/01618



where

r is 0 to 6;

X is OR<sub>2</sub>,

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

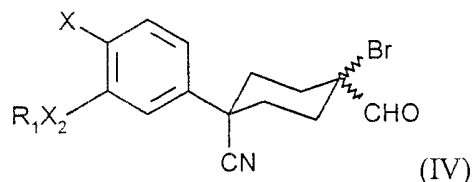
R<sub>1</sub> is -(CR<sub>4</sub>R<sub>5</sub>)<sub>r</sub>R<sub>6</sub>,

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;

R<sub>6</sub> is C<sub>3-6</sub> cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

X<sub>2</sub> is O;

which process comprises treating an aldehyde of formula (IV)

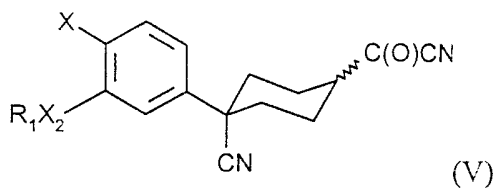


wherein X and R<sub>1</sub>X<sub>2</sub> are the same as in formula I(a) and I(b) with an alkali metal cyanide.

29. The process according to claim 28 wherein the cyanide is LiCN.

30. The process according to claim 28 or 29 wherein, in formula (IV), X is methoxy, R<sub>1</sub> is cyclopentyl and X<sub>2</sub> is oxygen.

31. A process for preparing an acyl nitrile of formula (V)



wherein

r is 0 to 6;

X is OR<sub>2</sub>,

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

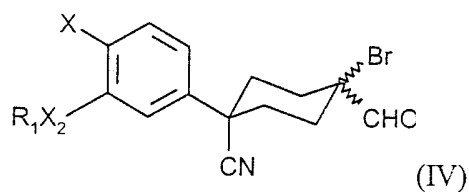
R<sub>1</sub> is -(CR<sub>4</sub>R<sub>5</sub>)<sub>r</sub>R<sub>6</sub>,

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;

R<sub>6</sub> is C<sub>3-6</sub> cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

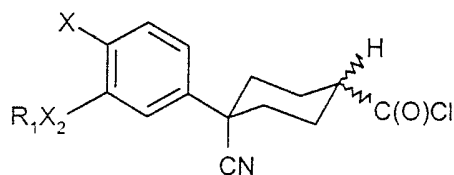
X<sub>2</sub> is O;

which process comprises treating an aldehyde of formula (IV)



wherein X, and R<sub>1</sub>X<sub>2</sub> are the same as in formula (V) with LiCN and a catalytic amount of dimethyl formamide.

32. A compound according to formula (VI)



wherein

r is 0 to 6;

X is OR<sub>2</sub>,

R<sub>2</sub> is independently selected from -CH<sub>3</sub> or -CH<sub>2</sub>CH<sub>3</sub> optionally substituted by 1 or more halogens;

R<sub>1</sub> is -(CR<sub>4</sub>R<sub>5</sub>)<sub>r</sub>R<sub>6</sub>,

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen or a C<sub>1-2</sub> alkyl;

R<sub>6</sub> is C<sub>3-6</sub> cycloalkyl which may be optionally substituted by 1 to 3 methyl groups or one ethyl group; and

X<sub>2</sub> is O.

33. A compound according to claim 32 wherein X is cyclopentyloxy, and R<sub>2</sub> is -CH<sub>3</sub>.

34. A process for enriching the *c*-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)-*r*-cyclohexanecarboxylic acid form from a mixture of *cis* and *trans* isomers of the acid, which process comprises crystallizing from a hexane/ethyl acetate solution of *cis* and *trans* isomers the *cis* isomer essentially free of the *trans* isomer.

35. The process of claim 34 wherein the *cis/trans* mixture is dissolved in ethyl acetate and hexanes.

36. The process of claim 35 where the *cis/trans* mixture is dissolved in ethyl acetate and then hexanes are added.

37. The process of claim 36 wherein the ethyl acetate solution of *cis/trans* isomers are heated to reflux, cooled and then hexanes added after which crystallization is carried out.

AP/F/99/01618