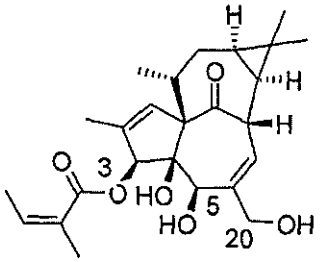
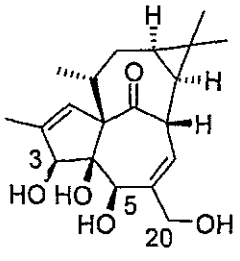
CLAIMS

1. Methods of producing ingenol-3-angelate (I) from ingenol (II).

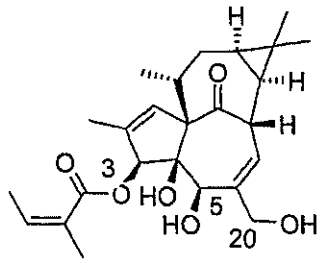


(I)

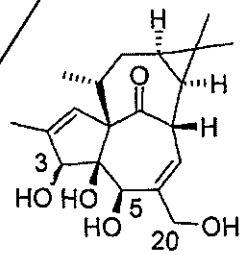


(II)

2. A method according to claim 1 of producing ingenol-3-angelate (2-Methyl-2(*Z*)-butenoic acid (1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1H-2,8a-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl ester) (I) from ingenol (II)



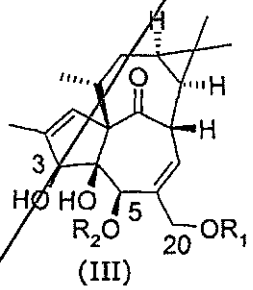
(I)



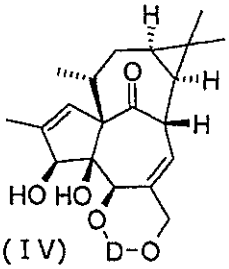
(II)

comprising the steps of:

(a) reacting one or both hydroxyl groups in positions 5 and 20 of ingenol with suitable hydroxyl protecting agents, same or different, to obtain a compound of the general formula (III) or (IV)



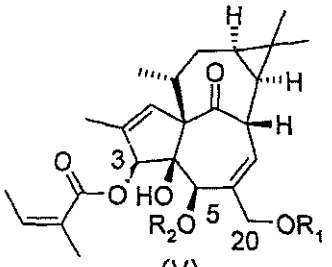
(III)



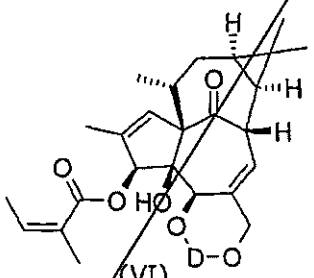
(IV)

wherein R_1 represents hydrogen or a hydroxyl protective group and R_2 represents hydrogen or a hydroxyl protective group,
with the proviso that not both R_1 and R_2 represent hydrogen,
or wherein D represents a dihydroxyl protective group

(b) esterifying the hydroxyl group at the 3-position of compounds (III) or (IV) to obtain compounds of the general formula (V) or (VI)



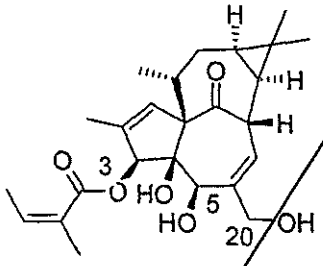
(V)



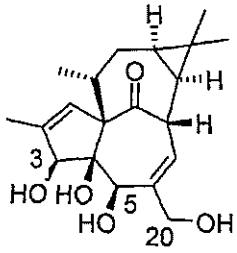
(VI)

wherein R_1, R_2 and D are as described above, and

(c) removing the hydroxyl protective groups R_1 or R_2, or R_1 and R_2, or D from compounds (V) or (VI) to obtain ingenol-3-angelate (I).

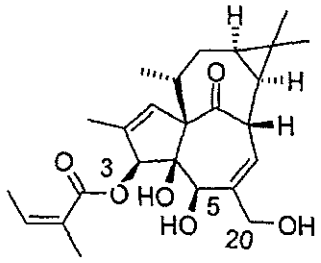


(I)

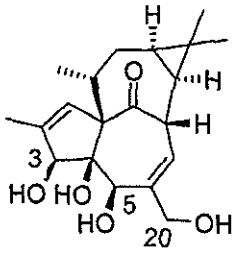


(II)

3. A method according to claim 1 of producing ingenol-3-angelate (2-Methyl-2(*Z*)-butenoic acid (1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1H-2,8a-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl ester) (I) from ingenol (II)



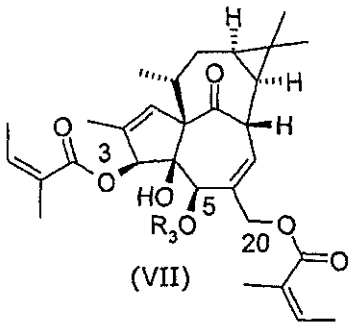
(I)



(II)

comprising the steps of:

(d) esterifying the 3- and the 20-hydroxyl group and optionally esterifying the 5-hydroxyl group of ingenol (II) to obtain a compound of the formula (VII)

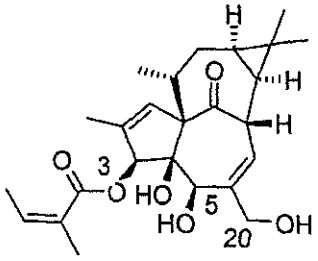


(VII)

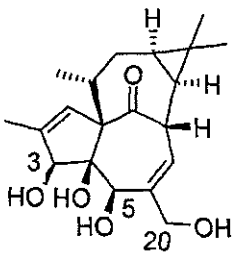
wherein R_3 represents hydrogen or angeloyl, and

(e) cleaving the angelate ester(s) in position 20 or in position 5 and 20 of compound (VII) to obtain ingenol-3-angelate (I).

4. A method according to claim 1 of producing ingenol-3-angelate (2-Methyl-2(*Z*)-butenoic acid (1a*R*,2*S*,5*R*,5a*S*,6*S*,8a*S*,9*R*,10a*R*)-5,5a-dihydroxy-4-(hydroxymethyl)-1,1,7,9-tetramethyl-11-oxo-1a,2,5,5a,6,9,10,10a-octahydro-1H-2,8a-methanocyclopenta[a]cyclopropa[e]cyclodecen-6-yl ester) (I) from ingenol (II)



(I)



(II)

comprising the step of:

(f) selective esterification of the 3-hydroxy group of compound (II) to obtain ingenol-3-angelate (I).

5. A method according to claim 2 wherein R_1 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl protective group, and R_2 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl protective group.

6. A method according to claim 2, wherein D represents an acetal , ketal , diacetal , diketal , ortho ester, silyl, boronate or a carbonate derived dihydroxyl protective group.

7. A method according to claim 2 or 5 wherein R_1 is selected from the group *consisting of* hydrogen or [(3,4-dimethoxybenzyl)oxy]methyl, guaiacolmethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, prenyl, *p*-methoxybenzyl, triphenylmethyl, 2-(trimethylsilyl)ethoxymethyl, triethylsilyl, triisopropylsilyl, *tert*-butyldimethylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, *tert*-butyldiphenylsilyl, triphenylsilyl, acetyl, chloroacetyl,phenoxyacetyl or angeloyl.

8. A method according to claim 2, 5 or 7 wherein R_2 is selected from the group consisting of hydrogen or [(3,4-dimethoxybenzyl)oxy]methyl, guaiacolmethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, prenyl, *p*-methoxybenzyl, triphenylmethyl, 2-(trimethylsilyl)ethoxymethyl, triethylsilyl, triisopropylsilyl, *tert*-butyldimethylsilyl,

dimethylisopropylsilyl, diethylisopropylsilyl, *tert*-butyldiphenylsilyl, triphenylsilyl, acetyl, chloroacetyl,phenoxyacetyl or angeloyl.

9. A method according to claim 2 or 6, wherein D is selected from the group consisting of isopropylidene, cyclopentylidene, cyclohexylidene, *p*-methoxybenzylidene, methoxymethylene, 2-oxacyclopentylidene, 2,3-dimethoxybutane-2,3-di-yl, 1,2-dimethoxycyclohexan-1,2-di-yl, octahydro-[2,2']-bipyran-2,2'-di-yl, di-*tert*-butylsilylene, 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene), phenyl boronate, 3-pentylidene, 2,4-dimethyl-3-pentylidene, 2,6-dimethyl-4-heptylidene, 3,3-dimethyl-2-butylidene, 1-phenyl-1-ethylidene,benzylidene, 2,4-dimethoxybenzylidene, 4-nitrobenzylidene, 2,4,6-trimethylbenzylidene, 2,2-dimethyl-1-propylidene, ethoxymethylene or isopropoxymethylene.

10. A method according to claim 2, 5 or 7 wherein R_1 represents a hydroxyl protective group and R_2 represents hydrogen.

11. A method according to claim 3 wherein R_3 represents hydrogen.

12. A method according to claim 2, 5, 6, 7, 8, 9 or 10 wherein step (b) comprises reacting compound (III) or (IV), wherein R_1, R_2 and D are as defined above with angelic acid in the presence of a coupling reagent or an enzyme.

13. A method according to claim 2, 5, 6, 7, 8, 9, 10 or 11 wherein step (b) comprises reacting compound (III) or (IV), wherein R_1, R_2 and D are as defined above with angelic acid in the presence of a coupling reagent.

14. A method according to claim 2, 5, 6, 7, 8, 9, 10, 12 or 13 wherein step (b) comprises reacting compound (III) or (IV), wherein R_1, R_2 and D are as defined above, with angelic acid in the presence of *N,N'*-Dicyclohexylcarbodiimide, *N,N,N',N'*-Tetramethyl-*O*-(7-azabenzotriazol-1-yl)uranium hexafluorophosphate , *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide or 2-chloro-1-methyl-pyridinium iodide.

15. A method according to claim 2, 5, 6, 7, 8, 9 or 10 wherein step (b) comprises reacting compound (III) or (IV), wherein R_1, R_2 and D are as defined above, with an activated derivative of angelic acid.

16. A method according to claim 2, 5, 6, 7, 8, 9, 10 or 15 wherein step (b) comprises reacting compound (III) or (IV), wherein R_1, R_2 and D are as defined above, with methyl angelate, angeloyl chloride, angelic acid anhydride, [(*Z*)-2-methylbut-2-enoyl] 2,4,6-trichlorobenzoate or angeloyl 4-nitrobenzoyl anhydride.

17. A method according to claim 2, 5, 6, 7, 8, 9 or 10 wherein step (b) comprises reacting compound (III) or (IV), wherein R_1, R_2 and D are as defined above, with an angelic acid halide or with angelic acid anhydride or with a mixed angelic acid anhydride.

18. A method according to claim 2, 5, 6, 7, 8, 9, 10 or 17 wherein step (b) comprises reacting compound (III) or (IV), wherein R_1, R_2 and D are as defined above, with angeloyl chloride, angelic acid anhydride, [(*Z*)-2-methylbut-2-enoyl] 2,4,6-trichlorobenzoate or angeloyl 4-nitrobenzoyl anhydride.

19. A compound of general formula (V) wherein R_1 represents hydrogen or a hydroxyl protective group and R_2 represents hydrogen or a hydroxyl protective group;
with the proviso that not both R_1 and R_2 represent hydrogen:
and with the proviso that R_1 and R_2 do not represent acetyl;
and with the proviso that R_1 and R_2 do not represent 2-[(2-aminobenzoyl)amino]benzoyl;
and with the proviso that R_1 does not represent decanoyl;
and with the proviso that R_1 does not represent 3-phenyl-2-propenoyl.

20. A compound according to claim 19 wherein R_1 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl

protective group, and R_2 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl protective group;

21. A compound according to claim 18 or 20 wherein R_1 and R_2 independently represents hydrogen or [(3,4-dimethoxybenzyl)oxy]methyl, guaiacolmethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, prenyl, *p*-methoxybenzyl, triphenylmethyl, 2-(trimethylsilyl)ethoxymethyl, triethylsilyl, triisopropylsilyl, *tert*-butyldimethylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, *tert*-butyldiphenylsilyl, triphenylsilyl, chloroacetyl or phenoxyacetyl.

22. A compound according to claim 19, 20 or 21 wherein R_1 represents a hydroxyl protective group and R_2 represents hydrogen;

23. A compound according to claim 19, 20, 21 and 22 chosen from the group consisting of
Ingenol-20-(*tert*-butyldimethylsilyl)-ether-3-angelate

24. A compound of general formula (VI) wherein D represents a dihydroxyl protective group; with the proviso that D does not represent isopropylidene.

25. A compound according to claim 24 wherein D represents an acetal , ketal , diacetal , diketal , ortho ester, silyl, boronate or a carbonate dihydroxyl protective group.

26. A compound according to claim 24 or 25 wherein D represents cyclopentylidene, cyclohexylidene, *p*-methoxybenzylidene, methoxymethylene, 2-oxacyclopentylidene, 2,3-dimethoxybutane-2,3-di-yl, 1,2-dimethoxycyclohexan-1,2-di-yl, octahydro-[2,2']-bipyran-2,2'-di-yl, di-*tert*-butylsilylene, 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene), phenyl boronate, 3-pentylidene, 2,4-dimethyl-3-pentylidene, 2,6-dimethyl-4-heptylidene, 3,3-dimethyl-2-butylidene, 1-phenyl-1-ethylidene,benzylidene, 2,4-dimethoxybenzylidene, 4-nitrobenzylidene, 2,4,6-trimethylbenzylidene, 2,2-dimethyl-1-propylidene, ethoxymethylene or isopropoxymethylene.

27. A compound according to claim 24, 25 or 26 chosen from the group consisting of
ingenol-5,20-(di(*tert*-butyl)silylene)-ether-3-angelate

28. A compound of general formula (III) wherein R_1 and R_2 independently represents hydrogen or an ether, acetal, ketal, silylether, or a sulfenate derived hydroxyl protective group;
with the proviso that not both R_1 and R_2 represent hydrogen;
and with the proviso that R_1 does not represent triphenylmethyl;
and with the proviso that R_1 does not represent t-butyldimethylsilyl.

29. A compound of general formula IV wherein D represents a dihydroxyl protective group;
with the proviso that D does not represent isopropylidene.

30. A compound according to claim 29 wherein D represents an acetal , ketal , diacetal , diketal , ortho ester, silyl, boronate or a carbonate derived dihydroxyl protective group.

31. A compound according to claim 29 and 30 wherein D represents cyclopentylidene, cyclohexylidene, *p*-methoxybenzylidene, methoxymethylene, 2-oxacyclopentylidene, 2,3-dimethoxybutane-2,3-di-yl, 1,2-dimethoxycyclohexan-1,2-di-yl, octahydro-[2,2']-bipyran-2,2'-di-yl, di-*tert*-butylsilylene, 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene), phenyl boronate, 3-pentylidene, 2,4-dimethyl-3-pentylidene, 2,6-dimethyl-4-heptylidene, 3,3-dimethyl-2-butylidene, 1-phenyl-1-ethylidene,benzylidene, 2,4-dimethoxybenzylidene, 4-nitrobenzylidene, 2,4,6-trimethylbenzylidene, 2,2-dimethyl-1-propylidene, ethoxymethylene or isopropoxymethylene.

32. A compound according to claim 29, 30 and 31 chosen from the group consisting of
Ingenol-5,20-(3-pentylidene)-ketal,
Ingenol-5,20-(2,4-dimethyl-3-pentylidene)-ketal,

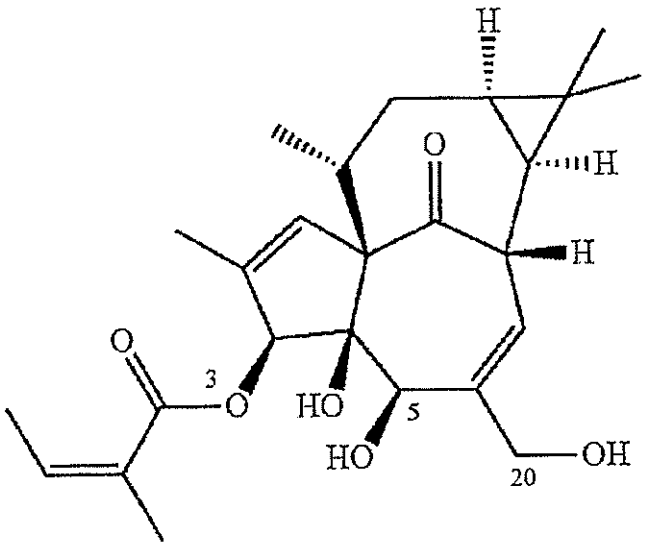
Ingenol-5,20-(2,6-dimethyl-4-heptylidene)-ketal,
Ingenol-5,20-cyclopentylidene-ketal,
Ingenol-5,20-cyclohexylidene-ketal,
Ingenol-5,20-(3,3-dimethyl-2-butylidene)-ketal,
Ingenol-5,20-(1-phenyl-1-ethylidene)-ketal,
Ingenol-5,20-benzylidene-acetal,
Ingenol-5,20-(4-methoxybenzylidene)-acetal,
Ingenol-5,20-(2,4-dimethoxybenzylidene)-acetal,
Ingenol-5,20-(4-nitrobenzylidene)-acetal,
Ingenol-5,20-(2,4,6-trimethylbenzylidene)-acetal,
Ingenol-5,20-(2,2-dimethyl-1-propylidene)-acetal,
Ingenol-5,20-methyl-orthoformate,
Ingenol-5,20-ethyl-orthoformate,
Ingenol-5,20-(prop-2-yl)-orthoformate,
Ingenol-5,20-(di(*tert*-butyl)silylene)-ether.

33. A compound of general structure (VII) wherein R_3 represents hydrogen or angeloyl.

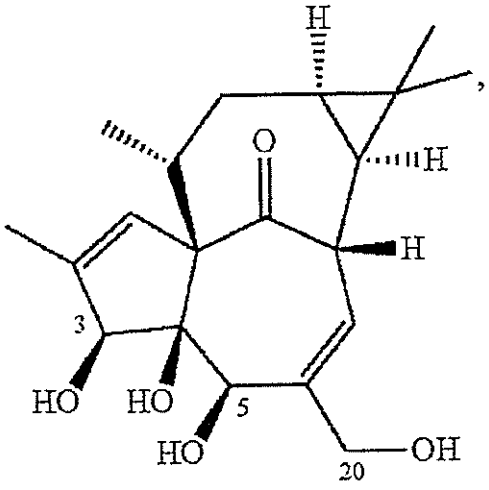
Claims

1. A method of producing ingenol-3-angelate (I) from ingenol (II):

(I)



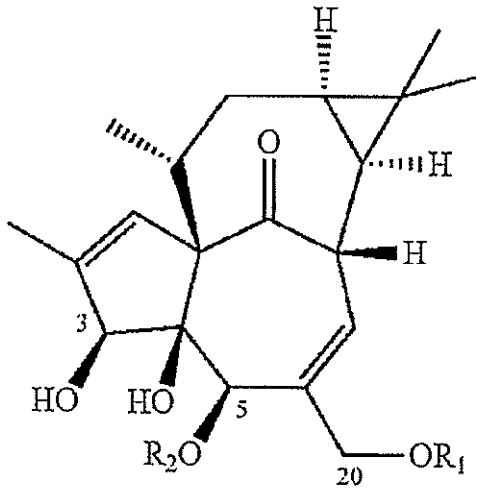
(II)



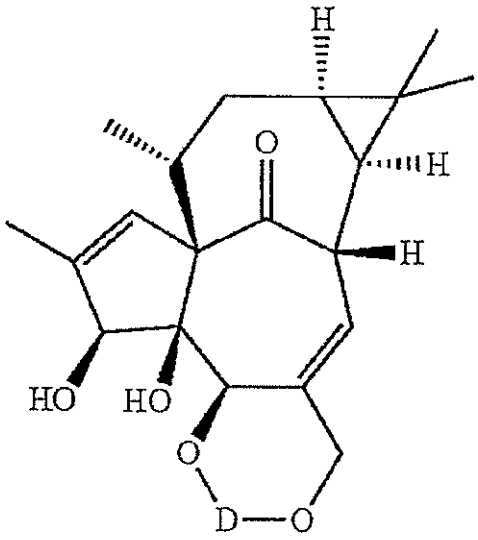
the method comprising the steps of:

(a) reacting one or both hydroxyl groups in positions 5 and 20 of ingenol (II) with suitable hydroxyl protecting agents, which may be the same or different, to obtain a compound of the general formula (III) or (IV)

(III)



(IV)

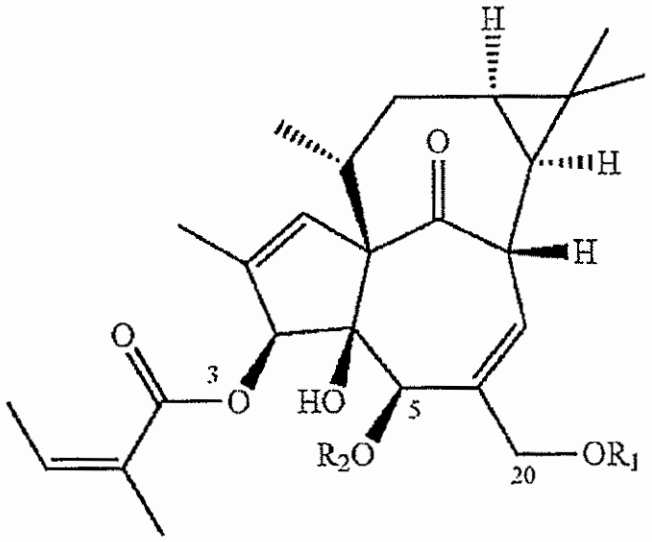


wherein R_1 represents hydrogen or a hydroxyl protective group and R_2 represents hydrogen or a hydroxyl protective group,

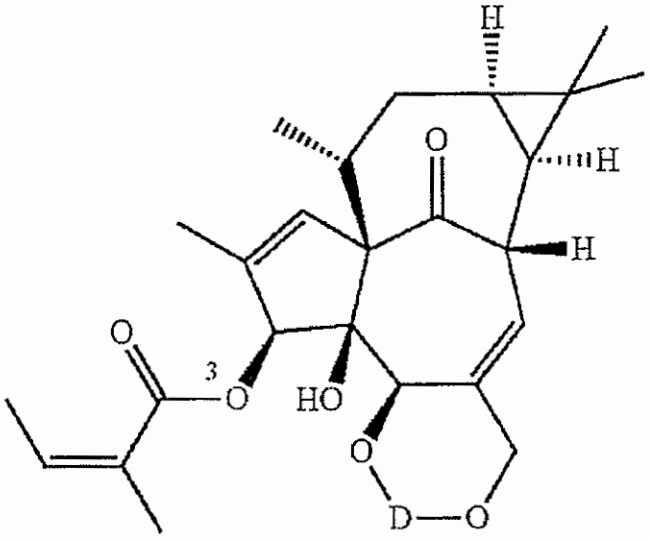
with the proviso that R_1 and R_2 are not both hydrogen, and wherein D represents a dihydroxyl protective group;

(b) esterifying the hydroxyl group at the 3-position of the compound of formula (III) or (IV) to obtain a compound of the general formula (V) or (VI)

(V)



(VI)

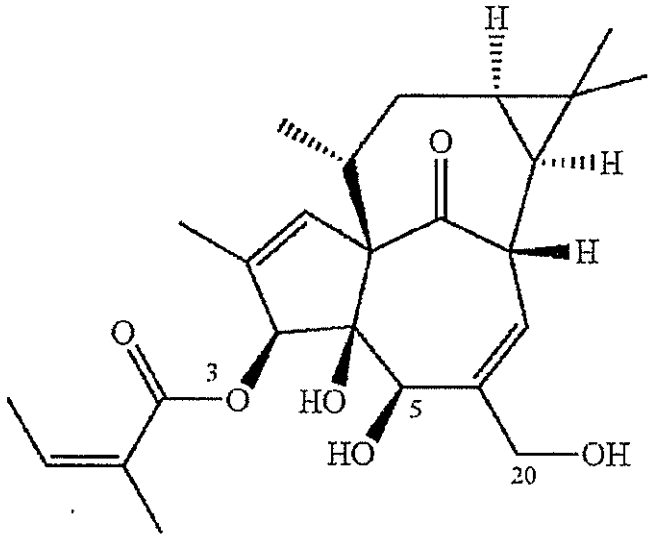


wherein R_1, R_2 and D are as described above; and

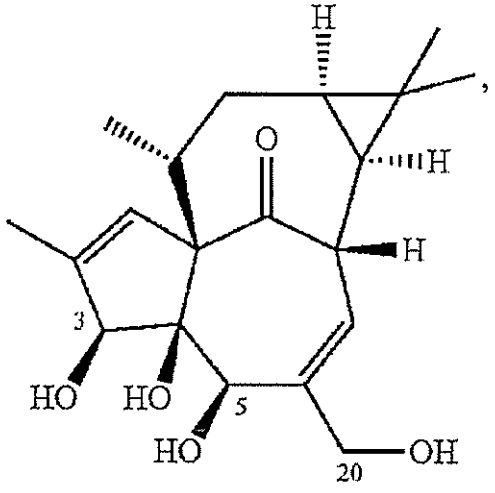
(c) removing the hydroxyl protective groups R_1 or R_2, or R_1 and R_2, or D from the compound of formula (V) or (VI) to obtain ingenol-3-angelate (I).

2. A method of producing ingenol-3-angelate (I) from ingenol (II):

(I)



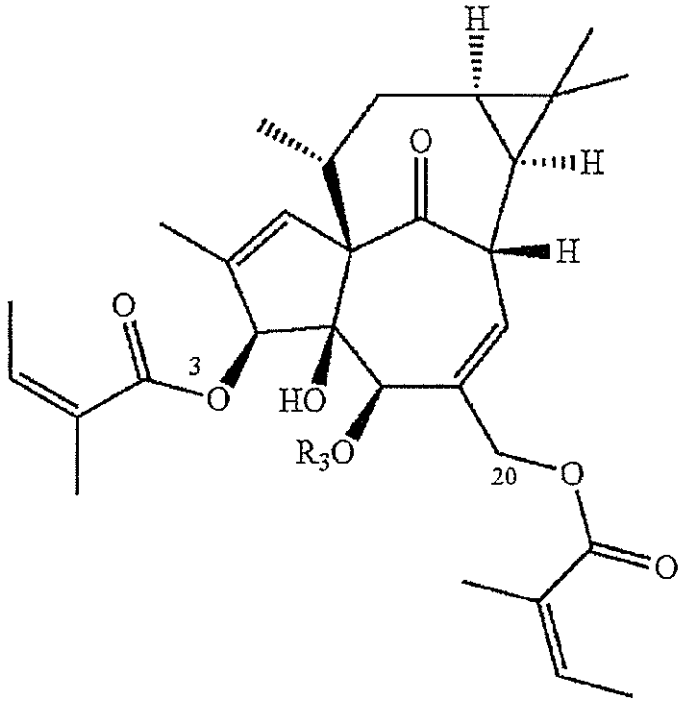
(II)



the method comprising the steps of:

(d) esterifying the 3- and the 20-hydroxyl group and optionally esterifying the 5-hydroxyl group of ingenol (II) to obtain a compound of the formula (VII)

(VII)



wherein R_3 represents hydrogen or angeloyl; and

(e) cleaving the angelate ester(s) in position 20 or in position 5 and 20 of the compound of formula (VII) to obtain ingenol-3-angelate (I).

3. The method according to claim **1**, wherein R_1 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl protective group, and R_2 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl protective group.

4. The method according to claim **1**, wherein D represents an acetal, ketal, diacetal, diketal, ortho ester, silyl, boronate or a carbonate derived dihydroxyl protective group.

5. The method according to claim **1**, wherein R_1 is selected from the group consisting of hydrogen or [(3,4-dimethoxybenzyl)oxy]methyl, guaiacolmethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, prenyl, p-methoxybenzyl, triphenylmethyl, 2-(trimethylsilyl)ethoxymethyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, tert-butyldiphenylsilyl, triphenylsilyl, acetyl, chloroacetyl, phenoxyacetyl or angeloyl.

6. The method according to claim **1**, wherein R_2 is selected from the group consisting of hydrogen or [(3,4-dimethoxybenzyl)oxy]methyl, guaiacolmethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, prenyl, p-methoxybenzyl, triphenylmethyl, 2-(trimethylsilyl)ethoxymethyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, tert-butyldiphenylsilyl, triphenylsilyl, acetyl, chloroacetyl, phenoxyacetyl or angeloyl.

7. The method according to claim **1**, wherein D is selected from the group consisting of isopropylidene, cyclopentylidene, cyclohexylidene, p-methoxybenzylidene, methoxymethylene, 2-oxacyclopentylidene, 2,3-dimethoxybutane-2,3-di-yl, 1,2-dimethoxycyclohexan-1,2-di-yl, octahydro-[2,2']-bipyran-2,2'-di-yl, di-tert-butylsilylene, 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene), phenyl boronate, 3-pentylidene, 2,4-dimethyl-3-pentylidene, 2,6-dimethyl-4-heptylidene, 3,3-dimethyl-2-butylidene, 1-phenyl-1-ethylidene, benzylidene, 2,4-dimethoxybenzylidene, 4-nitrobenzylidene, 2,4,6-trimethylbenzylidene, 2,2-dimethyl-1-propylidene, ethoxymethylene or isopropoxymethylene.

8. The method according to claim **1**, wherein R_1 represents a hydroxyl protective group and R_2 represents hydrogen.

9. The method according to claim **2**, wherein R_3 represents hydrogen.

10. The method according to claim **1**, wherein step (b) comprises reacting compound (III) or (IV) with angelic acid in the presence of a coupling reagent or an enzyme.

11. The method according to claim **1**, wherein step (b) comprises reacting the compound of formula (III) or (IV) with angelic acid in the presence of a coupling reagent.

12. The method according to claim **1**, wherein step (b) comprises reacting the compound of formula (III) or (IV) with angelic acid in the presence of N,N'-Dicyclohexylcarbodiimide, N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate, N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide or 2-chloro-1-methyl-pyridinium iodide.

13. The method according to claim **1**, wherein step (b) comprises reacting the compound of formula (III) or (IV) with an activated derivative of angelic acid.

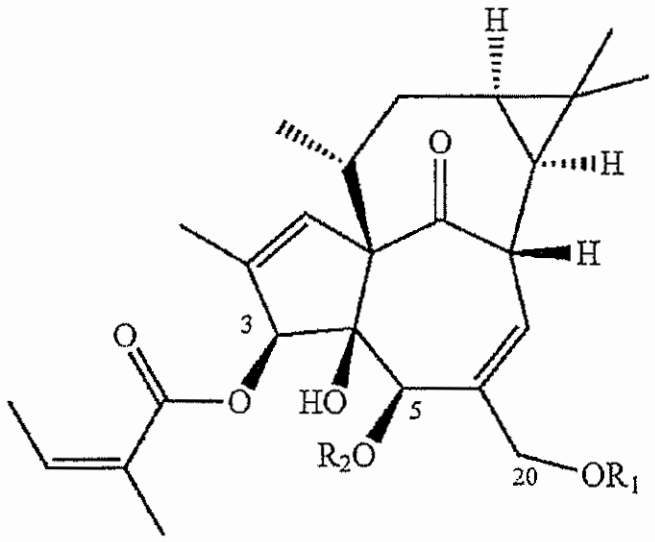
14. The method according to claim **1**, wherein step (b) comprises reacting the compound of formula (III) or (IV) with methyl angelate, angeloyl chloride, angelic acid anhydride, [(Z)-2-methylbut-2-enoyl]2,4,6-trichlorobenzoate, or angeloyl 4-nitrobenzoyl anhydride.

15. The method according to claim **1**, wherein step (b) comprises reacting the compound of formula (III) or (IV) with an angelic acid halide or with angelic acid anhydride or with a mixed angelic acid anhydride.

16. The method according to claim **1**, wherein step (b) comprises reacting the compound of formula (III) or (IV) with angeloyl chloride, angelic acid anhydride, [(Z)-2-methylbut-2-enoyl]2,4,6-trichlorobenzoate, or angeloyl 4-nitrobenzoyl anhydride.

17. A compound of general formula (V):

(V)



wherein R_1 represents hydrogen or a hydroxyl protective group and R_2 represents hydrogen or a hydroxyl protective group;

with the proviso that not both R_1 and R_2 represent hydrogen:

and with the proviso that R_1 and R_2 do not represent acetyl;

and with the proviso that R_1 and R_2 do not represent 2-[(2-aminobenzoyl)amino]benzoyl;

and with the proviso that R_1 does not represent decanoyl;

and with the proviso that R_1 does not represent 3-phenyl-2-propenoyl.

18. The compound according to claim 17, wherein R_1 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl protective group, and R_2 represents hydrogen or an ether, acetal, ketal, silylether, ester, carbonate, or a sulfenate derived hydroxyl protective group.

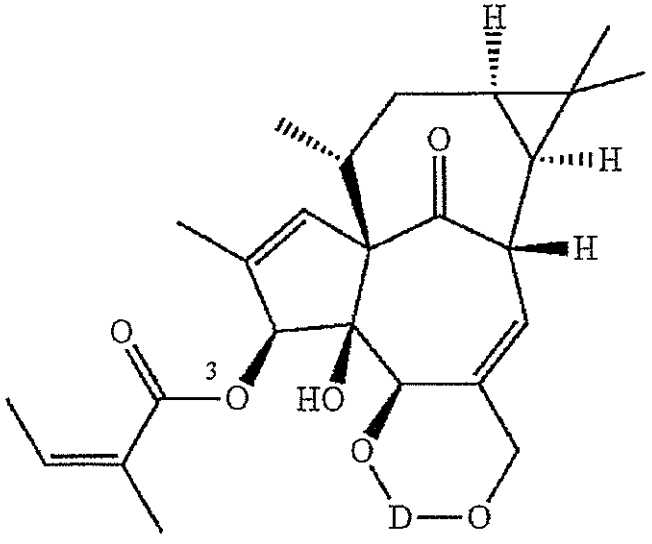
19. The compound according to claim **17**, wherein R_1 and R_2 independently represents hydrogen or [(3,4-dimethoxybenzyl)oxy]methyl, guaiacolmethyl, 2-methoxyethoxymethyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, allyl, prenyl, p-methoxybenzyl, triphenylmethyl, 2-(trimethylsilyl)ethoxymethyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, tert-butyldiphenylsilyl, triphenylsilyl, chloroacetyl or phenoxyacetyl.

20. The compound according to claim **17**, wherein R_1 represents a hydroxyl protective group and R_2 represents hydrogen.

21. The compound according to claim **17**, wherein the compound is Ingenol-20-(tert-butyldimethylsilyl)-ether-3-angelate.

22. A compound of general formula (VI):

(VI)



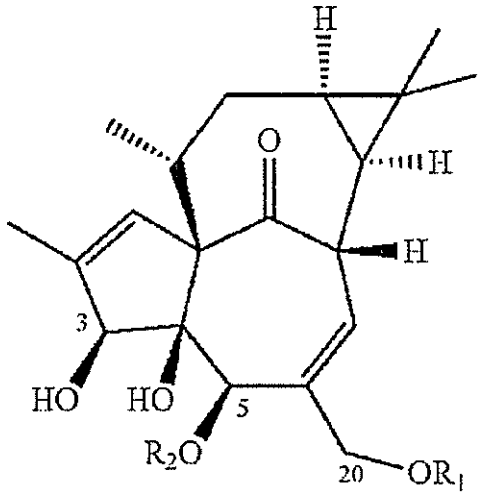
wherein D represents a dihydroxyl protective group; with the proviso that D does not represent isopropylidene.

23. A compound according to claim **22**, wherein D represents cyclopentylidene, cyclohexylidene, p-methoxybenzylidene, methoxymethylene, 2-oxacyclopentylidene, 2,3-dimethoxybutane-2,3-di-yl, 1,2-dimethoxycyclohexan-1,2-di-yl, octahydro-[2,2']-bipyran-2,2'-di-yl, di-tert-butylsilylene, 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene), phenyl boronate, 3-pentylidene, 2,4-dimethyl-3-pentylidene, 2,6-dimethyl-4-heptylidene, 3,3-dimethyl-2-butylidene, 1-phenyl-1-ethylidene,benzylidene, 2,4-dimethoxybenzylidene, 4-nitrobenzylidene, 2,4,6-trimethylbenzylidene, 2,2-dimethyl-1-propylidene, ethoxymethylene or isopropoxymethylene.

24. The compound according to claim **22**, wherein the compound is ingenol-5,20-(di(tert-butyl)silylene)-ether-3-angelate.

25. A compound of general formula (III):

(III)



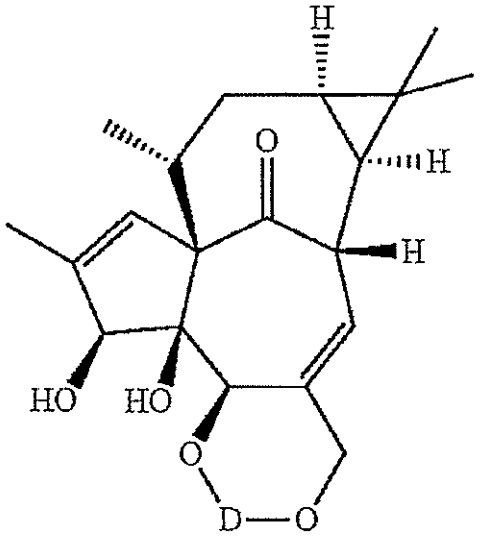
wherein R_1 and R_2 independently represents hydrogen or an ether, acetal, ketal, silylether, or a sulfenate derived hydroxyl protective group;

with the proviso that not both R_1 and R_2 represent hydrogen;

and with the proviso that R_1 does not represent triphenylmethyl;
and with the proviso that R_1 does not represent t-butyldimethylsilyl.

26. A compound of general formula IV:

(IV)

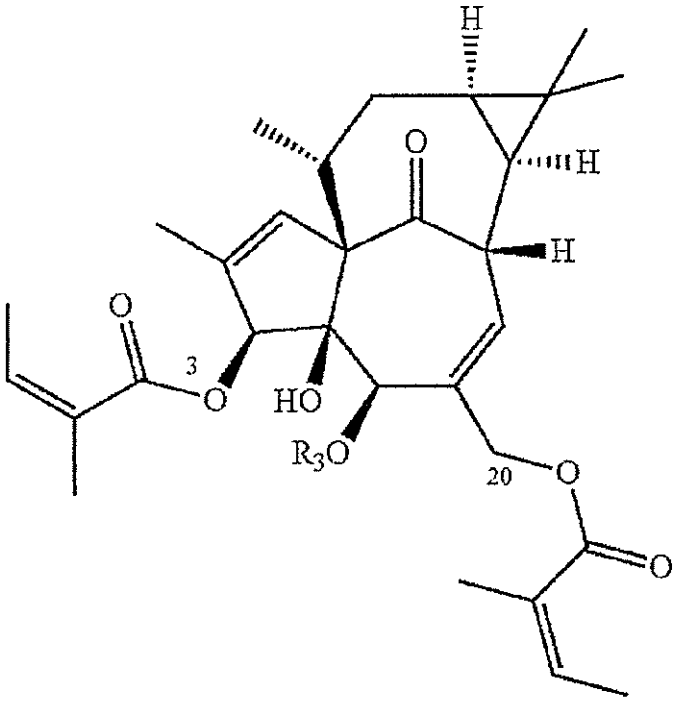


wherein D represents cyclopentylidene, cyclohexylidene, p-methoxybenzylidene, methoxymethylene, 2-oxacyclopentylidene, 2,3-dimethoxybutane-2,3-di-yl, 1,2-dimethoxycyclohexan-1,2-di-yl, octahydro-[2,2']-bipyran-2,2'-di-yl, di-tert-butylsilylene, 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene), phenyl boronate, 3-pentylidene, 2,4-dimethyl-3-pentylidene, 2,6-dimethyl-4-heptylidene, 3,3-dimethyl-2-butylidene, 1-phenyl-1-ethylidene,benzylidene, 2,4-dimethoxybenzylidene, 4-nitrobenzylidene, 2,4,6-trimethylbenzylidene, 2,2-dimethyl-1-propylidene, ethoxymethylene or isopropoxymethylene.

27. The compound according to claim **26**, wherein the compound is selected from the group consisting of
Ingenol-5,20-(3-pentylidene)-ketal,
Ingenol-5,20-(2,4-dimethyl-3-pentylidene)-ketal,
Ingenol-5,20-(2,6-dimethyl-4-heptylidene)-ketal,
Ingenol-5,20-cyclopentylidene-ketal,
Ingenol-5,20-cyclohexylidene-ketal,
Ingenol-5,20-(3,3-dimethyl-2-butylidene)-ketal,
Ingenol-5,20-(1-phenyl-1-ethylidene)-ketal,
Ingenol-5,20-benzylidene-acetal,
Ingenol-5,20-(4-methoxybenzylidene)-acetal,
Ingenol-5,20-(2,4-dimethoxybenzylidene)-acetal,
Ingenol-5,20-(4-nitrobenzylidene)-acetal,
Ingenol-5,20-(2,4,6-trimethylbenzylidene)-acetal,
Ingenol-5,20-(2,2-dimethyl-1-propylidene)-acetal,
Ingenol-5,20-methyl-orthoformate,
Ingenol-5,20-ethyl-orthoformate,
Ingenol-5,20-(prop-2-yl)-orthoformate, and
Ingenol-5,20-(di(tert-butyl)silylene)-ether.

28. A compound of general structure (VII):

(VII)



wherein R_3 represents hydrogen or angeloyl.