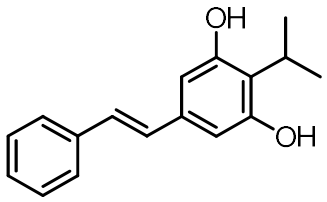
CLAIMS

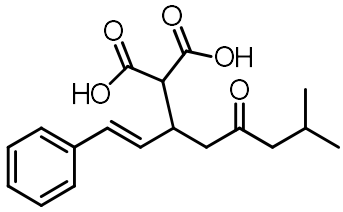
1 A process for preparing a compound of Formula (I) or a salt or solvate thereof



(I)

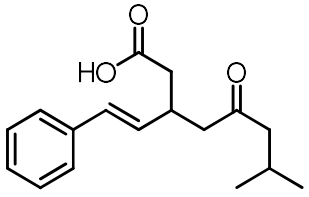
comprising:

a) decarboxylating a compound of Formula (VI)



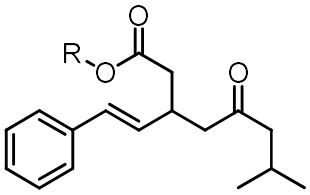
(VI) ,

to form a compound of Formula (V) or a salt thereof



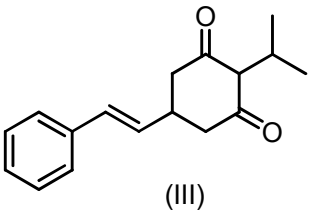
(V) ;

b) esterifying the compound of Formula (V) or a salt thereof to form a compound of Formula (IV)



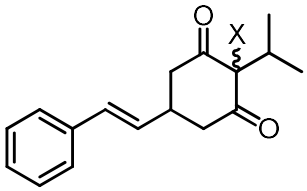
(IV) , wherein R is C_{1-4} alkyl;

c) cyclizing the compound of Formula (IV) to form a compound of Formula (III)



(III) ;

d) halogenating the compound of Formula (III) to form a compound of Formula (II)



(II)

wherein X is selected from Br, Cl and I; and

e) aromatizing the compound of Formula (II) to form the compound of Formula (I) or a salt or solvate thereof.

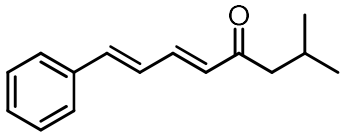
2. The process of claim 1, further comprising

f) purifying the compound of Formula (I) obtained from step e) by crystallization.

3. The process of claim 1 wherein R in step (b) is methyl and X in step (d) is chloro.

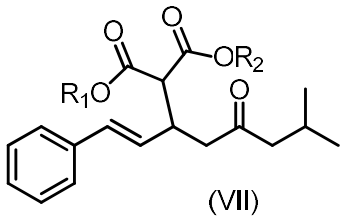
4. The process of claim 1, wherein the compound of Formula (VI) is prepared by a process comprising:

i. condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII)



(VIII) ;

ii. adding a dialkyl malonic ester of the Formula $R_1O(O)C\text{-}CH_2\text{-}C(O)OR_2$, wherein each of R_1 and R_2 is independently $C_{1\text{-}4}$ alkyl, to the compound of Formula (VIII) to form a compound of Formula (VII)



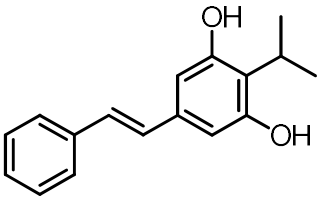
(VII) ,

wherein each of R_1 and R_2 is as defined for the dialkyl malonic ester;

iii. hydrolyzing the compound of Formula (VII) to form the compound of Formula (VI).

5. The process of claim 4, wherein each of R_1 and R_2 is independently ethyl.

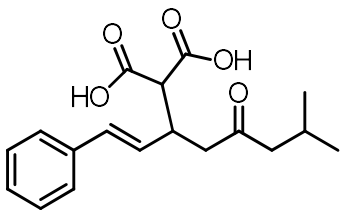
6. A process for preparing a compound of Formula (I) or a salt or solvate thereof



(I)

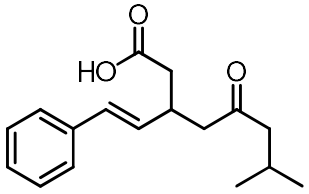
comprising:

a) heating a compound of Formula (VI)



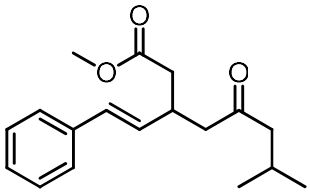
(VI) ;

with catalytic triethylamine to form a compound of Formula (V)



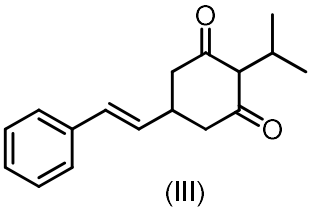
(V) ;

b) heating the compound of Formula (V) with methanol and aqueous hydrochloric acid to form a compound of Formula (IVa)



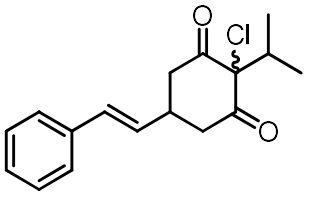
(IVa) ;

c) treating a cooled solution of the compound of Formula (IVa) with potassium *tert*-butoxide to form a compound of Formula (III)



(III) ;

d) heating the compound of Formula (III) with 1, 3-dichloro-5,5-dimethylhydantoin to form a compound of Formula (IIa)



(IIa) ; and

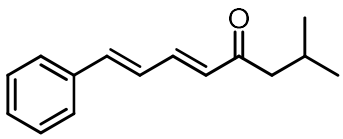
e) heating the compound of Formula (IIa) with tetraethylammonium chloride to form the compound of Formula (I).

7. The process of claim 6, further comprising

f) purifying the compound of Formula (I) from step e) by crystallization.

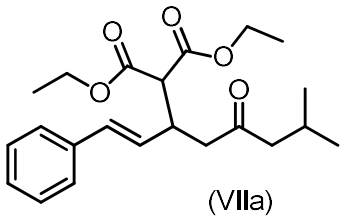
8. The process of claim 6, wherein the compound of Formula (VI) is prepared by a process comprising:

i. treating methyl isobutyl ketone with *trans*-cinnamaldehyde in the presence of methanolic sodium hydroxide to form a compound of Formula (VIII)



(VIII) ;

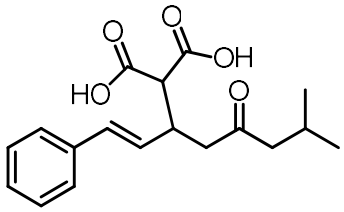
ii. treating the compound of Formula (VIII) with diethyl malonate in the presence of lithium bromide and triethylamine to form a compound of Formula (VIIa)



(VIIa) ;

iii. hydrolyzing the compound of Formula (VIIa) with sodium hydroxide and ethanol to obtain the compound of Formula (VI).

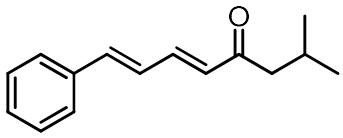
9. A process for preparing a compound of Formula (VI)



(VI)

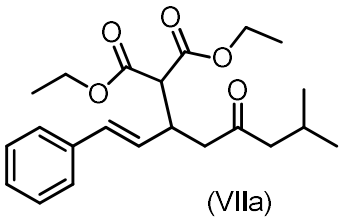
comprising:

a) condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII)



(VIII) ;

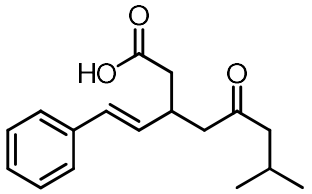
b) adding diethyl malonate to the compound of Formula (VIII) to form a compound of Formula (VIIa)



(VIIa) ; and

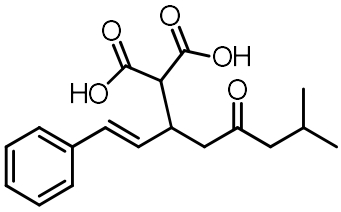
c) hydrolyzing the compound of Formula (VIIa) to form the compound of Formula (VI).

10. A process for preparing a compound of Formula (V) or a salt thereof



(V) ,

comprising decarboxylating a compound of Formula (VI) or

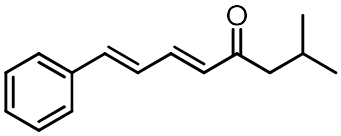


(VI) ,

in the presence of a base, to form the compound of Formula (V) or a salt thereof.

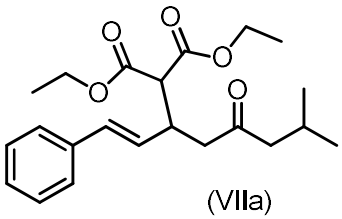
11. The process of claim 10, wherein the compound of Formula (VI) is prepared by a process comprising:

i. condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII)



(VIII) ;

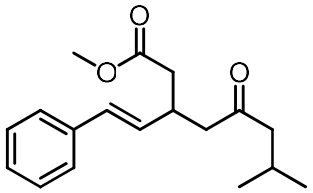
ii. adding diethyl malonate to the compound of Formula (VIII) to form a compound of Formula (VIIa)



(VIIa) ; and

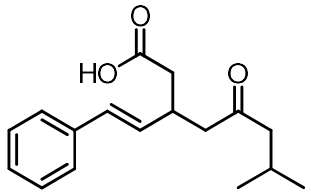
iii. hydrolyzing the compound of Formula (VIIa) to form the compound of Formula (VI).

12. A process for preparing a compound of Formula (IVa),



(IVa)

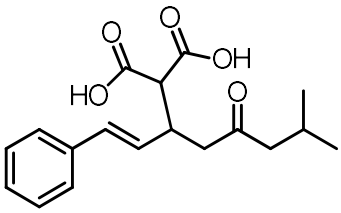
comprising esterifying a compound of Formula (V) or a salt thereof,



(V)

to form the compound of Formula (IVa).

13. The process of claim 12 wherein the compound of Formula (V) or a salt thereof, is prepared by a process comprising decarboxylating a compound of Formula (VI),,

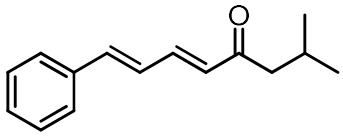


(VI) ,

in the presence of a base, to form the compound of Formula (V) or a salt thereof.

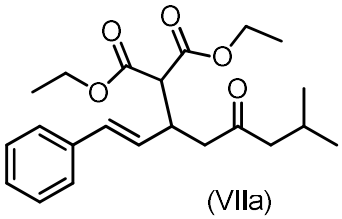
14. The process of claim 13, wherein the compound of Formula (VI), is prepared by a process comprising:

i. condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII),



(VIII) ;

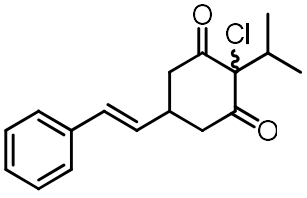
ii. adding diethyl malonate to the compound of Formula (VIII), to form a compound of Formula (VIIa),



(VIIa) ; and

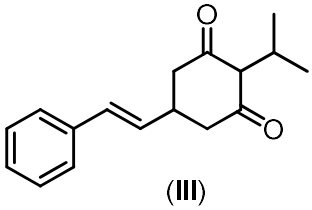
iii. hydrolyzing the compound of Formula (VIIa), to form the compound of Formula (VI).

15. A process for preparing a compound of Formula (IIa),



(IIa) ,

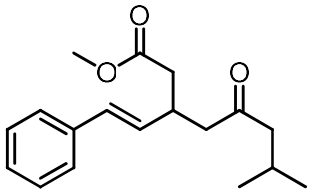
comprising halogenating a compound of Formula (III),



(III)

to form the compound of Formula (IIa).

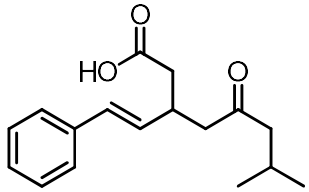
16. The process of claim 15 wherein the compound of Formula (III), is prepared by a process comprising cyclizing a compound of Formula (IVa),



(IVa)

to form the compound of Formula (III).

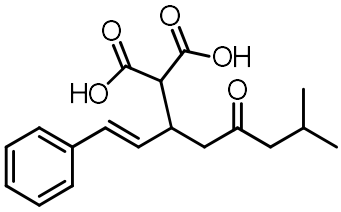
17. The process of claim 16, wherein the compound of Formula (IVa) , is prepared by a process comprising esterifying a compound of Formula (V) or a salt thereof,



(V)

to form the compound of Formula (IVa).

18. The process of claim 17, wherein the compound of Formula (V) or a salt thereof, is prepared by a process comprising decarboxylating a compound of Formula (VI)

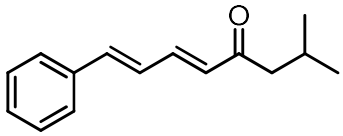


(VI) ,

in the presence of a base, to form the compound of Formula (V) or a salt thereof.

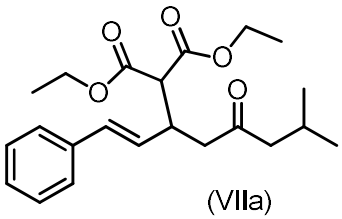
19. The process of claim 18, wherein the compound of Formula (VI), is prepared by a process comprising

i. condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII),



(VIII) ;

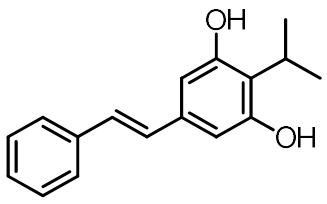
ii. adding diethyl malonate to the compound of Formula (VIII), to form a compound of Formula (VIIa),



(VIIa) ; and

iii. hydrolyzing the compound of Formula (VIIa), to form the compound of Formula (VI).

20. A compound of Formula (I) or a salt or solvate thereof

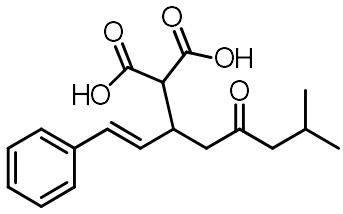


(I)

wherein the compound or a salt or solvate thereof is about 98% pure by weight and wherein the compound is at least 95% form 1, characterised by an X-ray powder diffraction pattern having peaks at 15.0, 17.8, 19.1, 20.2, 21.5, 22.4, 23.3, 24.5, 26.2 and 27.9 degrees2θ (± 0.1° 2θ);

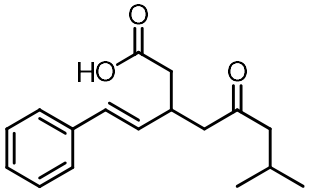
prepared by a process comprising:

a) decarboxylating a compound of Formula (VI)



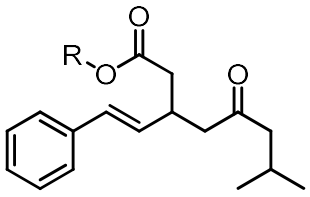
(VI) ,

to form a compound of Formula (V) or a salt thereof



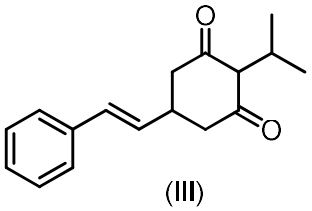
(V) ;

b) esterifying the compound of Formula (V) or a salt thereof to form a compound of Formula (IV)



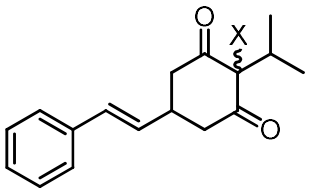
(IV) , wherein R is C_{1-4} alkyl;

c) cyclizing the compound of Formula (IV) to form a compound of Formula (III)



(III) ;

d) halogenating the compound of Formula (III) to form a compound of Formula (II)

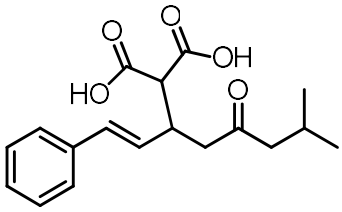


(II) ,

wherein X is selected from Br, Cl and I; and

e) aromatizing the compound of Formula (II) to form the compound of Formula (I) or a salt or solvate thereof.

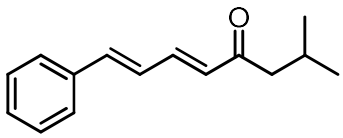
21. A compound of Formula (VI)



(VI)

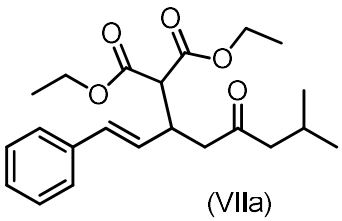
prepared by a process comprising:

a) condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII)



(VIII) ;

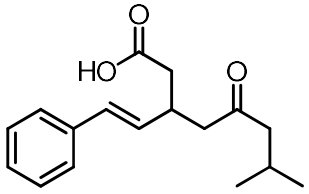
b) adding diethyl malonate to the compound of Formula (VIII) to form a compound of Formula (VIIa)



(VIIa) ; and

c) hydrolyzing the compound of Formula (VIIa) to form the compound of Formula (VI).

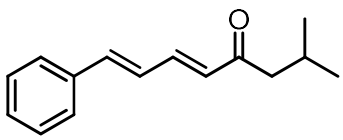
22. A compound of Formula (V) or a salt thereof



(V) ,

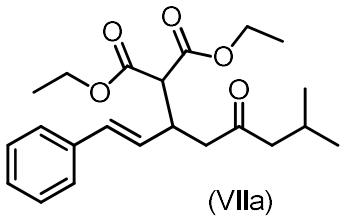
prepared by a process comprising:

a) condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII)



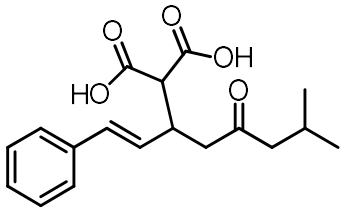
(VIII) ;

b) adding diethyl malonate to the compound of Formula (VIII) to form a compound of Formula (VIIa)



(VIIa) ;

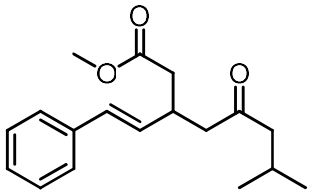
c) hydrolyzing the compound of Formula (VIIa) to form the compound of Formula (VI)



(VI) ; and

d) decarboxylating the compound of Formula (VI), in the presence of a base, to form the compound of Formula (V) or a salt thereof.

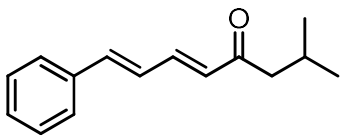
23 A compound of Formula (IVa)



(IVa)

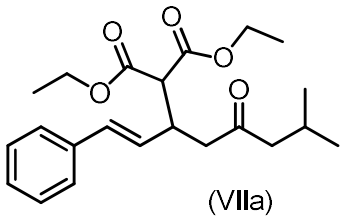
prepared by a process comprising:

a) condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII)



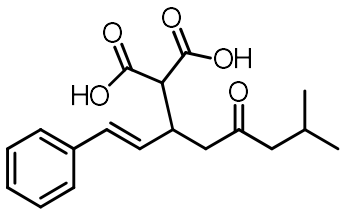
(VIII) ;

b) adding diethyl malonate to the compound of Formula (VIII) to form a compound of Formula (VIIa)



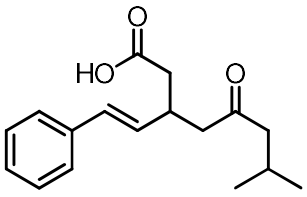
(VIIa) ;

c) hydrolyzing the compound of Formula (VIIa) to form the compound of Formula (VI)



(VI) ;

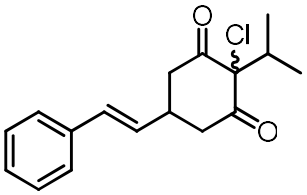
d) decarboxylating the compound of Formula (VI), in the presence of a base, to form the compound of Formula (V) or a salt thereof



(V) ; and

e) esterifying a compound of Formula (V) or a salt thereof to form the compound of Formula (IVa).

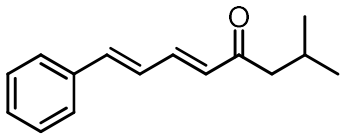
24. A compound of Formula (IIa)



(IIa) ,

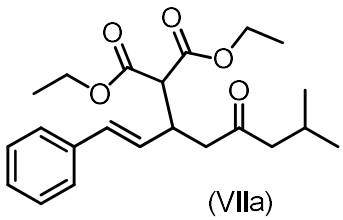
prepared by a process comprising:

a) condensing *trans*-cinnamaldehyde with methyl isobutyl ketone to form a compound of Formula (VIII)



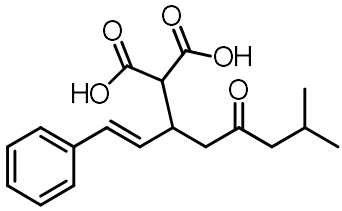
(VIII) ;

b) adding diethyl malonate to the compound of Formula (VIII) to form a compound of Formula (VIIa)



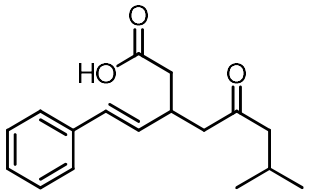
(VIIa) ;

c) hydrolyzing the compound of Formula (VIIa) to form the compound of Formula (VI)



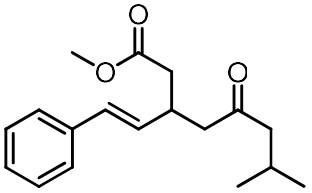
(VI) ;

d) decarboxylating the compound of Formula (VI), in the presence of a base, to form the compound of Formula (V) or a salt thereof



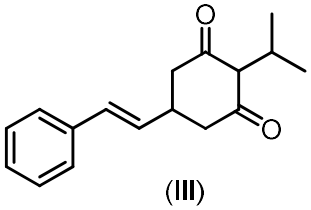
(V) ;

e) esterifying a compound of Formula (V) or a salt thereof to form the compound of Formula (IVa)



(IVa) ;

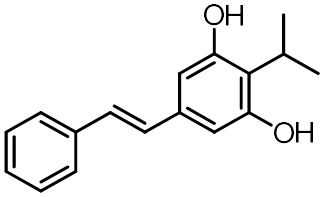
f) cyclizing a compound of Formula (IVa) to form the compound of Formula (III)



(III) ; and

g) halogenating a compound of Formula (III) to form the compound of Formula (IIa).

25. A compound of Formula (I)

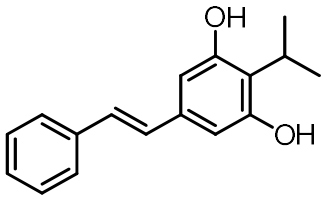


(I)

in the form of an acetic acid solvate thereof.

26. The compound of claim 25, characterised by an X-ray powder diffraction pattern having peaks at 6.7, 10.2, 11.1, 15.4, 16.9, 17.2, and 24.8 degrees 2θ (± 0.1° 2θ).

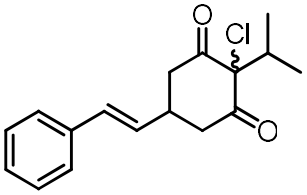
27. A compound of Formula (I)



(I) ,

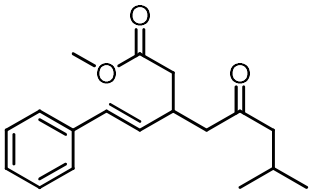
wherein the compound is about 98% pure by weight and wherein the compound is at least 95% form 1, characterised by an X-ray powder diffraction pattern having peaks at 15.0, 17.8, 19.1, 20.2, 21.5, 22.4, 23.3, 24.5, 26.2 and 27.9 degrees2θ (± 0.1° 2θ).

28. A compound of Formula (IIa)



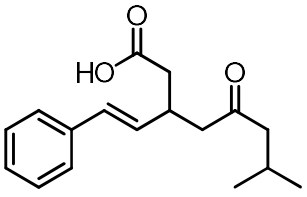
(IIa) .

29. A compound of Formula (IVa)



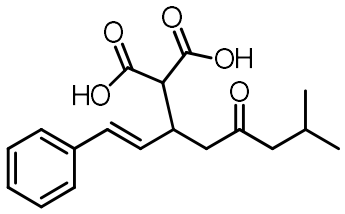
(IVa) .

30. A compound of Formula (V) or a salt thereof



(V) .

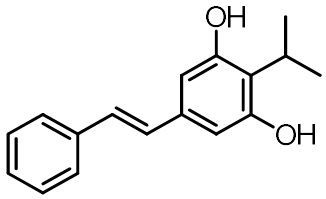
31. A compound of Formula (VI)



(VI)

.

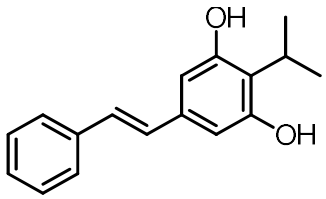
32. A pharmaceutical composition comprising a therapeutically effective amount of compound of Formula (I)



(I)

wherein the compound is about 98% pure by weight, and wherein the compound is at least 95% form 1, characterised by an X-ray powder diffraction pattern having peaks at 15.0, 17.8, 19.1, 20.2, 21.5, 22.4, 23.3, 24.5, 26.2 and 27.9 degrees2θ (± 0.1° 2θ); and a pharmaceutically acceptable excipient.

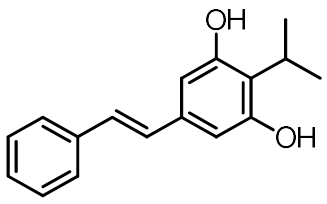
33. A pharmaceutical composition comprising a therapeutically effective amount of an acetic acid solvate of the compound of Formula (I)



(I)

and a pharmaceutically acceptable excipient.

34. A compound of Formula (I) or a salt or solvate thereof

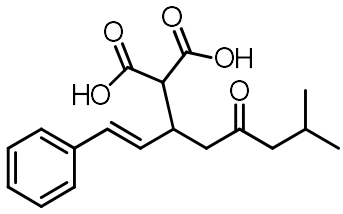


(I)

wherein the compound or a salt or solvate thereof is about 99% pure by weight and wherein the compound is at least 95% form 1, characterised by an X-ray powder diffraction pattern having peaks at 15.0, 17.8, 19.1, 20.2, 21.5, 22.4, 23.3, 24.5, 26.2 and 27.9 degrees2θ (± 0.1° 2θ);

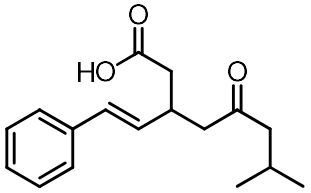
prepared by a process comprising:

a) decarboxylating a compound of Formula (VI)



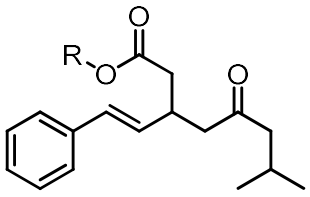
(VI) ,

to form a compound of Formula (V) or a salt thereof



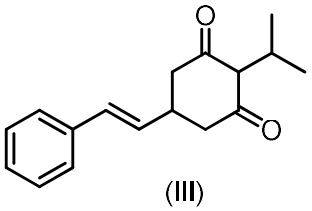
(V) ;

b) esterifying the compound of Formula (V) or a salt thereof to form a compound of Formula (IV)



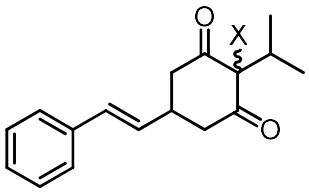
(IV) , wherein R is C_{1-4} alkyl;

c) cyclizing the compound of Formula (IV) to form a compound of Formula (III)



(III) ;

d) halogenating the compound of Formula (III) to form a compound of Formula (II)

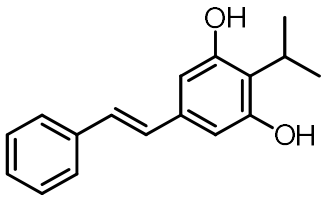


(II) ,

wherein X is selected from Br, Cl and I; and

e) aromatizing the compound of Formula (II) to form the compound of Formula (I) or a salt or solvate thereof.

35. A compound of Formula (I)

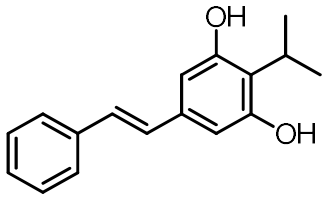


(I) ,

wherein the compound is about 99% pure by weight and wherein the compound is at least 95% form 1, characterised by an X-ray powder diffraction pattern having peaks at 15.0, 17.8, 19.1, 20.2, 21.5, 22.4, 23.3, 24.5, 26.2 and 27.9 degrees2θ (± 0.1° 2θ).

36. The compound of claim 20, 27, 34 or 35, wherein the compound is any one of the following: about 96% form 1, about 97% form 1, about 98% form 1, about 99% form 1, and at least 99% form 1.

37. A pharmaceutical composition comprising a therapeutically effective amount of compound of Formula (I)



(I)

wherein the compound is about 99% pure by weight, and wherein the compound is at least 95% form 1, characterised by an X-ray powder diffraction pattern having peaks at 15.0, 17.8, 19.1, 20.2, 21.5, 22.4, 23.3, 24.5, 26.2 and 27.9 degrees2θ (± 0.1° 2θ); and a pharmaceutically acceptable excipient.

38. The pharmaceutical composition of claim 32 or 37, wherein the compound is any one of the following: about 96% form 1, about 97% form 1, about 98% form 1, about 99% form 1, and at least 99% form 1.