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(71) Applicant: **THE UNIVERSITY OF SYDNEY** [AU/AU]; Parramatta Road, The University of Sydney, New South Wales 2006 (AU).

(72) Inventors: **REEKIE, Tristan**; c/- Parramatta Road, The University of Sydney, New South Wales 2006 (AU). **SCOTT, Michael**; c/- Parramatta Road, The University of Sydney, New South Wales 2006 (AU). **KASSIOU, Michael**; c/- Parramatta Road, The University of Sydney, New South Wales 2006 (AU).

(74) Agent: **FPA PATENT ATTORNEYS PTY LTD**; Level 43, 101 Collins Street, Melbourne, Victoria 3000 (AU).

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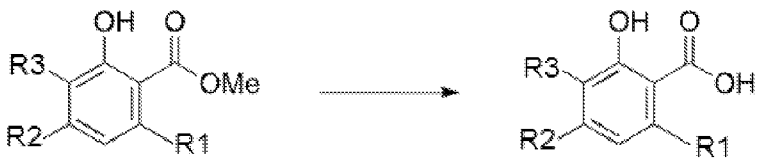
(54) Title: SYNTHESIS OF PHYTOCANNABINOIDS INCLUDING A DEMETHYLATION STEP



Formula I Formula II

(57) Abstract: A method for demethylating a methylated phytocannabinoid compound of Formula I to form a phytocannabinoid compound of Formula II: Formula I Formula II wherein: R1 is selected from the group consisting of: substituted or unsubstituted C_1-C_5 alkyl; R2 is selected from the group consisting of: OH or O, and R3 is selected from the group consisting of: a substituted or unsubstituted cyclohexene, a substituted or unsubstituted C_2-C_8 alkene, or a substituted or unsubstituted C_2-C_8 dialkene; or R2 is O, and R2 and R3 together form a ring structure in which R2 is an internal ring atom; wherein the method includes: heating a reaction mixture comprising the methylated phytocannabinoid compounds and a polar aprotic solvent in the presence of a dissolved inorganic alkaline salt for a time sufficient to demethylate at least a portion of the methylated phytocannabinoid compounds and form the phytocannabinoid compound.

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Synthesis of Phytocannabinoids including a demethylation step

Field of the invention

The present invention relates to methods for the synthesis of phytocannabinoids.

Background of the invention

Cannabis has been used in traditional medicine for thousands of years and was first introduced to Western medicine in the 1830's. Initial uses were claimed for its analgesic, sedative, anti-inflammatory, antispasmodic and anticonvulsant effects. Over 100 years later, with concerns over its safety, cannabis moved from being listed as a drug used for medical treatment, to narcotic drug, before, in 1970 in the US, being classed as Schedule I drug meaning it had no accepted medicinal use.

Despite being classed as a scheduled narcotic, cannabis was still investigated for its neurobiology, which led to the discovery of the endocannabinoid system (ECS) in 1988, identifying the cannabinoid receptor 1 (CB1) and CB2 five years later. CB1 is concentrated in the central nervous system (CNS) while CB2 is found predominately in the periphery giving rise to different functions. CB1 modulates mood, appetite, memory and pain whereas CB2 is associated with a role in immunity.

Phytocannabinoids exist as six main structural classes; tetrahydrocannabinol (THC), cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), cannabicyclol (CBL) and cannabinol (CBN). When a carboxylic acid is incorporated on the aromatic between the phenol and aliphatic chain then a suffix of A is included, while a propyl versus pentyl chain gets the suffix V or a combination of both. Quantities of each class available from extracts depends on the species of plant, growing conditions and location, method of extraction and whether it was leaves, buds, stems or roots and in which point in growth they were extracted.

Phytocannabinoids have returned to the pharmacy in the form of dronabinol, an orally taken capsule comprising THC as the active ingredient, and nabiximols (Sativex) a mouth spray comprising a 1:1 mixture of THC and CBD. Studies surrounding these two drugs have shown the vastly different outcomes achieved when single compounds or a formulation of multiple natural products are employed. Considering these

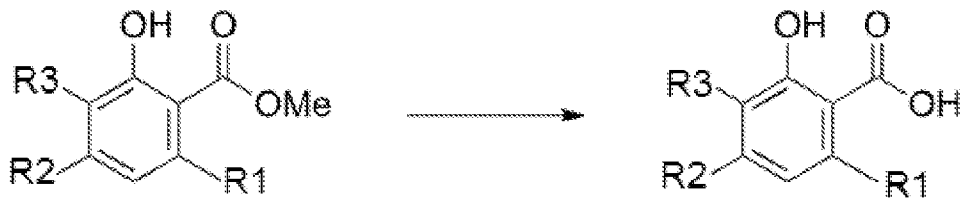
observations, it seems likely that the way forward for cannabis is various formulations of active ingredients combined in such a way that the desired effects are achieved. Full testing of individual components would be required. Plant extracts are limited in that some active ingredients are only available in small quantities or change structure during isolation so that getting sufficient quantities for testing, let alone drug formulation, is minimal. Therefore, fully- or semi-synthetic methodology are required to provide quantities of these compounds for testing, as individual active ingredients, or increasing active ingredient ratios from extracts for ideal drug formulation. However, synthetic protocols are also limited with very little reported for most compounds, and in those cases where methods are reported, only afford the target compounds in very small amounts. Furthermore, presently there are no reported methods for the synthesis of the majority of phytocannabinoids. Those few that are reported are not useful for large scale applications.

It is an object of the invention to address and/or ameliorate at least one of the problems of the prior art.

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

Summary of the invention

In a first aspect of the invention, there is provided a method for demethylating a methylated phytocannabinoid compound of Formula I to form a phytocannabinoid compound of Formula II:



Formula I Formula II

wherein:

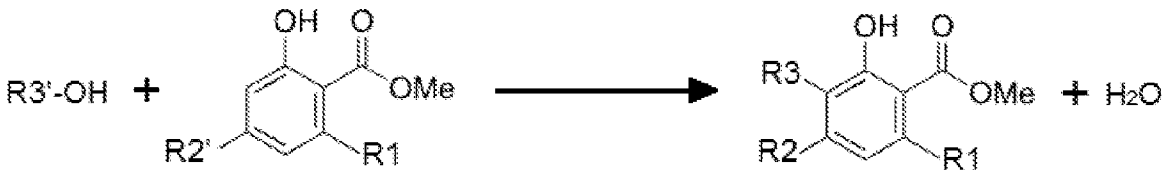
R1 is selected from the group consisting of: substituted or unsubstituted C_1-C_5 alkyl;

R2 is selected from the group consisting of: OH or O, and R3 is selected from the group consisting of: a substituted or unsubstituted cyclohexene, a substituted or unsubstituted C_2-C_8 alkene, or a substituted or unsubstituted C_2-C_8 dialkene; or R2 is O, and R2 and R3 together form a ring structure in which R2 is an internal ring atom;

wherein the method includes heating a reaction mixture comprising the methylated phytocannabinoid compound and a polar aprotic solvent in the presence of a dissolved inorganic alkaline salt for a time sufficient to demethylate at least a portion of the methylated phytocannabinoid compounds and form the phytocannabinoid compound.

In a second aspect of the invention, there is provided a method for the preparation of a phytocannabinoid compound of Formula II comprising:

subjecting a first reaction mixture comprising a compound of Formula A and a compound of Formula B in a solvent to reaction conditions such that the compound of Formula A and Formula B together undergo a condensation reaction according to Reaction Scheme I to form a methylated phytocannabinoid compound of Formula I:



Formula A Formula B Formula I

Reaction Scheme I

wherein:

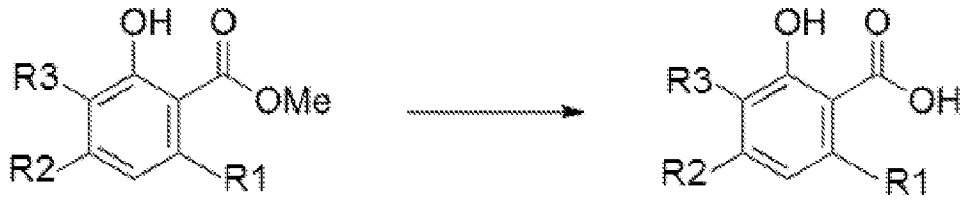
R1 is selected from the group consisting of: unsubstituted C_1-C_5 alkyl;

R2' is OH

R3' is selected from the group consisting of: a substituted or unsubstituted cyclohexene, a substituted or unsubstituted C_2-C_8 alkene, or a substituted or unsubstituted C_2-C_8 dialkene

R2 is R2' and R3 is R3'; or R2 is O and R2 and R3 together form a ring structure in which R2 is an internal ring atom

wherein the method further includes heating a second reaction mixture comprising the methylated phytocannabinoid compound and a polar aprotic solvent in the presence of a dissolved inorganic alkaline salt for a time sufficient to demethylate at least a portion of the methylated phytocannabinoid compounds and form the phytocannabinoid compound according to Reaction Scheme II;



Formula I Formula II

Reaction Scheme II

In an embodiment of the second aspect, the reaction conditions include a sub-zero temperature of around -10 °C or lower (while being above the freezing point of the solvent in the first reaction mixture), such as -10 °C to -30 °C. Preferably, the temperature is -15 °C or lower. More preferably, the temperature is about -20 °C.

In an embodiment of the second aspect, the first reaction mixture further comprises $BF_3.OEt_2$. Preferably, the $BF_3.OEt_2$ is present in an amount of from about 0.05 molar equivalents (relative to the compound of Formula B) to about 0.50 molar equivalents. More preferably, the $BF_3.OEt_2$ is present in an amount of from about 0.07 molar equivalents to about 0.45 molar equivalents.

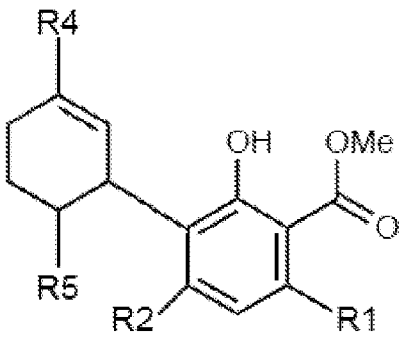
In one form of the above embodiment, the $BF_3.OEt_2$ is present in an amount of from about 0.05 molar equivalents to 0.25 molar equivalents. Preferably the $BF_3.OEt_2$ is present in an amount of from about 0.07 molar equivalents to about 0.20 molar equivalents. Most preferably, the $BF_3.OEt_2$ is present in an amount of about 0.10 molar equivalents. The inventors have found that using an amount of $BF_3.OEt_2$ within this range is conducive to the formation of a compound in which R2 and R3 are R2' and R3'.

In this form of the invention, the method can further include treating the compound of Formula II with an additional amount of $BF_3.OEt_2$ and warming the first

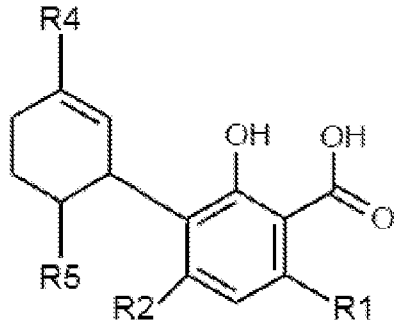
reaction mixture from the sub-zero temperature to form a compound according to Formula II in which R2 is O and R2 and R3 together form a ring structure in which R2 is an internal ring atom. Preferably, during this step, the reaction mixture is warmed from a sub-zero temperature to about 0°C. It is also preferred that the additional amount of $BF_3.OEt_2$ is about 0.10 molar equivalents.

In another form of the above embodiment, the $BF_3.OEt_2$ is present in an amount of greater than 0.25 molar equivalents to 0.50 molar equivalents. Preferably the $BF_3.OEt_2$ is present in an amount of from about 0.35 molar equivalents to about 0.45 molar equivalents. Most preferably, the $BF_3.OEt_2$ is present in an amount of about 0.40 molar equivalents. The inventors have found that using an amount of $BF_3.OEt_2$ within this range is conducive to the formation of a compound in which R2 is O and R2 and R3 together form a ring structure in which R2 is an internal ring atom.

In an embodiment of the first or second aspects, the methylated phytocannabinoid compound is a compound of Formula IA and the phytocannabinoid compound is a compound of Formula IIA:



Formula IA



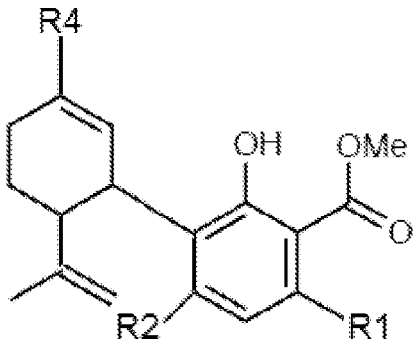
Formula IIA

wherein:

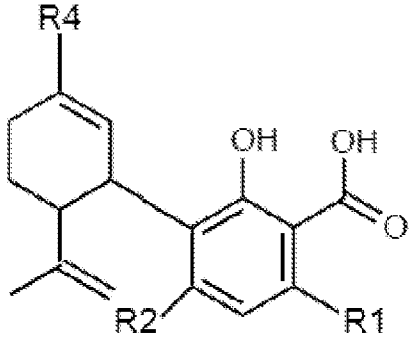
R2 is OH and R5 is $C(CH_3)=CH_2$, or R2 is O and R5 is $C(CH_2)_2$ and R2 and R5 are linked by a covalent bond; and

R4 is selected from the group consisting of: substituted or unsubstituted C_1-C_4 alkyl, COOH, $COOC_1$-C_4 alkyl, OC_1-C_4 alkyl, COC_1-C_4 alkyl, tetrahydropyran, benzyl, para-methoxybenzyl, and OH.

In an embodiment of the first or second aspects, the methylated phytocannabinoid compound is a compound of Formula IB and the phytocannabinoid compound is a compound of Formula IIB:

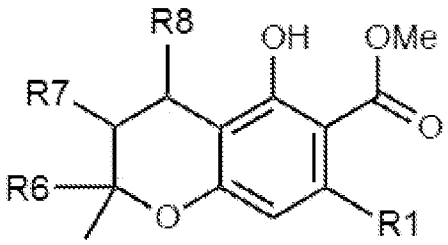


Formula IB

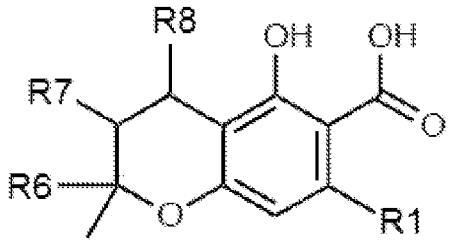


Formula IIB

In an embodiment of the first or second aspects, the methylated phytocannabinoid compound is a compound of Formula IC and the phytocannabinoid compound is a compound of Formula IIC:



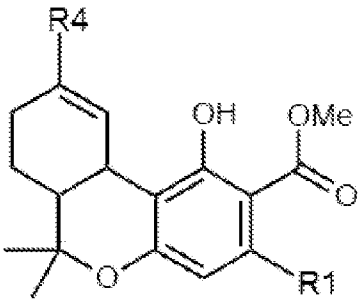
Formula IC



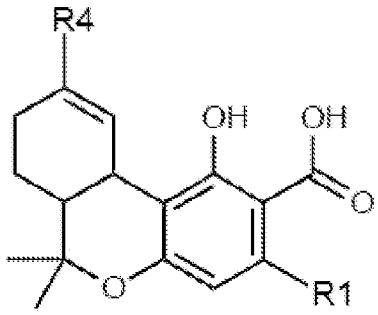
Formula IIC

wherein R6 and R7 together form a fused ring structure; R7 and R8 together form a fused ring structure; or R6, R7, and R8 together form a fused ring structure.

In an embodiment of the first or second aspects, the methylated phytocannabinoid compound is a compound of Formula ID and the phytocannabinoid compound is a compound of Formula IID:

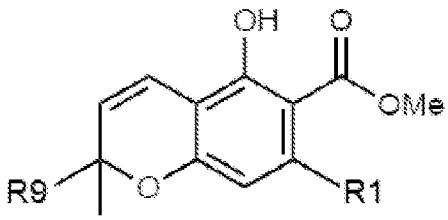


Formula ID

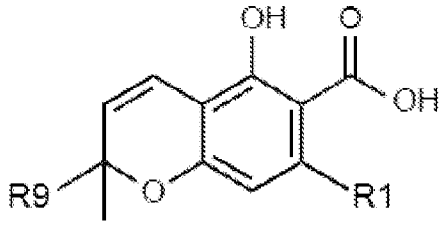


Formula IID

In an embodiment of the first or second aspects, the methylated phytocannabinoid compound is a compound of Formula IE and the phytocannabinoid compound is a compound of Formula IIE:



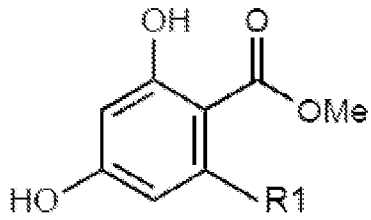
Formula IE



Formula IIE

wherein R9 is selected from the group consisting of: a substituted or unsubstituted C_2-C_8 alkene, or a substituted or unsubstituted C_2-C_8 dialkene.

In an embodiment the method includes reacting a compound of Formula IF with a compound of the form R9'=O to form a compound of Formula I, wherein R9' is selected from the group consisting of a substituted or unsubstituted C_5-C_{11} dialkene:



Formula IF

wherein the reaction is carried out in the presence of a hydroxide, such as $Ca(OH)_2$.

In a preferred form of this embodiment, the compound of Formula IF is treated with a halocarboxylic acid to form a compound of Formula IC wherein R6, R7, and R8

together form a fused ring structure. Preferably, the halocarboxylic acid is selected from the group consisting of: monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, dibromoacetic acid, tribromoacetic acid, monofluoroacetic acid, difluoroacetic acid, and trifluoroacetic acid. More preferably, the halocarboxylic acid is trifluoroacetic acid.

In one or more embodiments, R1 is selected from the group consisting of substituted or unsubstituted C_3-C_5 alkyl. Preferably, R1 is selected from the group consisting of: propyl or pentyl.

In one or more embodiments, R2 is O, and R2 and R3 together form a ring structure, the ring structure is a substituted or unsubstituted six membered heterocyclyl. Preferably the six membered heterocyclyl is a substituted or unsubstituted tetrahydropyran or a substituted or unsubstituted pyranyl.

In one or more embodiments, R4 is selected from substituted or unsubstituted C_1-C_2 alkyl, COOH, or OH.

In one or more embodiments, R6 and R7 together form a substituted or unsubstituted cyclopentyl.

In one or more embodiments, R7 and R8 together form a substituted or unsubstituted cyclobutyl.

In one or more embodiments, R9 is selected from the group consisting of: a substituted or unsubstituted C_4-C_8 alkene, or a substituted or unsubstituted C_4-C_8 dialkene.

In preferred embodiments, the substituents on the substituted moieties is selected from the group selected from -CH_3, -C2H_5, or -OH.

In an embodiment of the first or second aspects, the alkaline salt is selected from the group consisting of: Cs_2CO_3, Na_2S, NaOH, or combinations thereof. In one or more forms of the invention where the alkaline salt is Cs_2CO_3, the reaction mixture additionally includes thiophenol.

In one or more embodiments of the first or second aspects, the dissolved alkaline salt is a demethylation agent. For example, Na_2S is able to successfully demethylate the compound of Formula I in a wide range of polar aprotic solvents. Without wishing to be bound by theory, the inventors are of the view that the S^{2-} is able to attack the O-C bond and cleave the methyl group from the compound of Formula I to form the compound of Formula II.

In one or more embodiments of the first or second aspects, the reaction mixture includes an additive, wherein the dissolved alkaline salt reacts with the additive to form an intermediate compound, wherein the intermediate compound is a demethylation agent that demethylates the compound of Formula I to form the compound of Formula II. An example of this arrangement is the combination of Cs_2CO_3 and Ph-SH (thiophenol). In this example, the Cs_2CO_3 is sufficiently reactive to deprotonate thiophenol while not being too reactive to interfere with the demethylation reaction.

In one or more embodiments of the first or second aspects, the dissolved alkaline salt is a soluble alkaline salt and the polar aprotic solvent is DMSO or a mixture of one or more polar aprotic solvents at least one of which is DMSO. Without wishing to be bound by theory, the inventors are of the view that hydroxides, particularly NaOH, convert DMSO to an intermediate compound, wherein the intermediate compound is a demethylation agent that demethylates the compound of Formula I to form the compound of Formula II.

In an embodiment of the first or second aspects, the step of heating the reaction mixture includes heating the reaction mixture to a temperature of from about 50°C to about 100°C. Preferably, the temperature is from about 75°C to about 95°C. More preferably, the temperature is about 80 °C.

In an embodiment of the first or second aspects, the polar aprotic solvent mixed with up to 30 wt% water.

In an embodiment of the first or second aspects, the polar aprotic solvent is selected from the group consisting of: N-methylpyrrolidone, tetrahydrofuran (THF), ethyl acetate (EtOAc), acetone, dimethylformamide (DMF), acetonitrile (MeCN), dimethyl

sulfoxide (DMSO), propylene carbonate (PC), and combinations thereof. Preferably, the polar aprotic solvent is selected from the group consisting of: DMSO or DMF.

In an embodiment, the polar aprotic solvent has a boiling point that is above the temperature to which the reaction mixture is heated. In one form, the polar aprotic solvent has a boiling point that is above 100°C. Preferably, the polar aprotic solvent has a boiling point that is above 110°C. More preferably, the polar aprotic solvent has a boiling point that is above 120°C. Even more preferably, the polar aprotic solvent has a boiling point that is above 130°C. Most preferably, the polar aprotic solvent has a boiling point that is above 140°C.

In an embodiment of the first or second aspects, a yield of the phytocannabinoid compound is at least 40% based on the weight of the methylated phytocannabinoid compound. Preferably, the yield is at least 45%. More preferably, the yield is at least 50%.

In an embodiment of the first or second aspects, the method further includes separating the phytocannabinoid compound from the polar aprotic solvent.

In an embodiment of the first or second aspects, the phytocannabinoid compound is selected from the group consisting of those listed in Table 1.

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

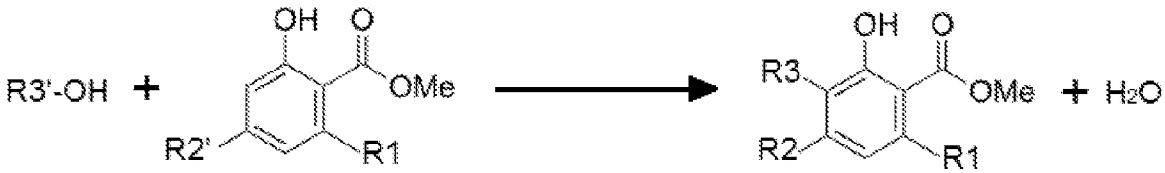
Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Detailed description of the embodiments

The invention relates to methods of demethylating compounds of Formula I to form compounds of Formula II. The invention also more broadly relates to methods of synthesising compounds of Formula I from precursor compounds, and then demethylating the compounds of Formula I to form compounds of Formula II.

In view of the above, the invention relates to a method for the preparation of a phytocannabinoid compound of Formula II comprising:

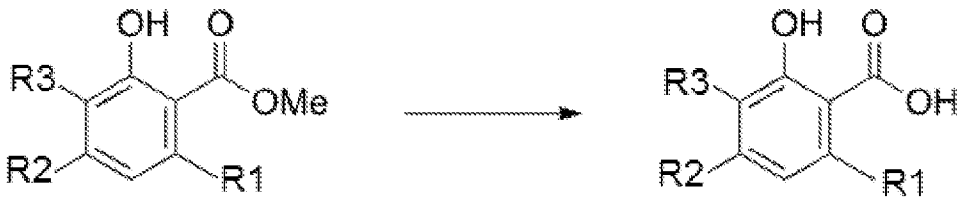
subjecting a first reaction mixture comprising a compound of Formula A and a compound of Formula B in a solvent to reaction conditions such that the compound of Formula A and Formula B together undergo a condensation reaction according to Reaction Scheme I to form a methylated phytocannabinoid compound of Formula I:



Formula A Formula B Formula I

Reaction Scheme I

wherein the method further includes heating a second reaction mixture comprising the methylated phytocannabinoid compound and a polar aprotic solvent in the presence of a dissolved alkaline salt for a time sufficient to demethylate at least a portion of the methylated phytocannabinoid compounds and form the phytocannabinoid compound according to Reaction Scheme II;



Formula I Formula II

Reaction Scheme II

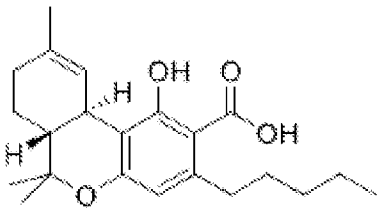
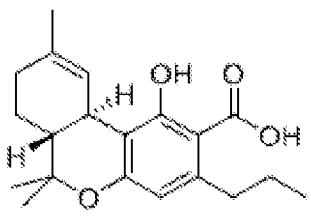
As used herein, the term "C_1-C_5 alkyl" either used alone or in compound terms refers to straight chain or branched saturated hydrocarbon groups, having 1 to 4 carbon atoms. Suitable alkyl groups include, but are not limited to: methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl. The "C_1-C_5 alkyl" may be optionally substituted with one or more substituents. The substituents may replace one or more hydrogen atoms on any carbon atom or carbon atoms in the "C_1-C_5 alkyl" carbon atom chain. Preferred substituents include methyl or ethyl groups, and more preferably methyl groups.

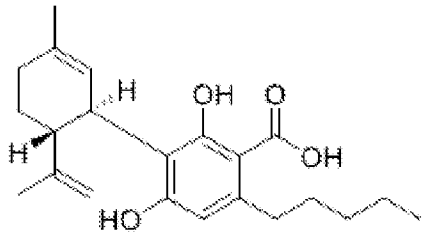
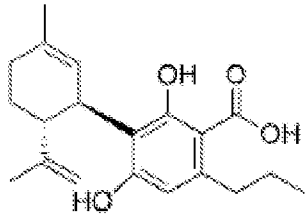
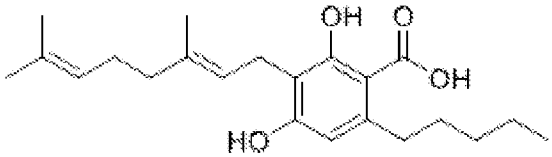
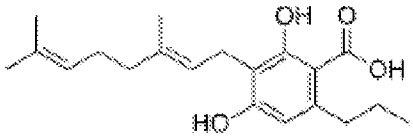
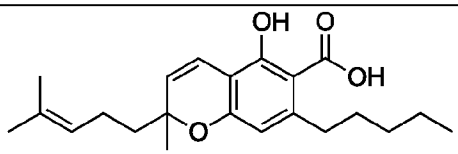
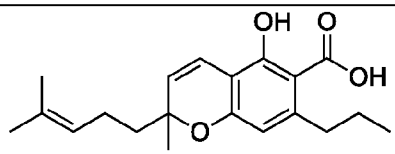
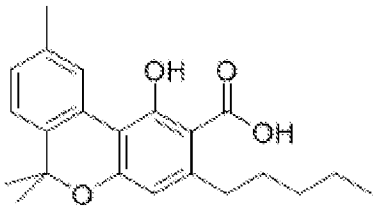
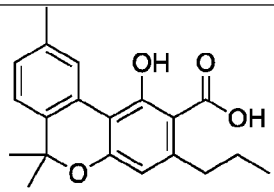
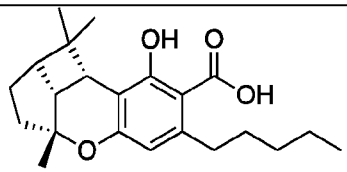
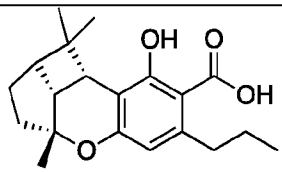
As used herein, the term "C_2-C_8 alkenyl" either used alone or in compound terms refers to straight chain or branched unsaturated hydrocarbon groups, having 2 to 4 carbon atoms and including at least one carbon to carbon double bond, for example, the alkenyl group may be a monoalkenyl group, a diene group, or a triene group. Suitable alkenyl groups include, but are not limited to: ethenyl, propenyl, propadiene, butenyl, butadiene, pentenyl, pentadiene, hexenyl, hexadiene, heptenyl, heptadiene, octenyl, or octadiene groups. The carbon to carbon double bond may be between any two adjacent carbon atoms. The "C_2-C_8 alkenyl" may be optionally substituted with one or more substituents. The substituents may replace one or more hydrogen atoms on any carbon atom or carbon atoms in the "C_2-C_8 alkenyl" carbon atom chain. Preferred substituents include methyl or ethyl groups, and more preferably methyl groups.

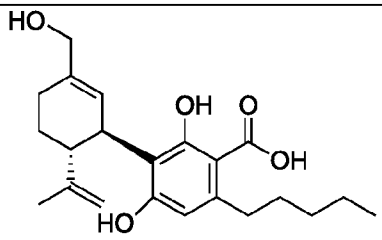
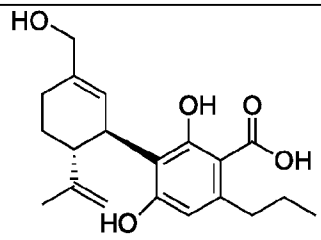
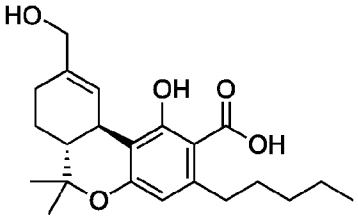
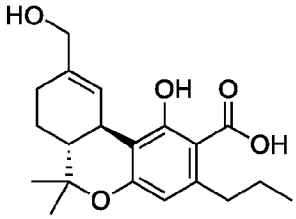
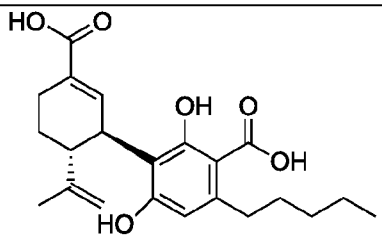
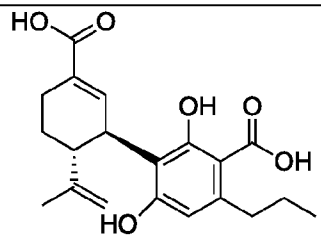
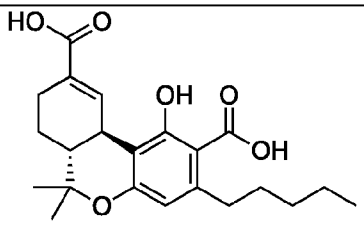
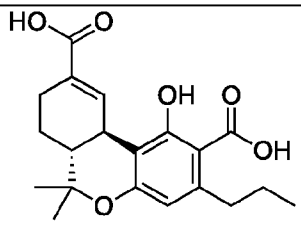
As used herein, the term "demethylation agent" is intended to refer to a compound that is able to cleave the methyl group from the compound of Formula I to form the compound of Formula II. The demethylation agent may be an alkaline salt compound, or an intermediate compound that is formed in a reaction between an alkaline salt compound and an additive or the polar aprotic solvent.

The method thus provides a mechanism for preparing a large range of different methylated phytocannabinoid compounds from a large range of precursor compounds, which can then be easily demethylated to provide an active phytocannabinoid compound. By way of example, the method of invention can be applied to form the phytocannabinoids outlined in Table 1 below:

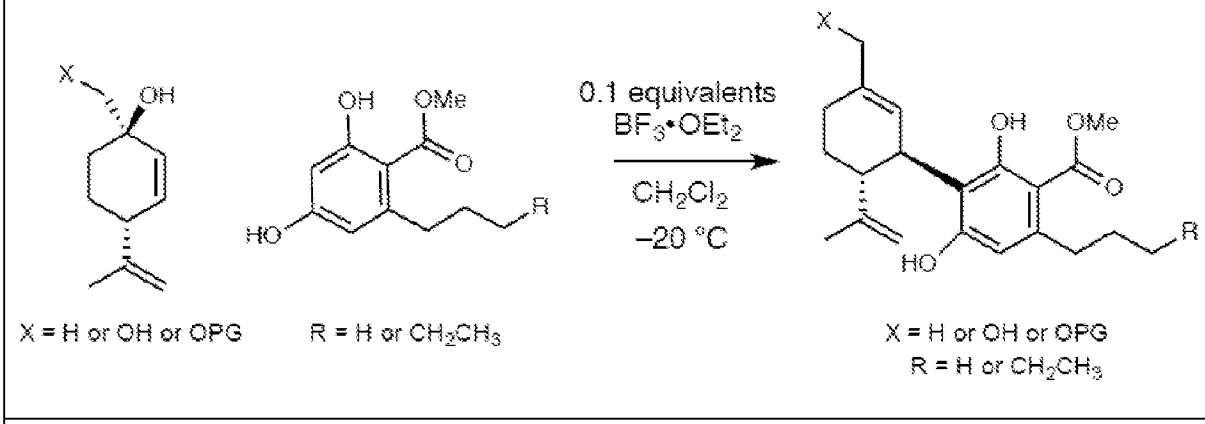
Table 1:

	
Tetrahydrocannabinolic acid THCA (6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid	Tetrahydrocannabivarinic acid THCVA (6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-3-propyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid

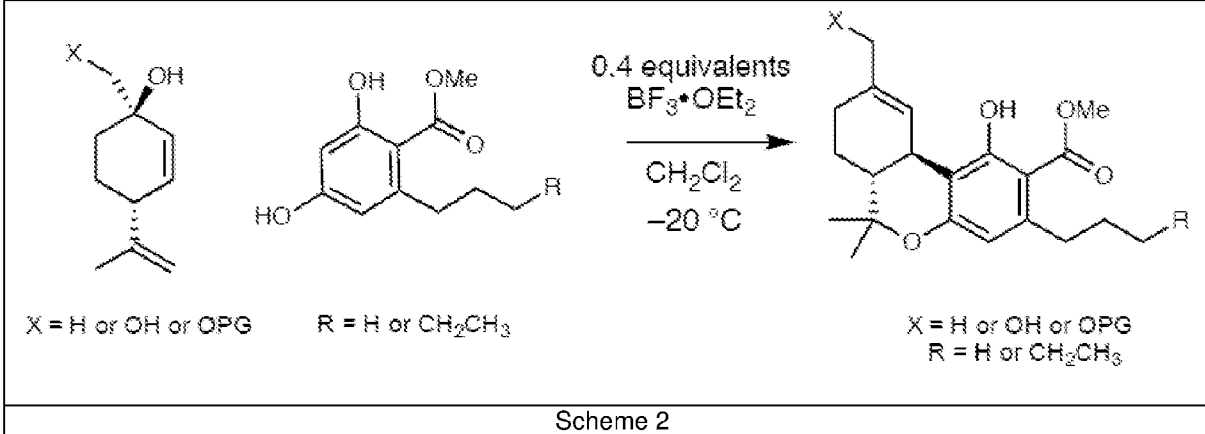
	
Cannabidiolic Acid (CBDA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid	Cannabidivarinic acid (CBDVA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-methyl-2'-(prop-1-en-2-yl)-4-propyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid
	
Cannabigerolic acid (CBGA) (*E*)-3-(3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxy-6-pentylbenzoic acid	Cannabigerovarinic acid (CBGVA) (*E*)-3-(3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxy-6-propylbenzoic acid
	
Cannabichromenic acid (CBCA) 5-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2*H*-chromene-6-carboxylic acid	Cannabichromevarinic acid (CBCVA) 5-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-7-propyl-2*H*-chromene-6-carboxylic acid
	
Cannabinolic acid (CBNA) 1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromene-2-carboxylic acid	Cannabinovarinic acid (CBNVA) 1-hydroxy-6,6,9-trimethyl-3-propyl-6*H*-benzo[*c*]chromene-2-carboxylic acid
	
Cannabicyclolic acid (CBLA) (1a*S*,1a^1*R*,3a*R*,8b*R*)-8-hydroxy-1,1,3a-trimethyl-6-pentyl-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]indene-7-carboxylic acid	Cannabicyclovarinic acid (CBLVA) (1a*S*,1a^1*R*,3a*R*,8b*R*)-8-hydroxy-1,1,3a-trimethyl-6-propyl-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]indene-7-carboxylic acid

	
11-Hydroxycannabidiolic acid (11-OH-CBDA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-(hydroxymethyl)-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid	11-Hydroxycannabidivarinic acid (11-OH-CBDVA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-(hydroxymethyl)-2'-(prop-1-en-2-yl)-4-propyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid
	
11-Hydroxytetrahydrocannabinolic acid (11-OH-THCA) (6a*R*,10a*R*)-1-hydroxy-9-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid	11-Hydroxytetrahydrocannabivarinic acid (11-OH-THCVA) (6a*R*,10a*R*)-1-hydroxy-9-(hydroxymethyl)-6,6-dimethyl-3-propyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid
	
11-Carboxycannabidiolic acid (11-COOH-CBDA) (1*R*,6*R*)-2',6'-dihydroxy-4'-pentyl-6-(prop-1-en-2-yl)-1,4,5,6-tetrahydro-[1,1'-biphenyl]-3,3'-dicarboxylic acid	11-Carboxycannabidivarinic acid (11-COOH-CBDVA) (1*R*,6*R*)-2',6'-dihydroxy-6-(prop-1-en-2-yl)-4'-propyl-1,4,5,6-tetrahydro-[1,1'-biphenyl]-3,3'-dicarboxylic acid
	
11-Carboxytetrahydrocannabinolic acid (11-COOH-THCA) (6a*R*,10a*R*)-1-hydroxy-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2,9-dicarboxylic acid	11-Carboxytetrahydrocannabinolic acid (11-COOH-THCVA) (6a*R*,10a*R*)-1-hydroxy-6,6-dimethyl-3-propyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2,9-dicarboxylic acid

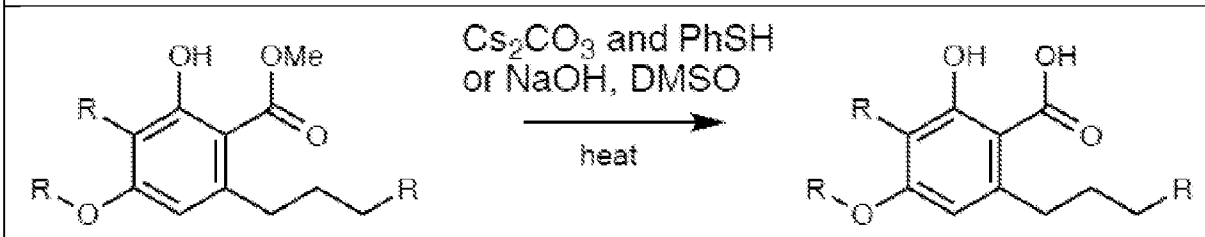
Exemplary reaction schemes are provided below:



Scheme 1

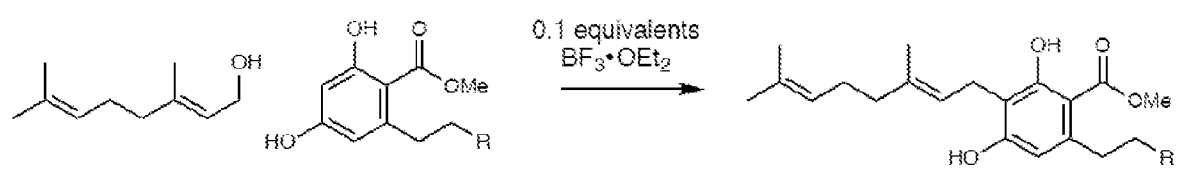


Scheme 2



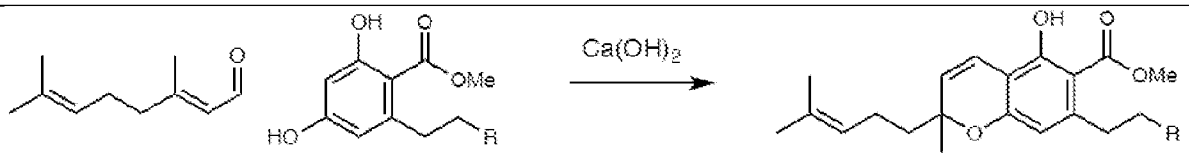
(where each R is as defined above)

Scheme 3



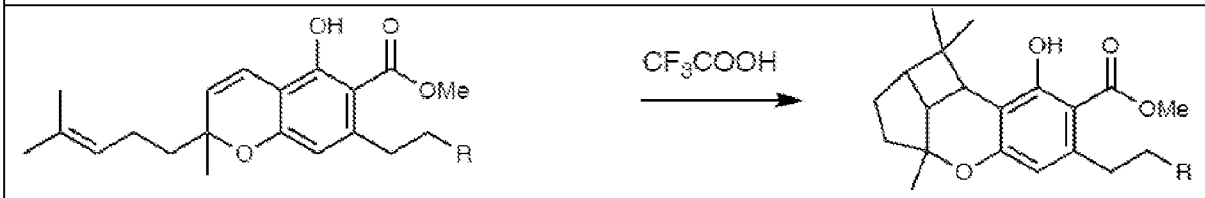
(where each R is as defined above)

Scheme 4



(where each R is as defined above)

Scheme 5



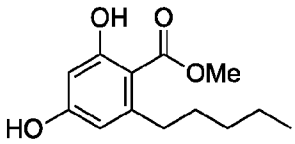
(where each R is as defined above)

Scheme 6

Examples

Example 1 – Forming precursor compounds of Formula B

Example 1A:

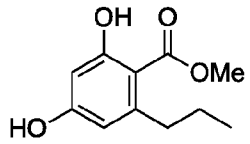


A solution of methanol (250 mL) at 0 °C was treated with sodium (12.0 g, 0.52 mol) in portions and stirred until dissolved. Dimethyl malonate (67.7 mL, 0.59 mol) was then added followed by (E)-non-3-en-2-one (59 g, 0.42 mol) and the solution heated at reflux for 8 h. The methanol was removed then diluted with water (400 mL) and washed with $CHCl_3$ (300 mL). The aqueous later was acidified and extracted with $CHCl_3$ (3 x 250 mL). The combined organic layers were dried (MgSO4) and concentrated to give a white solid.

The white solid (8.17 g, 34.0 mmol) was dissolved in DMF (20 ml) and cooled to 0 °C. A solution of Br_2 (1.75 mL, 34.0 mmol) in DMF (6.6 mL) was slowly added and the solution stirred at 20 °C for 1 h. The solution was then heated to 80 °C for 16 h before cooling and treatment with 5% $Na_2S_2O_3$ aqueous solution (200 mL) and being extracted

with ethyl acetate (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was recrystallized from DCM/hexane to give a white solid.

Example 1B:

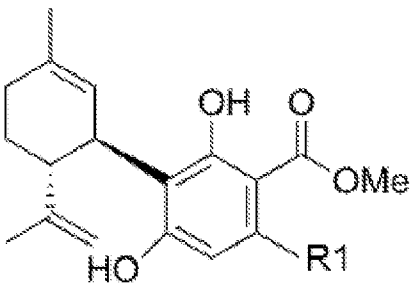


A solution of methanol (450 mL) at 0 °C was treated with sodium (25.5 g, 1.11 mol) in portions and stirred until dissolved. Dimethyl malonate (143 mL, 1.25 mol) was then added followed by (*E*)-hept-3-en-2-one (100 g, 0.89 mol) and the solution heated at reflux for 8 h. The methanol was removed then diluted with water (600 mL) and washed with $CHCl_3$ (500 mL). The aqueous later was acidified and extracted with $CHCl_3$ (3 x 400 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a white solid.

The white solid (5.37 g, 25.3 mmol) was dissolved in DMF (12 ml) and cooled to 0 °C. A solution of Br_2 (1.30 mL, 25.4 mmol) in DMF (6.6 mL) was slowly added and the solution stirred at 20 °C for 1 h. The solution was then heated to 80 °C for 16 h before cooling and treatment with 5% $Na_2S_2O_3$ aqueous solution (200 mL) and being extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was recrystallized from DCM/hexane to give a white solid.

Example 2 – Forming compounds of Formula I

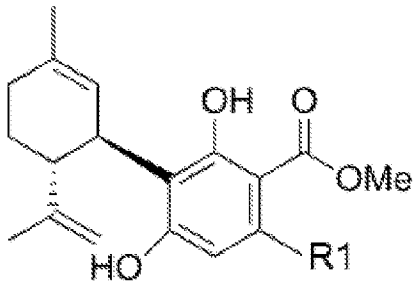
Example 2A:



R1 is propyl or pentyl.

A solution of (4*R*)-1-methyl-4-(prop-1-en-2-yl)cyclohex-2-en-1-ol (1.1 equiv) and methyl 2,4-dihydroxy-6-pentylbenzoate (1 equiv) or methyl 2,4-dihydroxy-6-propylbenzoate (1 equiv) and $MgSO_4$ (3 equiv) in DCM (0.1 M) at –20 °C was treated with $BF_3.OEt_2$ (0.1 equiv) in DCM (0.1 M) and stirred for 0.25 h. Water was added followed and extracted with DCM, dried ($MgSO_4$) and concentrated. The residue was subjected to flash column chromatography (silica, 0 to 5% EtOAc/Hexane gradient elution) to give a colourless oil. Yields 30-40%.

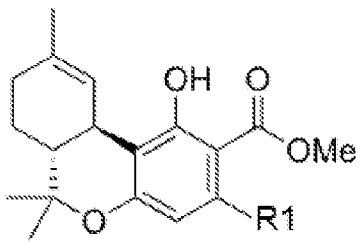
Example 2B:



R1 is propyl or pentyl.

A solution of (4*R*)-1-methyl-4-(prop-1-en-2-yl)cyclohex-2-en-1-ol (1 equiv) and methyl 2,4-dihydroxy-6-pentylbenzoate (1 equiv) or methyl 2,4-dihydroxy-6-propylbenzoate (1 equiv) in chlorobenzene (0.1 M) at room temperature was treated with BF3.OEt_2 (0.15 equiv) in chlorobenzene (0.05 M). The solution was stirred for 1 h then treated with aqueous $NaHCO_3$ and extracted with DCM, dried ($MgSO_4$) and concentrated. The residue was subjected to flash column chromatography (silica, 0 to 10% EtOAc/Hexane gradient elution) to give a colourless oil. Yields 60-70%

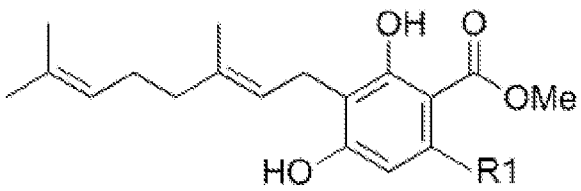
Example 2C:



R1 is propyl or pentyl.

A solution of methyl (1'*R*,2'*R*)-2,6-dihydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylate (1 equiv) or methyl (1'*R*,2'*R*)-2,6-dihydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylate (1 equiv) in DCM (0.1 M) at –20 °C was treated with $BF3.OEt_2$ (0.1 equiv) in DCM (0.05 M) and stirred for 1 h as it slowly warmed to 0 °C. $NaHCO_3$ in water was added and the aqueous phase extracted with DCM, dried ($MgSO_4$) and concentrated. The residue was subjected to flash column chromatography (silica, 0 to 5% EtOAc/Hexane gradient elution) to give a colourless oil. Yields 50-55%

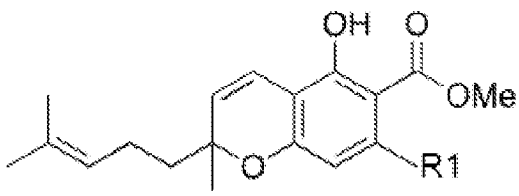
Example 2D:



R1 is propyl or pentyl.

A solution of geraniol (1 equiv) and methyl 2,4-dihydroxy-6-pentylbenzoate (3 equiv) or methyl 2,4-dihydroxy-6-propylbenzoate (3 equiv) in $CHCl_3$ (0.1 M) at –20 °C was treated with $BF_3.OEt_2$ (0.1 equiv) in $CHCl_3$ (0.1 M) and stirred for 0.25 h. Water was added followed and extracted with DCM, dried ($MgSO_4$) and concentrated. The residue was subjected to flash column chromatography (silica, 0 to 5% EtOAc/Hexane gradient elution) to give a colourless oil. Yields 30-40%.

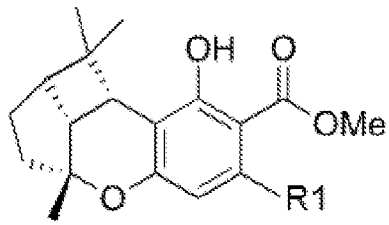
Example 2E:



R1 is propyl or pentyl.

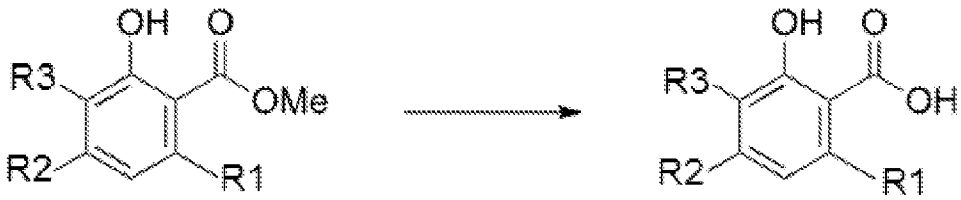
A solution of citral (3 equiv), 2,4-dihydroxy-6-pentylbenzoate (1 equiv) or methyl 2,4-dihydroxy-6-propylbenzoate (1 equiv) and $Ca(OH)_2$ (1 equiv) in methanol (0.5 M) in a sealed tube was heated at 140 °C for 1.5 h. The cooled solution was diluted with EtOAc and 1 M HCl. The separated aqueous phase was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was subjected to flash column chromatography (silica, 30% DCM/Hexane elution) to give a colourless oil. Yields 75-85%.

Example 2F:



R1 is propyl or pentyl.

Example 3 – demethylation of compounds of Formula I to form compound of Formula II according to Reaction scheme II



Reaction scheme II

Example 3A:

A solution of the methyl ester (1 equiv) in DMF (0.25 M) was treated with thiophenol (1.5 equiv) followed by Cs_2CO_3 (0.5 equiv) and stirred at 85 °C for 24 h. The cooled solution was acidified with 1 M HCl to pH 3 and extracted with EtOAc (3 times). The combined organic phases were dried ($MgSO_4$) and concentrated and the residue was subjected to flash column chromatography (silica, 0 to 20% EtOAc/Hexane gradient elution) to give the desired acid. Yields 60-80%.

THCA, THCVA, CBDA, CBDVA, CBGA, and CBGA have all been successfully synthesised using the method outlined in Example 3A.

Example 3B:

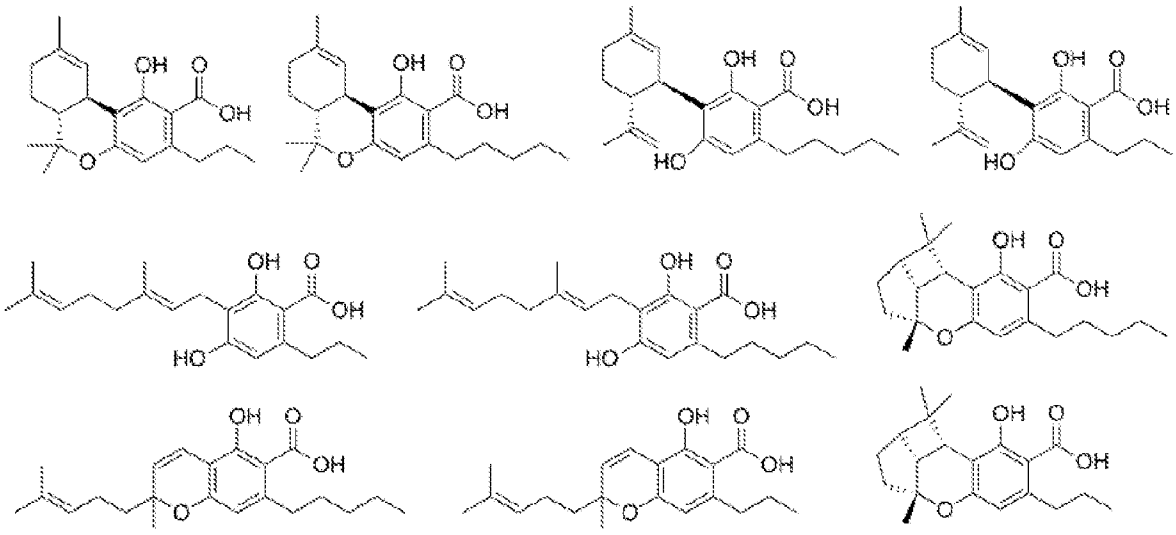
A solution of the methyl ester (1 equiv) in DMF (0.5 M) was treated with $Na_2S.9H_2O$ (10 equiv) stirred at reflux for 24 h. The cooled solution was acidified with 1 M HCl to pH 3 and extracted with EtOAc (3 times). The combined organic phases were dried ($MgSO_4$) and concentrated and the residue was subjected to flash column chromatography (silica, 0 to 20% EtOAc/Hexane gradient elution) to give the desired acid. Yields 50-70% but purification is simpler than with Example 3A.

THCA, THCVA, CBDA, CBDVA, CBGA, and CBGA have all been successfully synthesised using the method outlined in Example 3B.

Example 3C:

A solution of the methyl ester (1 equiv) in DMSO/20% aqueous NaOH (4:1) (0.2 M) was stirred at 80 °C for 24 h. The cooled solution was acidified with 1 M HCl to pH 3 and extracted with EtOAc (3 times). The combined organic phases were dried ($MgSO_4$) and concentrated and the residue was subjected to flash column chromatography (silica, 0 to 20% EtOAc/Hexane gradient elution) to give the desired acid. Yields 50-70% but purification is simpler than with Example 3A.

Compounds formed according to the methods of Examples 3A, 3B, and 3C:



CBCA, CBCVA, CBLA, and CBLVA have all been successfully synthesised using the method outlined in Example 3A.

Example 3D:

The inventors have conducted a number of further experiments. Demethylation of compounds of Formula I to compounds of Formula II has been successfully achieved using Na_2S in THF and MeCN. However, the following reagents and reaction conditions were found to be unsuccessful in demethylating compounds of Formula I to form compounds of Formula II:

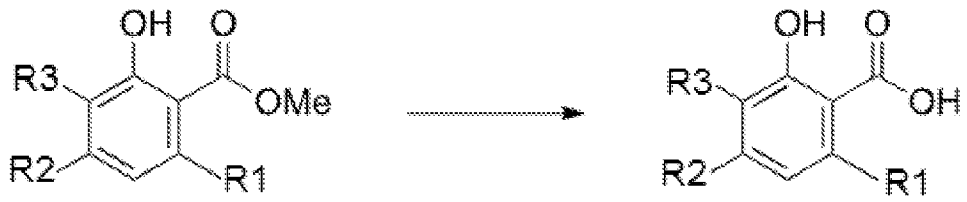
LiOH, MeOH/H_2O room temperature to reflux; LiOH, EtOH/H_2O room temperature to reflux; NaOH, MeOH/H_2O room temperature to reflux; NaOH, EtOH/H_2O room temperature to reflux; KOH, EtOH/H_2O room temperature to reflux; LiI, pyridine reflux; LiCl, DMF, 120 °C; $Ba(OH)_2$.8H2O, MeOH, room temperature reflux; $(Bu_3Sn)_2O$, toluene, reflux; KOtBu, DMSO, 80-100 °C.

These reactions were all unsuccessful in forming CBDA. Further, attempts to form CBGA and THCVA using LiOH in MeOH/H_2O and NaOH in EtOH/H_2O were also unsuccessful.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

CLAIMS

1. A method for demethylating a methylated phytocannabinoid compound of Formula I to form a phytocannabinoid compound of Formula II:



Formula I Formula II

wherein:

R1 is selected from the group consisting of: substituted or unsubstituted C_1-C_5 alkyl;

R2 is selected from the group consisting of: OH or O, and R3 is selected from the group consisting of: a substituted or unsubstituted cyclohexene, a substituted or unsubstituted C_2-C_8 alkene, or a substituted or unsubstituted C_2-C_8 dialkene; or R2 is O, and R2 and R3 together form a ring structure in which R2 is an internal ring atom;

wherein the method includes:

heating a reaction mixture comprising the methylated phytocannabinoid compounds and a polar aprotic solvent in the presence of a dissolved inorganic alkaline salt for a time sufficient to demethylate at least a portion of the methylated phytocannabinoid compounds and form the phytocannabinoid compound.

2. A method for the preparation of a phytocannabinoid compound of Formula II comprising:

subjecting a first reaction mixture comprising a compound of Formula A and a compound of Formula B in a solvent to reaction conditions such that the compound of Formula A and Formula B together undergo a condensation reaction according to Reaction Scheme I to form a methylated phytocannabinoid compound of Formula I:

Formula A Formula B Formula I

Reaction Scheme I

wherein:

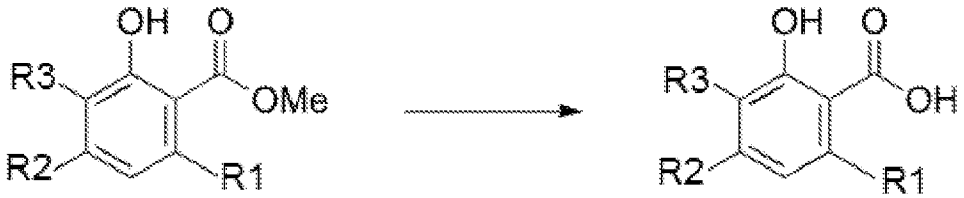
R1 is selected from the group consisting of: substituted or unsubstituted C_1-C_5 alkyl;

R2' is OH

R3' is selected from the group consisting of: a substituted or unsubstituted cyclohexene, a substituted or unsubstituted C_2-C_8 alkene, or a substituted or unsubstituted C_2-C_8 dialkene

R2 is R2' and R3 is R3'; or R2 is O and R2 and R3 together form a ring structure in which R2 is an internal ring atom

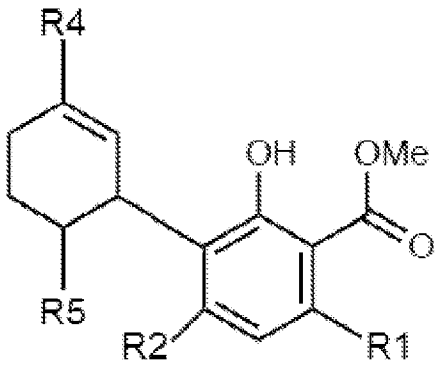
wherein the method further includes heating a second reaction mixture comprising the methylated phytocannabinoid compound and a polar aprotic solvent in the presence of a dissolved inorganic alkaline salt for a time sufficient to demethylate at least a portion of the methylated phytocannabinoid compounds and form the phytocannabinoid compound according to Reaction Scheme II;



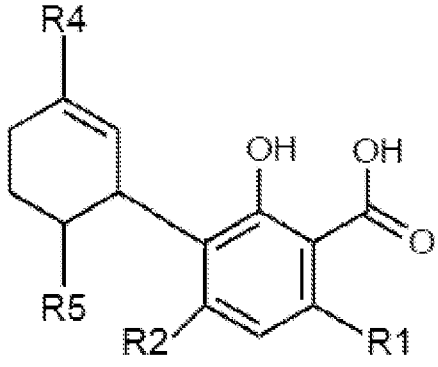
Formula I Formula II

Reaction Scheme II

3. The method of claim 1 or 2, wherein the methylated phytocannabinoid compound is a compound of Formula IA and the phytocannabinoid compound is a compound of Formula IIA:



Formula IA



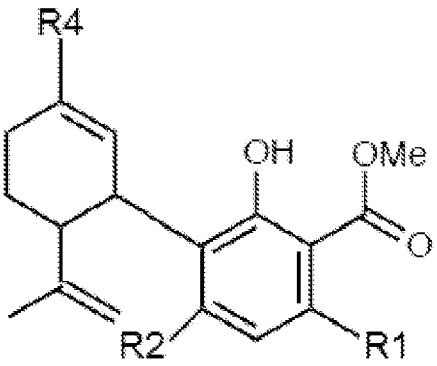
Formula IIA

wherein:

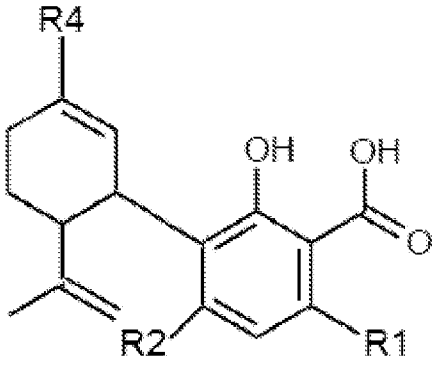
R2 is OH and R5 is $C(CH_3)=CH_2$, or R2 is O and R5 is $C(CH_2)_2$ and R2 and R5 are linked by a covalent bond; and

R4 is selected from the group consisting of: C_1-C_4 alkyl, COOH, $COOC_1$-C_4 alkyl, OC_1-C_4 alkyl, COC_1-C_4 alkyl, tetrahydropyran, benzyl, para-methoxybenzyl, and OH.

4. The method of claim 3, wherein the methylated phytocannabinoid compound is a compound of Formula IB and the phytocannabinoid compound is a compound of Formula IIB:

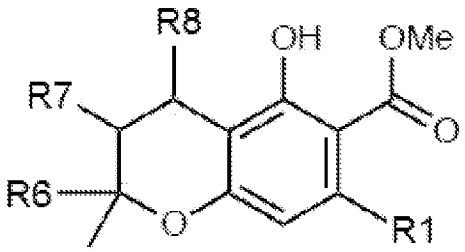


Formula IB

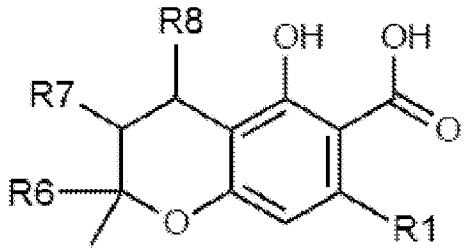


Formula IIB

5. The method of claim 1 or 2, wherein the methylated phytocannabinoid compound is a compound of Formula IC and the phytocannabinoid compound is a compound of Formula IIC:



Formula IC

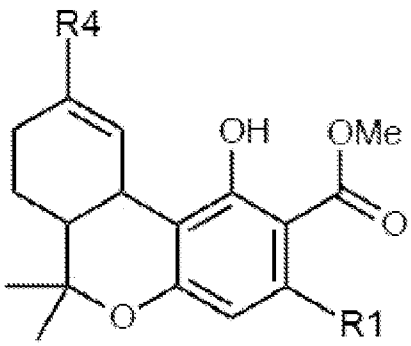


Formula IIC

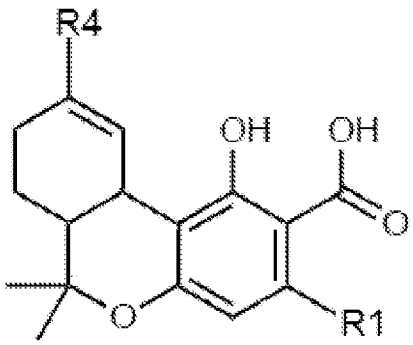
wherein:

R6 and R7 together form a fused ring structure; R7 and R8 together form a fused ring structure; or R6, R7, and R8 together form a fused ring structure.

6. The method of claim 3 or 5, wherein the methylated phytocannabinoid compound is a compound of Formula ID and the phytocannabinoid compound is a compound of Formula IID:

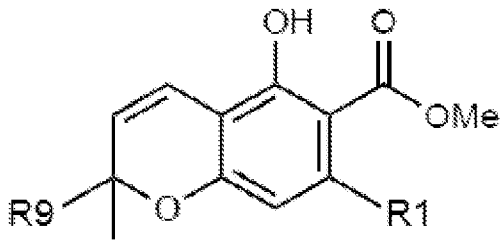


Formula ID

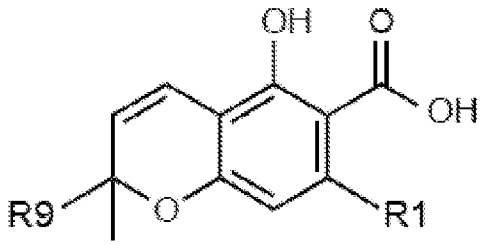


Formula IID

7. The method of claim 1 or 2, wherein the methylated phytocannabinoid compound is a compound of Formula IE and the phytocannabinoid compound is a compound of Formula IIE:



Formula IE



Formula IIE

wherein:

R9 is selected from the group consisting of: a substituted or unsubstituted C_2-C_8 alkene, or a substituted or unsubstituted C_2-C_8 dialkene.

8. The method of claim 2, wherein the first reaction mixture further comprises $BF_3.OEt_2$.

9. The method of any one of the preceding claims, wherein the dissolved alkaline salt is selected from the group consisting of: Cs_2CO_3, Na_2S, NaOH, or combinations thereof.

10. The method of any one of the preceding claims, wherein the step of heating the reaction mixture includes heating the reaction mixture to a temperature of from about 50°C to about 100°C.

11. The method of claim 10, wherein the temperature is from about 75°C to about 95°C.

12. The method of any one of claims 1 to 11, wherein the polar aprotic solvent mixed with up to 30 wt% water.

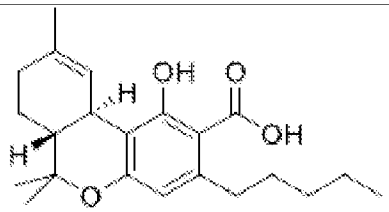
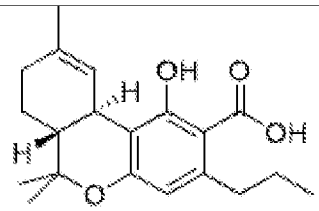
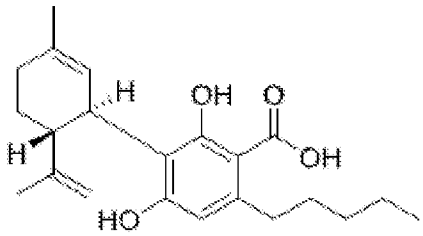
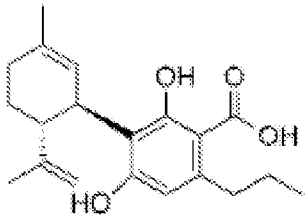
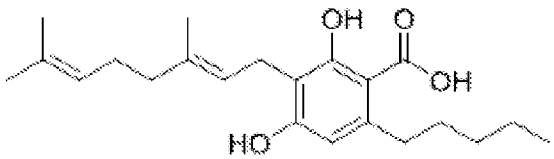
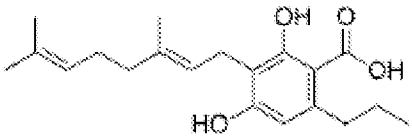
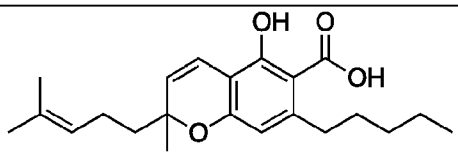
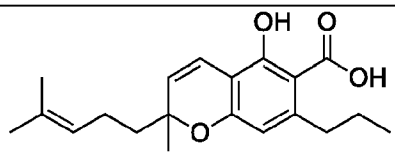
13. The method of any one of claims 1 to 11, wherein the polar aprotic solvent is selected from the group consisting of: N-methylpyrrolidone, tetrahydrofuran (THF), ethyl acetate (EtOAc), acetone, dimethylformamide (DMF), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), propylene carbonate (PC), and combinations thereof.

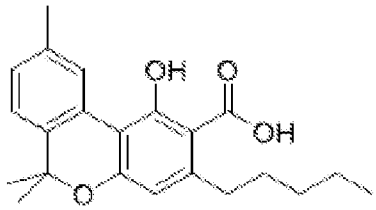
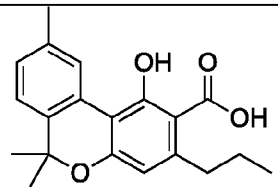
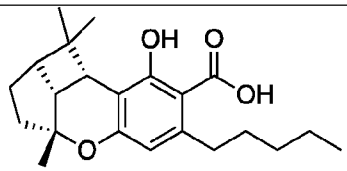
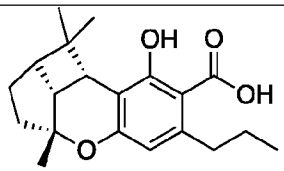
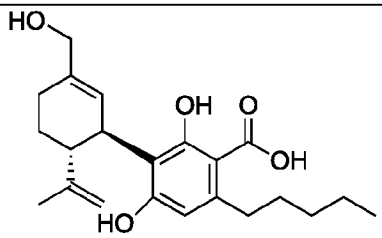
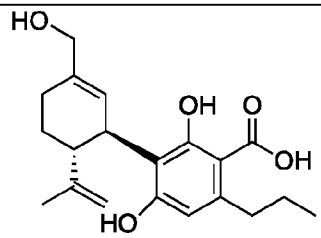
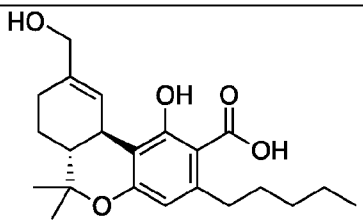
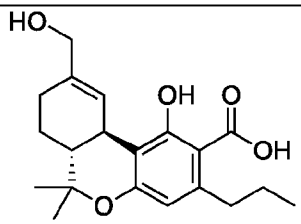
14. The method of any one of the preceding claims, wherein a yield of the phytocannabinoid compound is at least 40% based on the weight of the methylated phytocannabinoid compound.

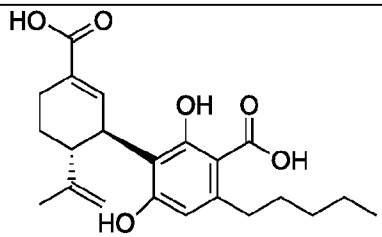
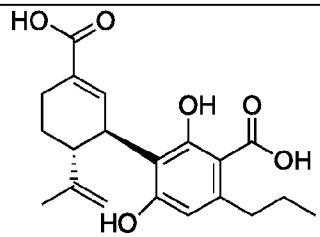
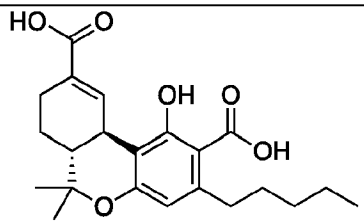
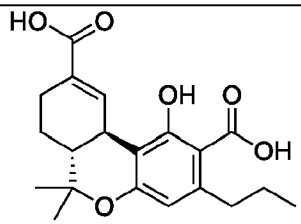
15. The method of claim 14, wherein the yield is at least 50%.

16. The method of any one of the preceding claims, wherein the method further includes separating the phytocannabinoid compound from the polar aprotic solvent.

17. The method of claim 1 or 2, wherein the phytocannabinoid compound is selected from the group consisting of:

	
Tetrahydrocannabinolic acid THCA (6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid	Tetrahydrocannabivarinic acid THCVA (6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-3-propyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid
	
Cannabidiolic Acid (CBDA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid	Cannabidivarinic acid (CBDVA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-methyl-2'-(prop-1-en-2-yl)-4-propyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid
	
Cannabigerolic acid (CBGA) (*E*)-3-(3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxy-6-pentylbenzoic acid	Cannabigerovarinic acid (CBGVA) (*E*)-3-(3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxy-6-propylbenzoic acid
	
Cannabichromenic acid (CBCA) 5-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2*H*-chromene-6-carboxylic acid	Cannabichromevarinic acid (CBCVA) 5-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-7-propyl-2*H*-chromene-6-carboxylic acid

	
Cannabinolic acid (CBNA) 1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromene-2-carboxylic acid	Cannabinovarinic acid (CBNVA) 1-hydroxy-6,6,9-trimethyl-3-propyl-6*H*-benzo[*c*]chromene-2-carboxylic acid
	
Cannabicyclolic acid (CBLA) (1a*S*,1a^1*R*,3a*R*,8b*R*)-8-hydroxy-1,1,3a-trimethyl-6-pentyl-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]indene-7-carboxylic acid	Cannabicyclovarinic acid (CBLVA) (1a*S*,1a^1*R*,3a*R*,8b*R*)-8-hydroxy-1,1,3a-trimethyl-6-propyl-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]indene-7-carboxylic acid
	
11-Hydroxycannabidiolic acid (11-OH-CBDA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-(hydroxymethyl)-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid	11-Hydroxycannabidivarinic acid (11-OH-CBDVA) (1'*R*,2'*R*)-2,6-dihydroxy-5'-(hydroxymethyl)-2'-(prop-1-en-2-yl)-4-propyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxylic acid
	
11-Hydroxytetrahydrocannabinolic acid (11-OH-THCA) (6a*R*,10a*R*)-1-hydroxy-9-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid	11-Hydroxytetrahydrocannabivarinic acid (11-OH-THCVA) (6a*R*,10a*R*)-1-hydroxy-9-(hydroxymethyl)-6,6-dimethyl-3-propyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid

	
11-Carboxycannabidiolic acid (11-COOH-CBDA) (1*R*,6*R*)-2',6'-dihydroxy-4'-pentyl-6-(prop-1-en-2-yl)-1,4,5,6-tetrahydro-[1,1'-biphenyl]-3,3'-dicarboxylic acid	11-Carboxycannabidivarinic acid (11-COOH-CBDVA) (1*R*,6*R*)-2',6'-dihydroxy-6-(prop-1-en-2-yl)-4'-propyl-1,4,5,6-tetrahydro-[1,1'-biphenyl]-3,3'-dicarboxylic acid
	
11-Carboxytetrahydrocannabinolic acid (11-COOH-THCA) (6a*R*,10a*R*)-1-hydroxy-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2,9-dicarboxylic acid	11-Carboxytetrahydrocannabinolic acid (11-COOH-THCVA) (6a*R*,10a*R*)-1-hydroxy-6,6-dimethyl-3-propyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene-2,9-dicarboxylic acid

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2018/050866

A. CLASSIFICATION OF SUBJECT MATTER

C07C 51/09 (2006.01) C07D 311/80 (2006.01) C07D 311/94 (2006.01) C07D 311/74 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

REGISTRY, CASREACT:Sub-structure search based on present formulae I and II.

GOOGLE SCHOLAR: Keyword search (cannabinoid, demethylation, saponification)

Applicant(s)/Inventor(s) name searched in Espacenet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2018	23 October 2018

Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Marc Kloth AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61399359609

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2018/050866**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Joseph P. Porwoll and Edward Leete, "Synthesis of [5,6-13C2, 1-14C] Olivetolic Acid, Methyl [1'-13C] Olivetolate and [5,6-13C2, 1-14C] Cannabigerolic Acid", Journal of Labelled Compounds and Radiopharmaceuticals, 1984, Vol. XXII No. 3, 257-271 abstract; page 259, Figure 2, Reaction step of compound 11 to yield compound 3; page 268, preparation of Cannabigerolic acid (3) abstract; page 259, Figure 2, Reaction step of compound 11 to yield compound 3; page 268, preparation of Cannabigerolic acid (3)	1, 9-17 2, 8
X Y	Crystal M. Darby et al, "Whole cell screen for inhibitors of pH homeostasis in Mycobacterium tuberculosis", PLOS ONE, 2013, Vol. 8 Issue 7, 1-12 abstract; Supplemental Information File S1 abstract; Supplemental Information File S1	1, 9-16 2, 8
Y	Theophil Eicher et al, "Synthese von Bryophyten-Inhaltsstoffen 2. Synthesen von prenylierten Bibenzyl-Derivaten", Synthesis, 1991, 98-102 page 101, preparation of compound 1c; page 101, preparation of compound 13	2, 8