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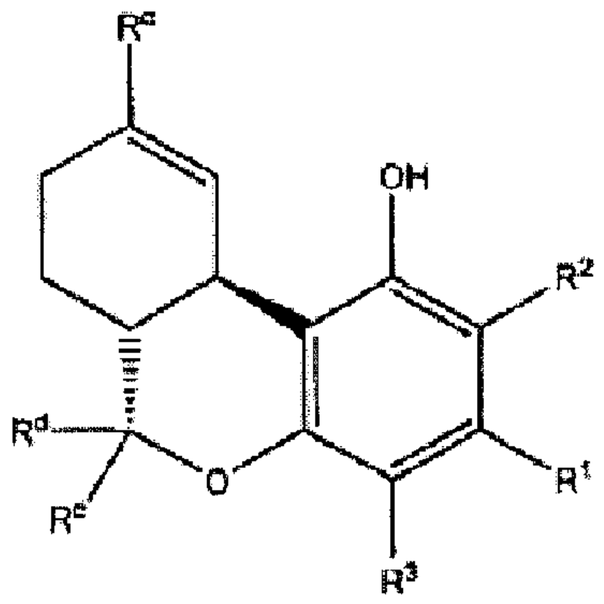
(54) Titre : PROCEDE POUR LA PREPARATION DU (-)-DELTA 9-TETRAHYDROCANNABINOL
(54) Title: PROCESS FOR THE PREPARATION OF (-)-DELTA 9-TETRAHYDROCANNABINOL



(I)

(57) Abrégé/Abstract:
The present disclosure is directed to a process for the chemical synthesis of (-)-Δ^9-^tetrahydrocannabinol (Δ^9-THC) and related compounds of formula (I). In particular, the process comprises a one-pot condensation and sulfonylatton reaction sequence that produces crude Δ^9-THC aryl sulfonate or related compounds. Sulfoπylatioπ of Δ^9-THC or related compounds immediately upon their formation imparts stability to the cannabinoids, and prevents formation of the corresponding Δ^8 isomer. Δ^9THC aryl sulfonates may be readily separated from A^{6}THC aryl sulfonates using reverse phase chromatography. Hydrolysis of the Δ^9-THC aryl sulfonates or related compounds produces Δ^9-THC or related compounds containing relatively low amounts of the corresponding Δ^8 isomer. (Formula I).

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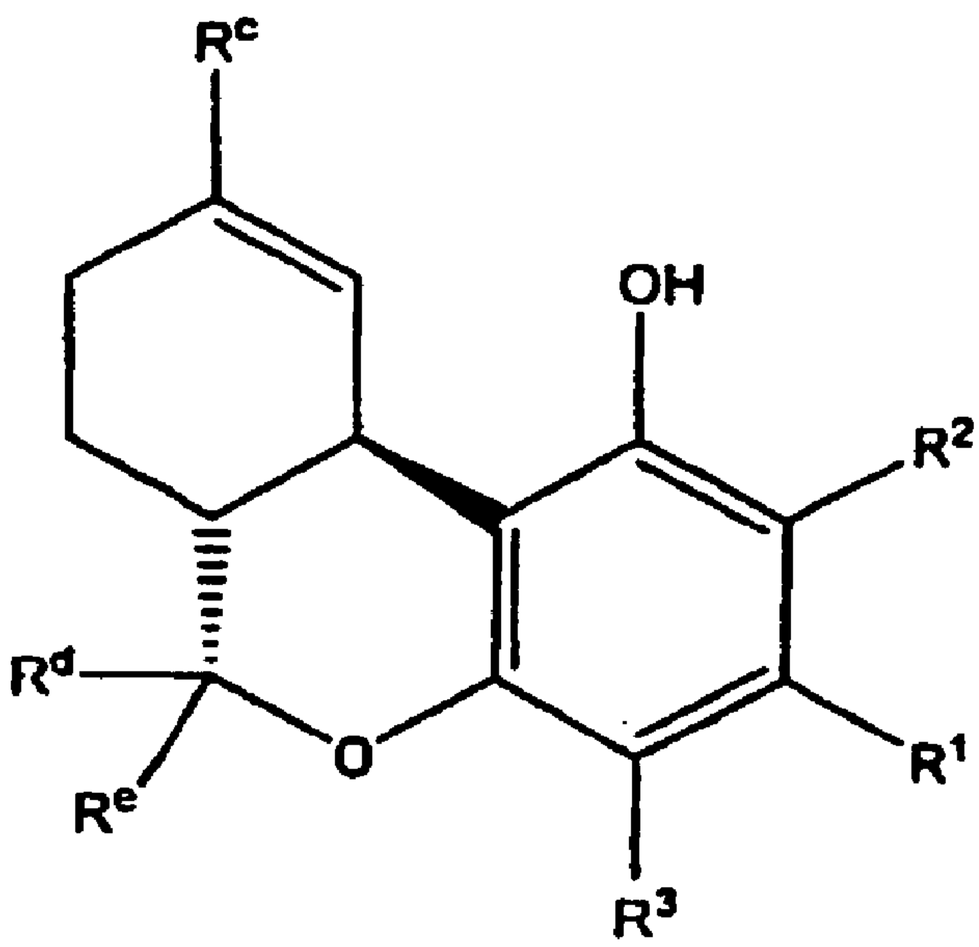
(54) **Title**: PROCESS FOR THE PREPARATION OF (-) -DELTA 9-TETRAHYDROCANNABINOL



(I)

(57) **Abstract**: The present disclosure is directed to a process for the chemical synthesis of (-)-Δ^9- ^tetrahydrocannabinol (Δ^9-THC) and related compounds of formula (I). In particular, the process comprises a one-pot condensation and sulfonylatton reaction sequence that produces crude Δ^9-THC aryl sulfonate or related compounds. Sulfoπylatioπ of Δ^9-THC or related compounds immediately upon their formation imparts stability to the cannabinoids, and prevents formation of the corresponding Δ^8 isomer. Δ^9THC aryl sulfonates may be readily separated from A^{6}THC aryl sulfonates using reverse phase chromatography. Hydrolysis of the Δ^9-THC aryl sulfonates or related compounds produces Δ^9-THC or related compounds containing relatively low amounts of the corresponding Δ^8 isomer. (Formula I).

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PROCESS FOR THE PREPARATION OF (-) – DELTA 9 -TETRAHYDROCANNABINOL

BACKGROUND OF THE DISCLOSURE

[0001] The present disclosure is generally directed to a process for the chemical synthesis of (-)-Δ^9-tetrahydrocannabinol (Δ^9-THC) and/or structurally related compounds. In particular, the process comprises a one-pot condensation and sulfonylation reaction sequence that produces crude Δ^9-THC aryl sulfonate ester or related compounds. Sulfonylation of Δ^9-THC, or structurally related compounds, immediately upon their formation imparts stability to the cannabinoids, and prevents formation of the thermodynamically more stable corresponding Δ^8-isomer. Δ^9-THC aryl sulfonate ester or structurally related compounds may also be readily separated from the corresponding Δ^8-THC isomer using reverse phase chromatography. Hydrolysis of the Δ^9-THC aryl sulfonate ester or related compounds after separation produces Δ^9-THC or related compounds containing relatively low amounts of the corresponding Δ^8-isomer.

[0002] Cannabis preparations in the form of marijuana, hashish, etc. have been known and used for many years for their psychoactive and therapeutic properties. The major active constituent of the resin which is extruded from the female plants of *Cannabis sativa L.* is (-)-Δ^9-tetrahydrocannabinol (Δ^9-THC). The FDA has approved Δ^9-THC for several therapeutic applications. In particular, the anti-emetic and appetite stimulating properties of Δ^9-THC have proven therapeutically beneficial. Consequently, research has been directed towards the preparation of Δ^9-THC via a synthetic method, in order to eliminate the need to obtain the material by extraction from natural sources.

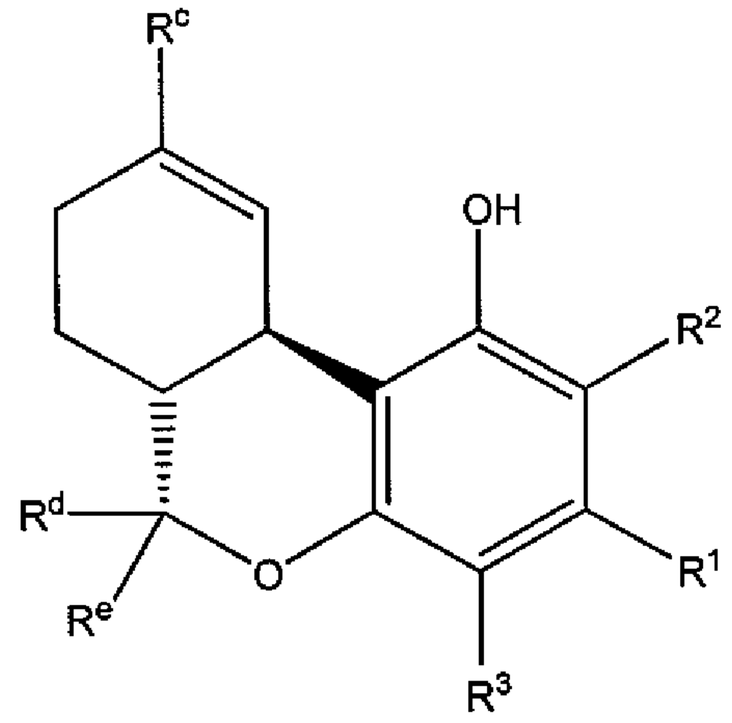
[0003] Also known by the generic name dronabinol, Δ^9-THC presents several unique challenges for its synthetic production on a commercial scale, the primary challenge being the instability of the double bond in the cyclohexane ring. In particular, Δ^9-THC readily undergoes double-bond isomerization to its more thermodynamically stable regioisomer, Δ^8-THC. Such an inherent propensity to isomerize means that precautions are to be taken when manipulating Δ^9-THC in both its crude and pure forms to minimize formation of Δ^8-THC. Minimizing Δ^8-THC formation is particularly desirable when the Δ^9-THC is to be used therapeutically, as USP guidelines limit Δ^8-THC levels in Δ^9-THC preparations to 2 weight% or less for the dronabinol API. Additionally, separation of Δ^8-THC from Δ^9-THC is challenging and typically requires multiple chromatographic purifications or the use of expensive silver-impregnated substrates for its removal. Such extensive handling and purification requirements tend to make commercial-scale production of Δ^9-THC economically unattractive.

[0004] It would therefore be desirable to provide a scalable process for synthesizing Δ^9-THC, or structurally related compounds, that minimizes the formation of the corresponding Δ^8-regioisomer, and furthermore allows for easy separation of Δ^9-THC (or related product compound) from the corresponding Δ^8-regioisomer.

SUMMARY OF THE DISCLOSURE

[0005] The present disclosure is generally directed to a process for the chemical synthesis of (-)-Δ^9-tetrahydrocannabinol (Δ^9-THC), or alternatively a structurally related compound. In general, the process comprises a "one-pot" condensation and sulfonylation reaction sequence that produces crude Δ^9-THC aryl sulfonate ester, or alternatively a structurally related compound. More particularly, the process comprises the preparation of a crude reaction mixture comprising, for example, Δ^9-THC, followed by the direct sulfonylation (e.g., tosylation) of that reaction mixture (i.e., sulfonylation without an intervening separation or purification step to isolate the Δ^9-THC reaction product, or other structurally related compound reaction product), in order to obtain the corresponding aryl sulfonate ester.

[0006] The present disclosure is further directed to a process for the synthesis of a cannabinoid having general Formula I:

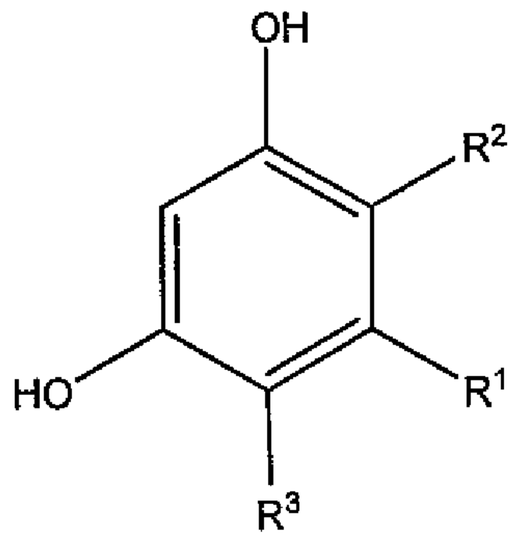


(I)

wherein:

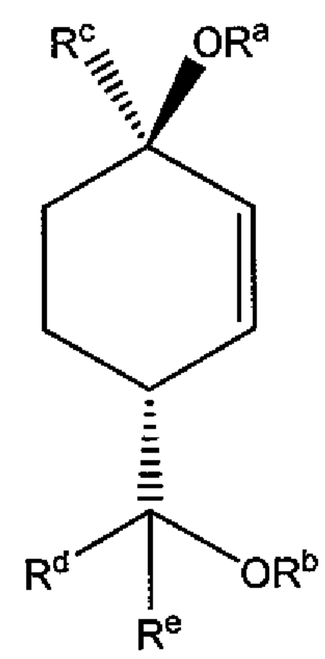
R^1 to R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, OH, aryl, acyl, halide, nitrate, sulphonate, phosphate, and OR', wherein R' is alkyl, aryl, substituted alkyl, substituted aryl, silyl, acyl, or phosphonate; and

R^c, R^d, and R^e are independently selected from the group consisting of H, alkyl, or substituted alkyl. The process comprises reacting a substituted resorcinol having general Formula II:



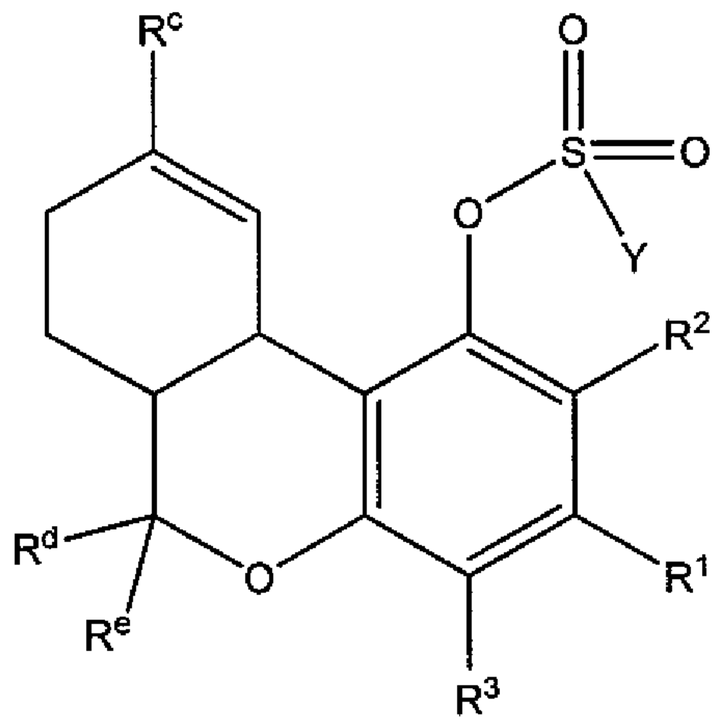
(II)

wherein R^1, R^2, and R^3 are as defined above, with a compound having general Formula III:



(III)

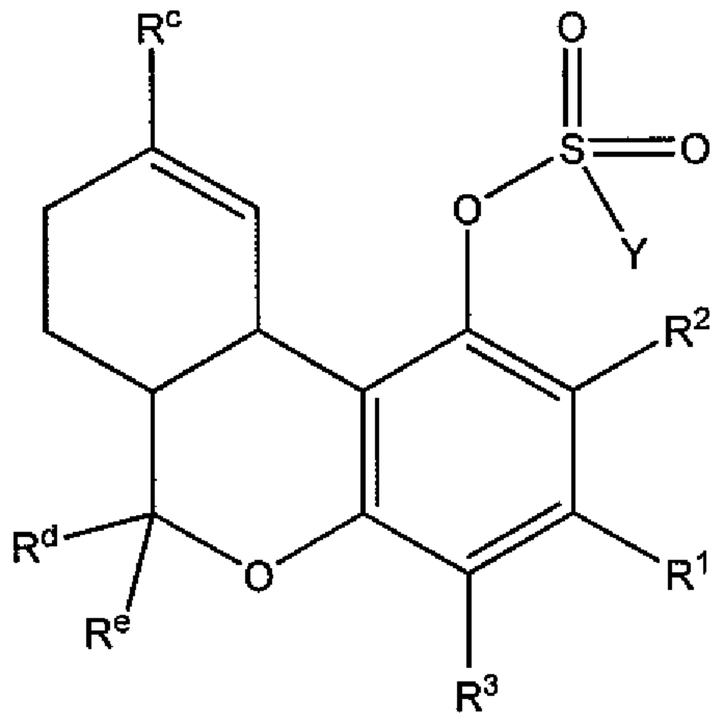
wherein: R^a is H, alkyl, aryl, acyl, or silyl; R^b is H, alkyl aryl, or acyl; and R^c, R^d, and R^e are as defined above, in the presence of an acid catalyst and a non-alkaline dehydrating agent to form a first reaction mixture comprising a cannabinoid having general Formula I. The first reaction mixture, which contains the cannabinoid having general Formula I, is then contacted with an aryl sulfonyl halide and a base to produce a second reaction mixture comprising an aryl sulfonate having general Formula IV:



(IV)

wherein R^1, R^2, R^3, R^c, R^d, and R^e are as defined above, and Y is selected from the group consisting of a substituted aryl group, an unsubstituted aryl group, a substituted alkyl group, and an unsubstituted alkyl group. The aryl sulfonate is isolated from the second reaction mixture, and is then hydrolyzed to produce the cannabinoid having general Formula I.

[0007] The present disclosure is still further directed to a process for the synthesis of an aryl sulfonate having general Formula IV:



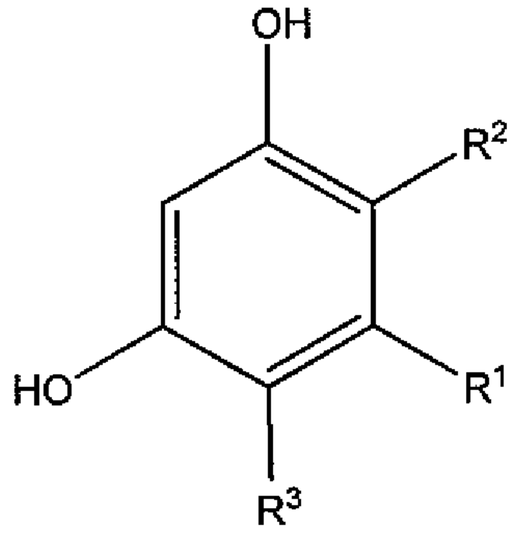
(IV)

wherein:

R^1 to R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, OH, aryl, acyl, halide, nitrate, sulphonate, phosphate, and OR', wherein R' is alkyl, aryl, substituted alkyl, substituted aryl, silyl, acyl, or phosphonate;

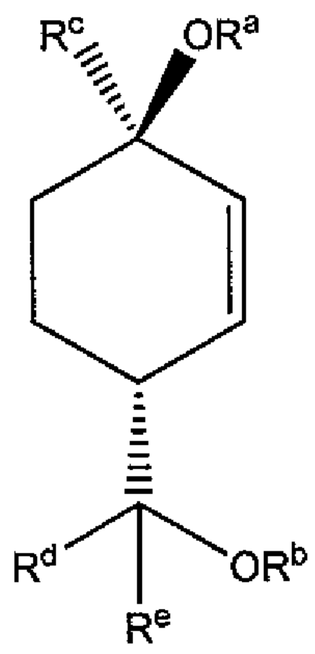
R^c, R^d, and R^e are independently selected from the group consisting of H, alkyl, or substituted alkyl;

and Y is selected from the group consisting of a substituted aryl group, an unsubstituted aryl group, a substituted alkyl group, and an unsubstituted alkyl group. The process comprises reacting a substituted resorcinol having general Formula II:



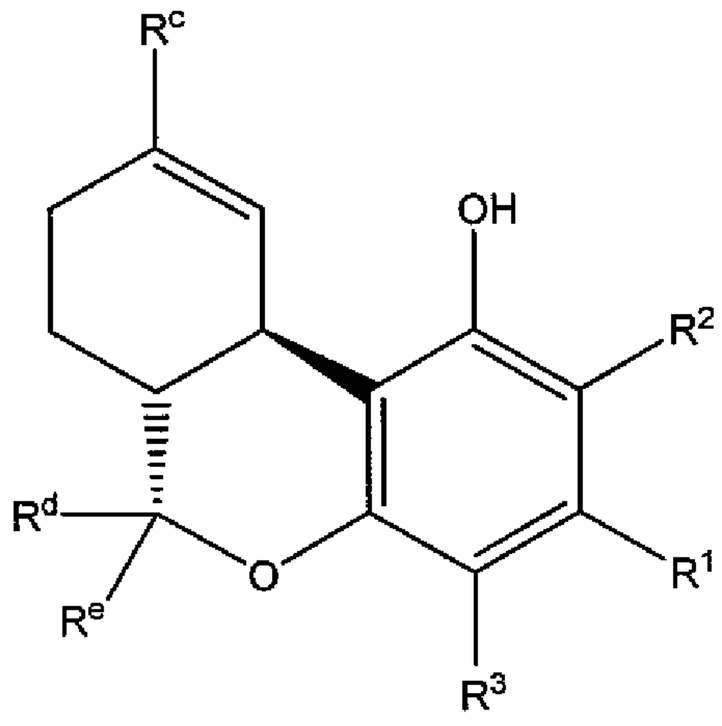
(II)

wherein R^1, R^2, and R^3 are as defined above, with a compound having general Formula III:



(III)

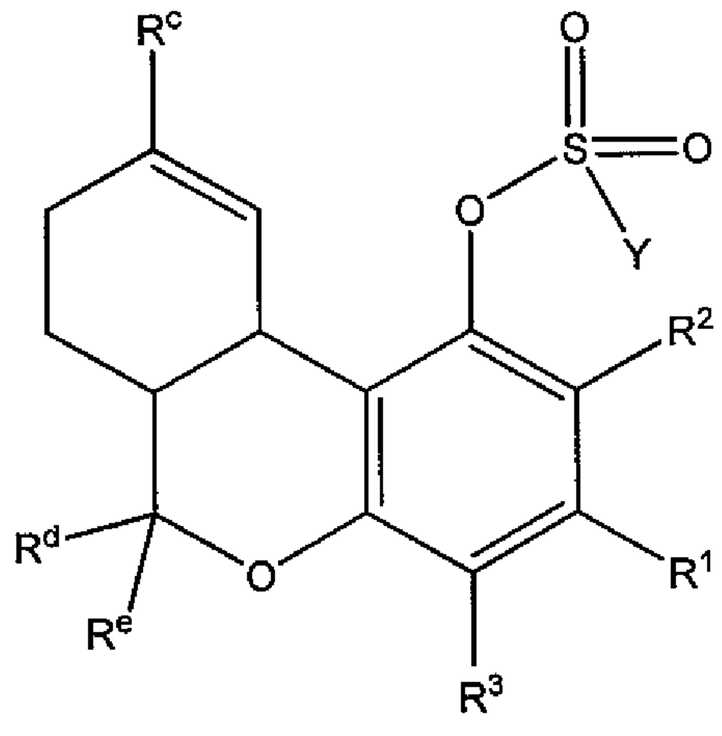
wherein R^a is H, alkyl, aryl, acyl, or silyl; R^b is H, alkyl aryl, or acyl; and R^c, R^d, and R^e are as defined above, in the presence of an acid catalyst and a non-alkaline dehydrating agent to form a first reaction mixture comprising a cannabinoid having general Formula I:



(II)

wherein R^1, R^2, R^3, R^c, R^d, and R^e are as defined above. The first reaction mixture containing the cannabinoid having general Formula I is then contacted with an aryl sulfonyl halide and a base to produce a second reaction mixture comprising the aryl sulfonate.

[0008] The present disclosure is still further directed to a process for the synthesis of an aryl sulfonate having general Formula IV:



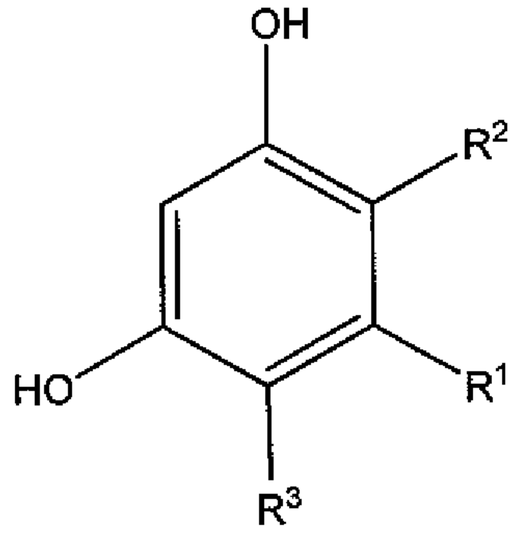
(IV)

wherein

R^1 to R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, OH, aryl, acyl, halide, nitrate, sulphonate, phosphate, and OR', wherein R' is alkyl, aryl, substituted alkyl, substituted aryl, silyl, acyl, or phosphonate;

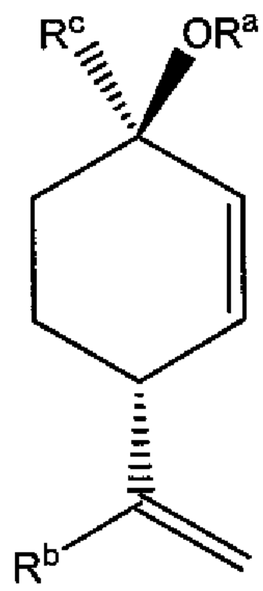
R^c, R^d, and R^e are independently selected from the group consisting of H, alkyl, or substituted alkyl; and

Y is selected from the group consisting of a substituted aryl group, an unsubstituted aryl group, a substituted alkyl group, and an unsubstituted alkyl group. The process comprises reacting a substituted resorcinol having general Formula II:



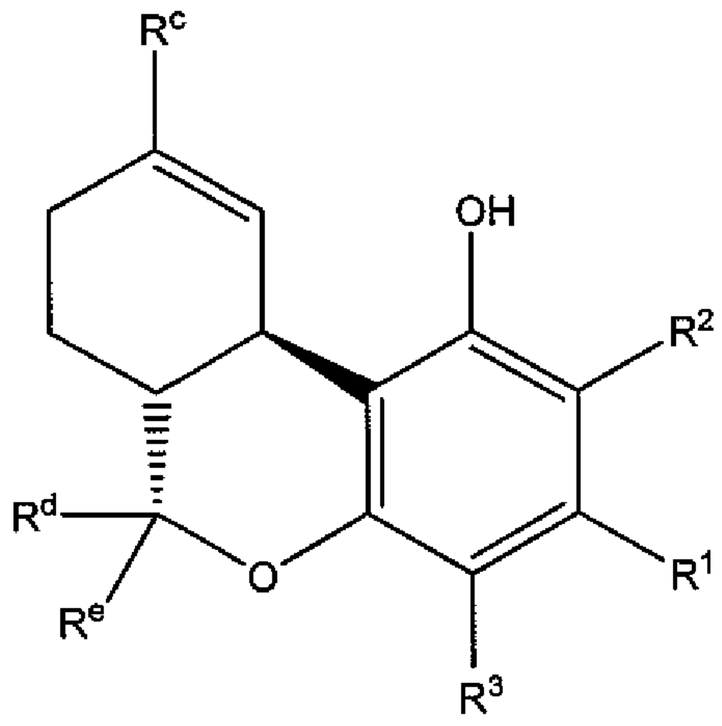
(II)

wherein R^1, R^2, and R^3 are as defined above; with a compound having general Formula VI:



(VI)

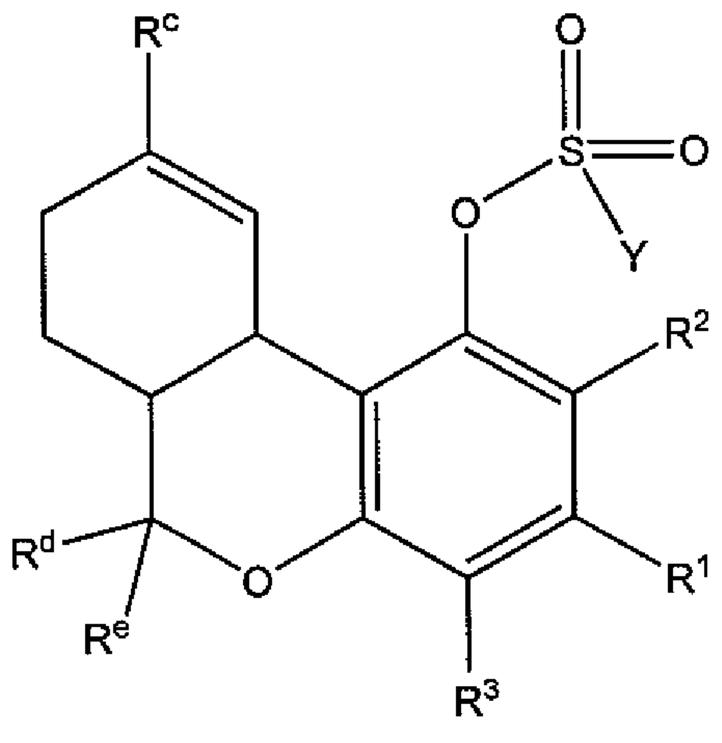
wherein R^a is H, alkyl, aryl, acyl, or silyl; R^b is H, alkyl, aryl, or acyl; and R^c is as defined above, in the presence of an acid catalyst and an excess of a non-alkaline dehydrating agent to form a first reaction mixture comprising a cannabinoid having general Formula I:



(I)

wherein R^1, R^2, R^3, and R^c are as defined above, and R^d and R^e are as defined above. The first reaction mixture, and in particular the cannabinoid having general Formula I present therein, is then reacted with an aryl sulfonyl halide in the presence of a base to produce a second reaction mixture comprising the aryl sulfonate.

[0009] The present disclosure is still further directed to a process for the preparation of (-)-Δ^9-tetrahydrocannabinol aryl sulfonate. The process comprises reacting olivetol with a compound selected from the group consisting of p-mentha-2-en-1,8-diol and p-mentha-2,8-dien-1-ol in the presence of an acid catalyst and an excess of a non-alkaline dehydrating agent to form a first reaction mixture comprising (-)-Δ^9-tetrahydrocannabinol. The first reaction mixture, and in particular the (-)-Δ^9-tetrahydrocannabinol therein, is then reacted with an aryl sulfonyl halide in the presence of a base to produce a second reaction mixture comprising an aryl sulfonate having general Formula IV:



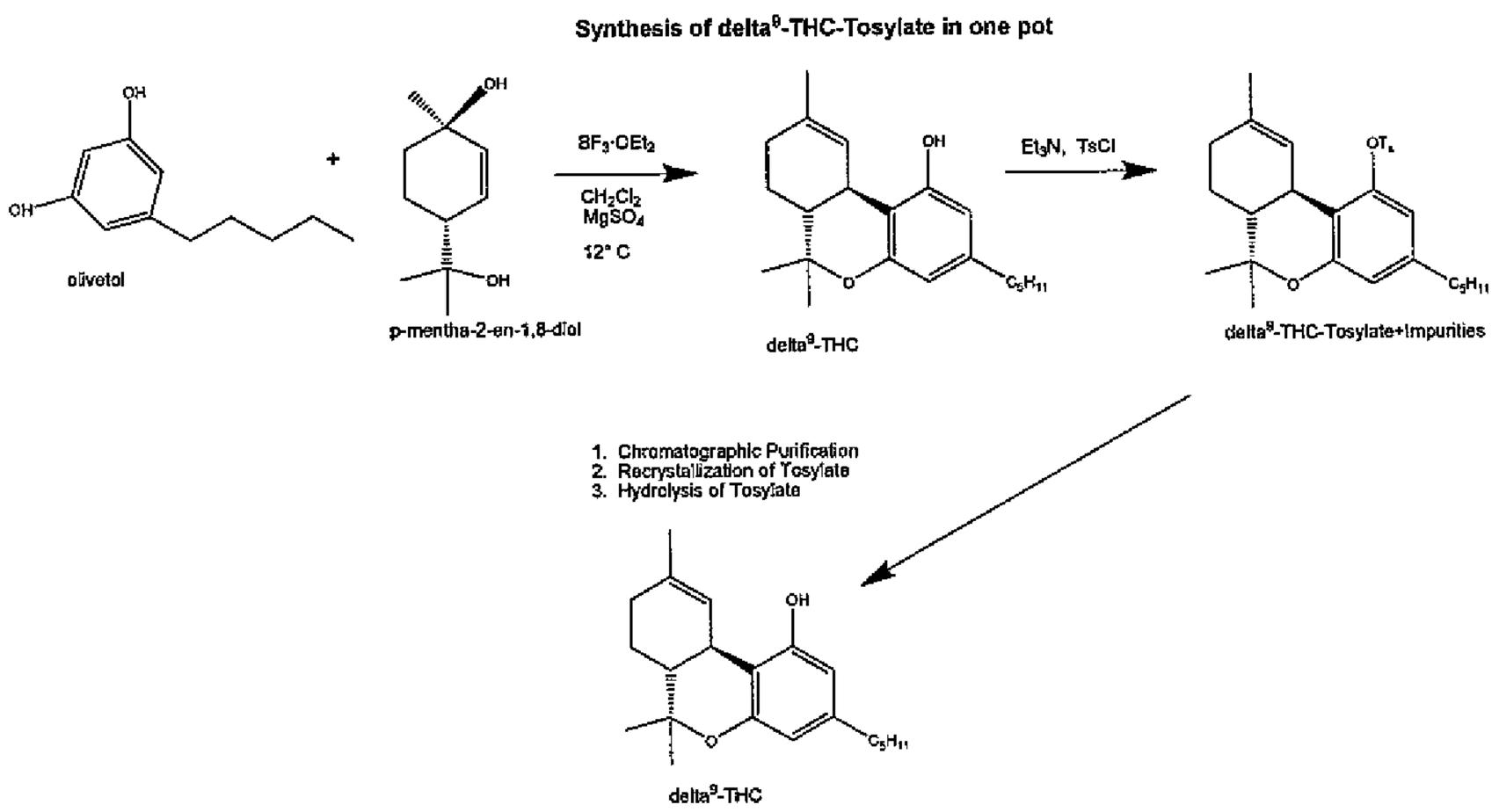
(IV)

wherein R^1 is C_5H_{11}; R^2 and R^3 are H; R^c, R^d, and R^e are $-CH_3$; and Y is a substituted or unsubstituted aryl group.

[0010] Other features will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0011] As generally illustrated in Reaction Scheme I, below, the present disclosure is generally directed to a process for the chemical synthesis of (-)-Δ^9-tetrahydrocannabinol (Δ^9-THC), or alternatively a structurally similar or related compound. In particular, the process comprises a one-pot condensation and sulfonylation reaction sequence that produces crude sulfonated reaction product (e.g., a Δ^9-THC aryl sulfonate, or alternatively a structurally similar or related sulfonate compound), which may then be converted (e.g., hydrolyzed) to the desired product.



REACTION SCHEME I

[0012] By monitoring the progression of the reaction (by means generally known in the art), and in particular the ratio of the desired isomer (e.g., Δ^9-THC, or a structurally similar or related compound) to the undesired isomer (e.g., Δ^8-THC, or a structurally similar or related compound) to ensure it does not exceed a desired threshold (e.g., the ratio of the desired isomer, such as Δ^9-THC, to the undesired isomer, such as Δ^8-THC, being about 49:1 or more), and/or by sulfonating the desired isomer (e.g., Δ^9-THC, or some other structurally similar or related compound) soon after it has been

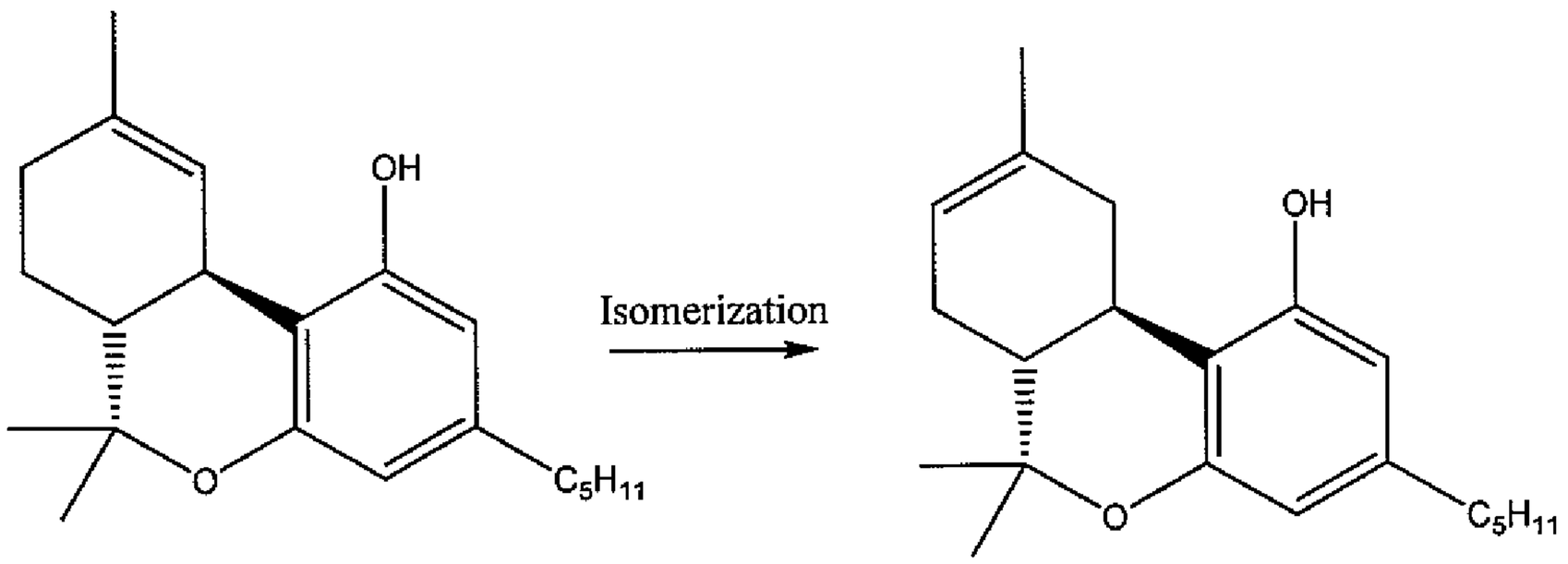
formed in order to impart stability thereto, formation of the undesired isomer may be limited. Δ^9-THC aryl sulfonate, or a structurally similar or related compound, may also be readily separated from Δ^8-THC aryl sulfonate isomer, using for example reverse phase chromatography. Subsequent conversion (e.g., hydrolysis) of the Δ^9-THC aryl sulfonate, or other structurally related compound, produces the desired product (e.g., Δ^9-THC, or other structurally related compound) containing relatively low amounts of the corresponding Δ^8-isomer.

[0013] In this regard it is to be noted that the phrase "structurally similar or related" compound generally refers to a compound that has the same 3-ring core structure of THC, but that differs in terms of the substituent(s) and/or location of the substituent(s) on the 3-ring core structure. It is therefore to be understood that reference to the preparation of Δ^9-THC is also generally intended to refer to the preparation of other structurally similar or related compounds.

[0014] It is to be further noted that a "one-pot" reaction process generally refers to a process wherein (i) the condensation reaction to initially prepare a reaction product mixture that includes Δ^9-THC, or alternatively a structurally similar or related compound, and (ii) the subsequent sulfonylation (e.g., tosylation) reaction, are performed without an intervening step involving isolation or purification of the reaction product from the condensation reaction mixture (e.g., a filtration or washing step, a recrystallization step, chromatography step, etc.). Accordingly, the sulfonylation reaction may be performed in the same container or reaction vessel in which the condensation reaction was performed. Alternatively, however, the contents of that reaction container or vessel may be transferred to a new container or vessel without departing from the scope of the invention, provide this transfer does not involve some act of purification, as noted above (e.g., filtration, recrystallization, chromatography, etc.). Accordingly, the present process involves the "direct" sulfonylation of the first (or condensation) reaction mixture formed.

I. Overview

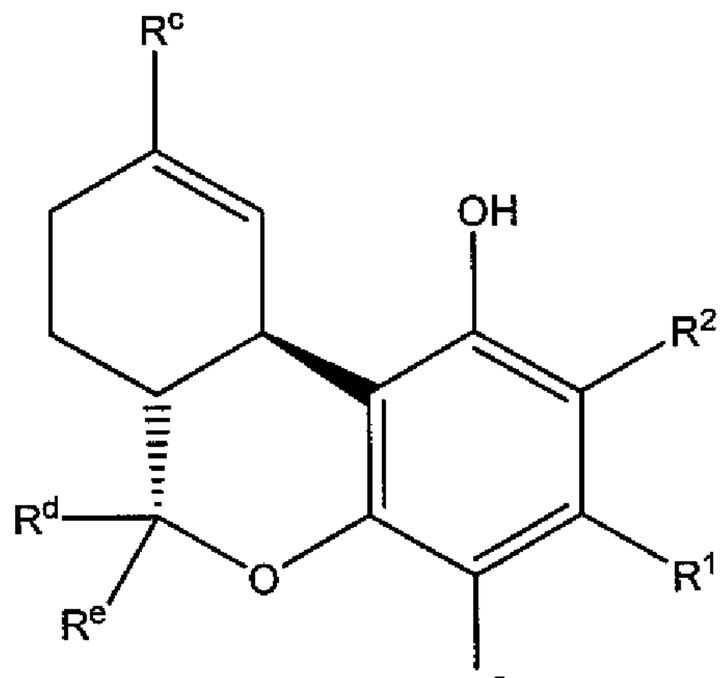
[0015] As noted above, the synthesis and isolation of Δ^9-THC and related compounds has proven difficult. In particular, Δ^9-THC is prone to acid-catalyzed isomerization to the thermodynamically more stable Δ^8-THC regioisomer. Isomerization of Δ^9-THC to Δ^8-THC is represented by the following formula:



Δ^9-THC Δ^8-THC

[0016] This inherent propensity to isomerize means precautions are to be taken when manipulating Δ^9-THC in both its crude and pure forms to minimize Δ^8-THC formation. As noted above, minimizing Δ^8-THC levels in synthetic Δ^9-THC reaction mixtures is particularly desirable when the Δ^9-THC is to be used in pharmaceutical products. Specifically, USP guidelines limit Δ^8-THC levels in a Δ^9-THC preparation to about 2 weight% or less, as compared to the sum of the weight of Δ^9-THC and Δ^8-THC; stated another way, USP guidelines call for the weight ratio of the Δ^9-THC to Δ^8-THC to be less than or equal to about 98:2 (or 49:1) or less. If the Δ^8-THC level exceeded this amount, further separation of the Δ^9-THC from Δ^8-THC contaminant will typically be needed. Separation of Δ^9-THC from its Δ^8 regioisomer has, however, proven to be challenging, and typically requires multiple chromatographic purifications or the use of expensive equipment.

[0017] In accordance with the present disclosure, it has now been discovered that cannabinoids, such as Δ^9-THC and structurally similar related compounds, having general Formula I:



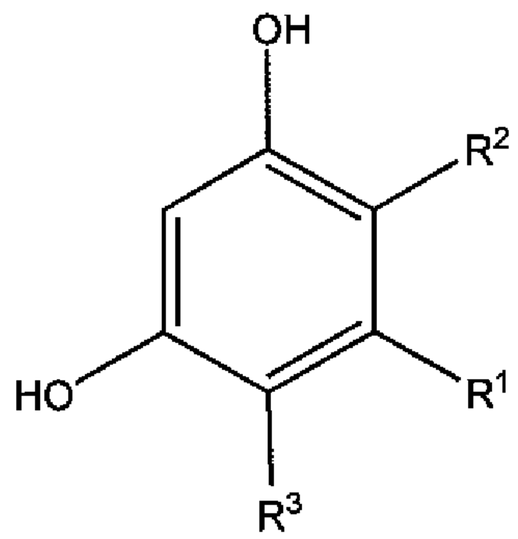
Formula I

wherein:

R^1 to R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl (e.g., substituted or unsubstituted C_1-C_{10}, including for example methyl, ethyl, propyl, butyl, pentyl, etc.,), -OH, aryl, acyl, halide, nitrate, sulphonate, phosphate, and -OR', wherein R' is alkyl, aryl, substituted alkyl or aryl, silyl, acyl, or phosphonate; and

R^c, R^d, and R^e are independently selected from the group consisting of H, alkyl, or substituted alkyl;

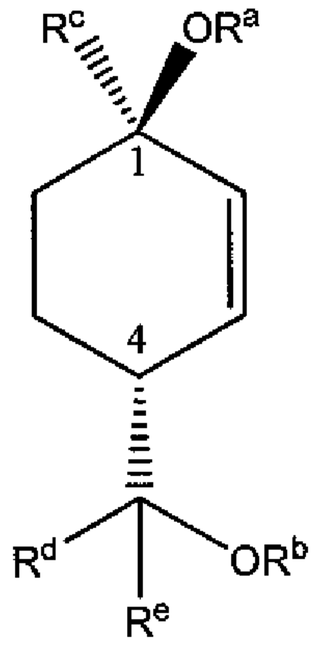
can be synthesized by condensing a substituted resorcinol compound having general Formula II:



Formula II

wherein:

R^1 to R^3 are as defined above, with a compound having general formula III (or a stereoisomer thereof, such as wherein the confirmation of the C1 chiral carbon is "S" rather than "R", as shown here, the combination of chiral carbons thus being S,R rather than R,R):



Formula III

wherein:

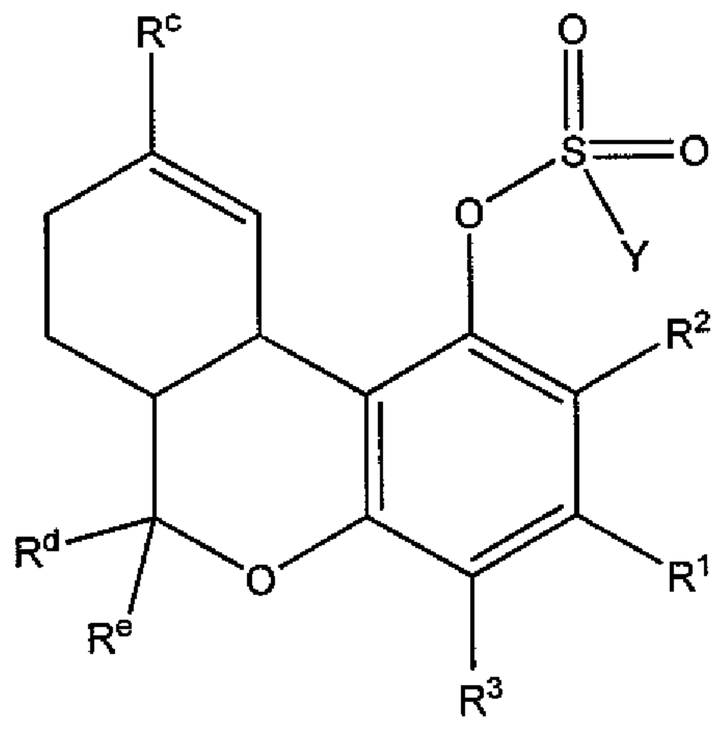
R^a is H, alkyl, aryl, acyl, or silyl; R^b is H, alkyl, aryl, or acyl; and,

Rc, Rd, and Re are as defined above,

in the presence of an acid catalyst and a non-alkaline dehydrating agent. As further discussed in greater detail herein below, in one particular embodiment, the reaction is optimized, and/or the progress of the reaction is monitored (e.g., by performing repeated analyses on the reaction over a period of time, using means generally known in the art, such as HPLC) such that the ratio of the Δ^9-THC isomer, relative to the Δ^8-THC isomer, is about 49:1 or greater (e.g., about 50:1, about 55:1, about 60:1, about 75:1, about 85:1, about 95:1, about 99:1, etc.). Such ratios may be achieved, for example, by monitoring the concentration of the Δ^8-THC isomer, relative to the Δ^9-THC, or both, during the reaction, and/or by monitoring first the appearance and then disappearance of a reaction intermediate (as further detailed herein below). The reaction may then be quenched once the presence of the intermediate is sufficiently low, or no longer detectable, and/or before the concentration of the Δ^8-THC isomer is too high (by, for example, introduction of a base, such as triethylamine, to the reaction mixture). In this way, the formation of the desired product (e.g., Δ^9-THC) is maximized, while the formation of the undesired product (e.g., Δ^8-THC) is minimized.

[0018] In this regard it is to be noted, however, that the ratio of the Δ^9-THC isomer, relative to the Δ^8-THC isomer, may in an alternative embodiment be less than about 49:1 without departing from the intended scope of the invention (the ratio, for example, being about 45:1, about 40:1, about 35:1 or less).

[0019] The reaction produces a first reaction mixture comprising a cannabinoid having general Formula I, which includes Δ^9-THC, as well as various impurities, including for example Δ^8-THC. Upon completion of the condensation reaction, the cannabinoids of Formula I present in the first reaction mixture are then sulfonated, and in one particular embodiment are immediately sulfonated (i.e., as soon as the desired ratio of isomers is achieved, sulfonylation is initiated by addition of the aryl sulfonyl halide reagent to the first reaction mixture), by treating the first reaction mixture with an aryl sulfonyl halide in the presence of a base (such as, for example, the base noted above added to quench the initial condensation reaction), to produce a second reaction mixture comprising an aryl sulfonate having general Formula IV:



Formula IV

wherein R^1, R^2, R^3, R^c, R^d, and R^e are as defined above, and Y is selected from the group consisting of a substituted or unsubstituted aryl group (e.g., an alkylaryl group, such as a methylphenyl group), and a substituted or unsubstituted alkyl group.

[0020] Sulfonylation of the compound of Formula I, present in the first reaction mixture, imparts stability to these compounds by preventing formation of the corresponding Δ^8-isomer. Addition of the aryl sulfonyl halide reagent to the first reaction mixture also acts to sulfonate any Δ^8-isomer of the Formula I compound that formed during the initial condensation reaction. Advantageously, the Formula IV aryl sulfonate may be readily separated from the corresponding Δ^8-isomer using chromatographic purification, for example, reverse phase chromatography. The isolated Formula IV aryl sulfonates may then be subjected to hydrolysis to re-form the cannabinoid of Formula I. The resulting Formula I cannabinoid therefore has high purity and a low level of Δ^8-isomer impurity.

[0021] Advantageously, the process of the present disclosure is a one-pot reaction, and therefore does not involve any isolation or purification of the Δ^9-THC (or structurally similar or related compound) between the condensation reaction and the subsequent sulfonylation (e.g., tosylation) reaction. Rather, the aryl sulfonyl halide and base are added to the first reaction mixture after completion of the condensation reaction, and in one particular embodiment immediately after the reaction (the base being added to quench the condensation reaction, for example, when the desired isomeric ratio is reached), to sulfonate the compound of Formula I present therein. In this way, further isomerization of the Formula I compound may be limited, and desirably is substantially prevented.

[0022] Sulfonylation of the Formula I compound present in the first reaction mixture also improves the ease with which the Δ^8-isomer impurity can be removed. As noted above, separation of,

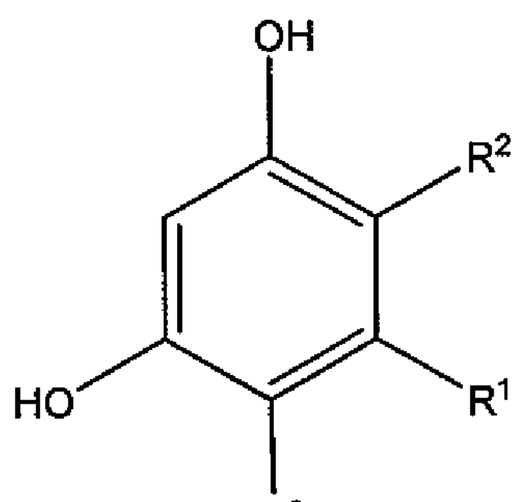
for example, the Δ^9-THC (or structurally related compounds) from the corresponding Δ^8-isomer is typically inefficient, requiring multiple chromatographic separations or use of expensive equipment. In accordance with the present disclosure, the Formula IV aryl sulfonate synthesized during the process of the present disclosure can be readily separated from the corresponding sulfonated Δ^8-isomer using reverse phase chromatography.

[0023] Following separation of the Formula IV aryl sulfonate from the corresponding Δ^8-isomer, the Formula IV aryl sulfonates may be hydrolyzed to re-form the compound having general Formula I, such as Δ^9-THC. Optionally, the Formula IV aryl sulfonates may be recrystallized, using means generally known in the art, following chromatographic purification to further purify the compounds prior to hydrolysis.

[0024] The process of the present disclosure advantageously produces compounds of Formula I, such as Δ^9-THC, that are at least 90% pure, at least about 92% pure, at least about 94% pure, at least about 95% pure, at least about 96% pure, at least about 98% pure or more (e.g., about 99%, or even about 100%). In particular embodiments, however, the compounds of Formula I produced using the process of the present disclosure are at least about 95% pure, or even at least about 98% pure. Additionally, or alternatively, as previously noted above, the concentration of the corresponding Δ^8-isomer is, in one particular embodiment, not more than about 2%, and may be not more than about 1%, or even about 0.5%, relative to the amount of the desired isomer of Formula I.

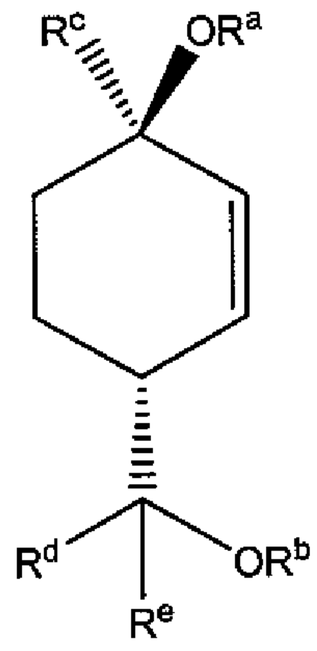
II. Condensation Reaction

[0025] As noted above, formation of the first reaction mixture occurs by way of a condensation reaction between a substituted resorcinol having general Formula II:



Formula II

wherein R^1 to R^3 are as previously defined above; and a compound of general Formula III:

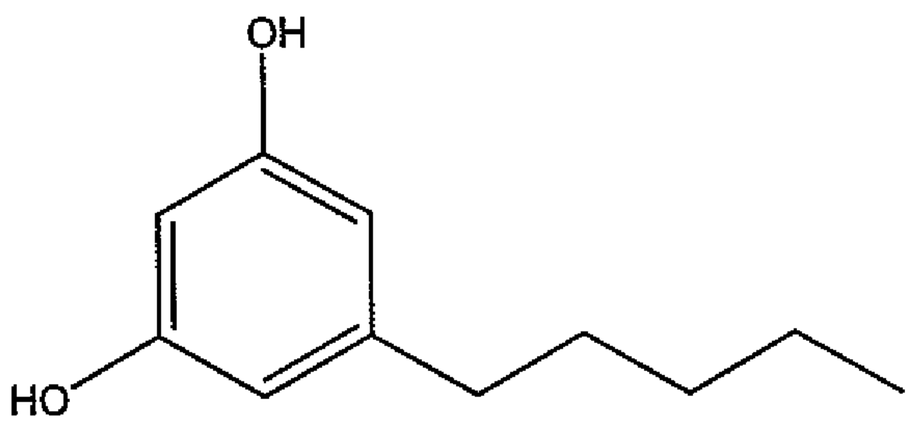


Formula III

wherein R^a, R^b, R^c, R^d and R^e are as defined above, in the presence of an acid catalyst and a non-alkaline dehydrating agent (and in a particular embodiment in the presence of a molar excess of the agent relative to the Formula III compound).

[0026] In this regard it is to be noted that, as used herein, a "substituted" alkyl group may contain substituents such as halide, hydroxyl, amine, and thiol. It is to be further noted that "alkyl," as used in various embodiments herein, may desirably refer to C_1 to C_{10} alkyl. Additionally, the alkyl group may optionally be saturated or unsaturated, acyclic or cyclic.

[0027] As noted above, the compound of Formula II is a substituted resorcinol. In one embodiment, R^2 and R^3 are H. R^1 may suitably be an alkyl group or substituted alkyl group. In a particular embodiment, R^1 is an alkyl having from about 1 to about 10 carbon atoms, or an alkyl having from 1 to 5 carbon atoms, and still more preferably is C_5H_{11}. Optionally or additionally, R^1 may contain groups (e.g., as a substituent or within the chain itself) that promote water solubility (e.g., ketone, ester, hydroxyl, or amine groups). In one particular embodiment, however, the substituted resorcinol of Formula II is olivetol, wherein R^2 and R^3 are H, and R^1 is C_5H_{11}. Olivetol has the following structure:



[0028] Other structures of interest include those wherein the side chain C_5H_{11} is replaced by a C_4H_9, a C_3H_7, a C_2H_5, or even a CH_3 side chain or group.

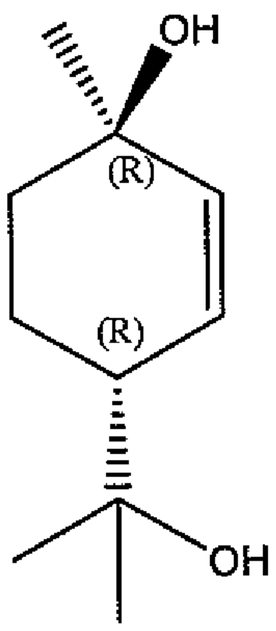
[0029] Referring again to Formula III, in one embodiment, R^b is acyl and OR^b is an ester group. Suitable ester groups include acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, p-nitrobenzoate, phthalate, and succinate.

[0030] In another embodiment, both R^a and R^b are acyl groups so that the compound of Formula III is a diester. The two ester groups are suitably chosen independently from acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, p-nitrobenzoate, phthalate, and succinate. In one particular aspect, both R^a and R^b are diphenylacetate.

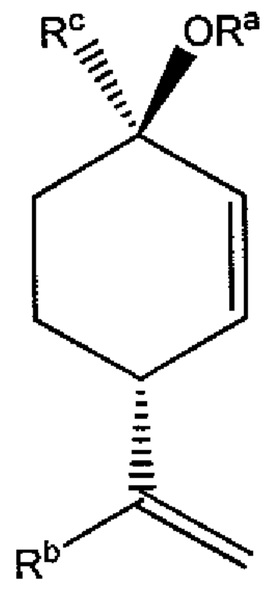
[0031] In yet another embodiment, both R^a and R^b are H.

[0032] R^c, R^d, and R^e can be varied independently of R^a and R^b. In one particular embodiment, R^c is selected from the group consisting of $-CH_3$ or H. In this or another embodiment, R^d and R^e are independently selected from the group consisting of $-CH_3$ or $-CH_2OH$. In one particular embodiment, one or more of R^c, R^d, and R^e is $-CH_3$.

[0033] In this or another particular embodiment, the compound of Formula III is p-mentha-2-en-1,8-diol, wherein R^c, R^d, and R^e are $-CH_3$, and R^a and R^b are both H. p-mentha-2-en-1,8-diol has the following structure (with the stereochemical conformation noted parenthetically):



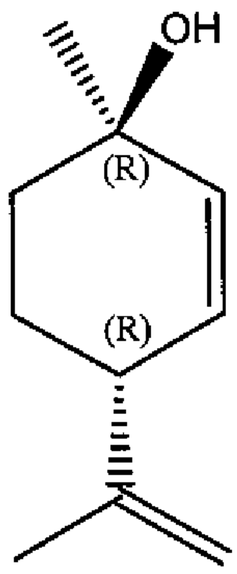
[0034] In one alternate embodiment, the first reaction mixture may be prepared by reacting a substituted resorcinol of Formula II with a compound of general Formula VI:



Formula VI

wherein R^a, R^b, and R^c are as defined above, in the presence of an acid catalyst and an excess of a non-alkaline dehydrating agent (and in a particular embodiment in the presence of a molar excess of the agent relative to the Formula VI compound).

[0035] In this or another particularly embodiment, the compound of Formula VI is p-mentha-2,8-dien-1-ol, wherein R^b and R^c are $-CH_3$, and R^a is –H. p-Mentha-2,8-dien-1-ol has the following structure (with the stereochemical conformation noted parenthetically):



[0036] The condensation reaction is typically carried out by combining about equal molar amounts of a compound of Formula II with a compound of Formula III or Formula VI, in order to obtain a reaction mixture that includes the compound of Formula I, plus impurities (including, for example, the Δ^8-isomer of the compound of Formula I). However, more generally speaking, the compound of Formula I may be prepared by combining a compound of Formula II with a compound of Formula III or VI in a molar ratio of from about 2:1 to about 0.75:1, or from about 1.5:1 to about 0.85:1. In one

embodiment, olivetol is reacted with about an equal molar amount of p-mentha-2-en-1,8-diol or p-mentha-2,8-dien-1-ol.

[0037] Although the condensation reaction does not exclusively yield the compound of Formula I, under optimal conditions (e.g., proper selection of reagents, concentration of reagents, reaction conditions, etc.), it is possible to obtain the compound of Formula I where the amount thereof, as compared to other products (such as the Δ^8-isomer), is maximized. For example, in various embodiments the yield of Formula I compound may be from about 15 wt.% to about 40 wt.%, or about 20 wt.% to about 35 wt.%, of the reaction product mixture.

[0038] In carrying out the condensation reaction, any conventional inert organic solvent, such as petroleum ether, diethyl benzene, toluene, tetrahydrofuran, dioxane, heptane, and halogenated aliphatic or aromatic hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, bromobenzene, and 2-methyl-THF can be used. When ethers such as diethyl ether, dioxane, and tetrahydrofuran are used, a higher concentration of acid catalyst may be needed. Use of chlorinated hydrocarbons, and in particular methylene chloride, may be particularly advantageous in one or more embodiments herein.

[0039] Generally speaking, a quantity of solvent will be used which acts to optimize the overall yield of the reaction. Typically, however, a quantity of solvent is used that is sufficient to dissolve (e.g., the compounds of Formula II, III and/or IV) and/or thorough suspend (e.g., the dehydrating agent) all the condensation reaction reagents therein. For example, a quantity of solvent will typically be used which ensure the concentration of the compound of Formula II, III and/or IV is within the range of about 15 g/L and about 200 g/L, or about 17 g/L to about 180 g/L, or about 18 g/L to about 170 g/L.

[0040] As noted above, the reaction between the substituted resorcinol of Formula II and the compound of Formula III or VI is carried out in the presence of an acid catalyst. The use of boron trifluoride may be advantageous, in one or more embodiments, although other Lewis acids such as aluminum chloride, zinc chloride, stannic chloride, iron chloride, and antimony pentafluoride can also be used. A convenient form for use of boron trifluoride is boron trifluoride complexed with diethyl ether, also known as boron trifluoride etherate. Boron trifluoride can also be dissolved in inert anhydrous solvents, and the use of such solutions would also be suitable. Protonic acids such as p-toluenesulfonic, methanesulfonic, and trifluoracetic acid can also be used, but the yields are generally lower. Other suitable catalysts include metal triflates, such as indium (III) triflate, scandium (III) triflate, ytterbium (III) triflate, bismuth (III) triflate, and the like.

[0041] A quantity of acid catalyst will be used which acts to optimize the overall yield of the reaction. Typically, the quantity of catalyst used is within the range of about 1 g/L to about 5 g/L, or about 1.2 g/L to about 4.8 g/L, or about 1.5 g/L to about 4.5 g/L, or about 1.75 g/L to about 4 g/L, relative to the volume of solvent used. Alternatively, the quantity of acid catalyst may be expressed in terms molar equivalents relative to the moles of the compound of Formula I to be formed. For example, in various embodiments the molar ratio of the acid catalyst to the moles of compound Formula I may be in the range of from about 0.1:1 to about 0.4:1, or from about 0.2:1 to about 0.3:1.

[0042] As noted above, a non-alkaline dehydrating agent is used in the preparation of the compound of Formula I. Any conventional material which has the ability to readily combine with a molecule of water, and is non-alkaline and otherwise chemically inert can be used. Agents useful in the practice of this disclosure include calcium sulfate, magnesium sulfate, sodium sulfate, calcium chloride, aluminum oxide, silica, and molecular sieves such as those formed from potassium aluminum silicate. The reaction is advantageously carried out by thoroughly mixing an excess of the non-alkaline dehydrating agent with the reactants so as to efficiently remove water as it is formed during the reaction.

[0043] In this regard it is to be noted that by "excess" is meant a quantity which is sufficient to react with the water formed during the condensation and any water which is present in the solvent. Typically, however, a quantity may be used within the range of the range of about 30 g/L to about 360 g/L, or about 60 g/L to about 330 g/L, or about 90 g/L to about 300 g/L, relative to the volume of solvent used.

[0044] In accordance with the present process, a compound of Formula II (e.g., olivetol) and of Formula III (e.g., p-mentha-2-en-1,8-diol) or Formula VI (e.g., p-mentha-2,8-dien-1-ol) are dissolved or suspended in a solvent (e.g., dicholoromethane) in the presence of a dehydrating agent (e.g., magnesium sulfate). The resulting solution or suspension is then optionally chilled or cooled (e.g., to a temperature of less than about 15°C, about 10°C or even 5°C), and then a catalyst (e.g., boron trifluoride etherate) is added, optionally in a solution of the same solvent (such as for example dichloromethane), and also optionally over a period of time (e.g., 5 minutes, 10 minutes, 20 minutes or more, depending on the quantity to be added, the quantity of the reaction mixture, and/or the ability to control the temperature adequately if an exothermic reaction occurs).

[0045] Once the addition of the catalyst is completed, the temperature of the resulting solution or suspension may then be heated, as necessary, in order to ensure the reaction proceeds within an acceptable period of time and to an acceptable endpoint (i.e., yield of the compound of

Formula I). Typically, the condensation reaction is carried out within a temperature range of from about 5°C to about 20°C, and more typically from about 8°C to about 15°C, for a period of time sufficient to optimize the yield of the compound of Formula I, and furthermore to minimize the formation of the Δ^8-isomer thereof. Typically, however, the reaction is carried out for about 1 to about 10 hours, or more typically about 3 to about 8 hours, with lower reaction temperatures requiring longer reaction times and vice versa.

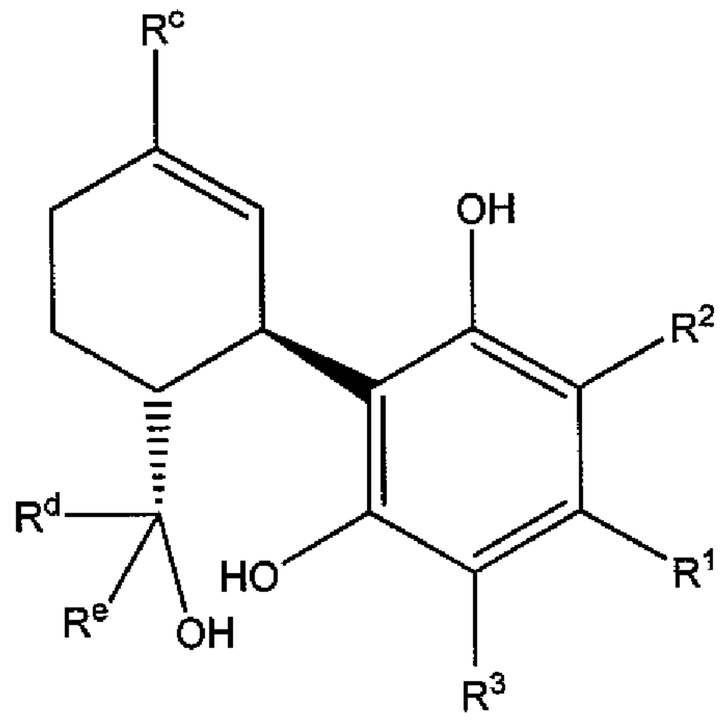
[0046] In this regard it is to be noted that experience to-date indicates the acid catalyst concentration (or amount used in the reaction) impacts the rate of reaction and/or yield of the desired product, this impact varying with the temperature at which the reaction is carried out. Additionally, the type of acid used may also impact the process conditions used. For example, Lewis acids, such as BF_3, allow the reaction to be carried out at a lower temperature than that needed for protic acids. When protic acids are used, the reaction is typically carried out under refluxing conditions, or extended reaction times (and may be more prone to yielding the Δ^8 isomer).

III. Sulfonylation

[0047] As noted above, once the desired condensation reaction endpoint is reached, the reaction is optionally quenched and the product compound I is sulfonated to prevent further conversion of this product compound to the Δ^8-isomer. Accordingly, following the condensation reaction between the Formula II substituted resorcinol with the Formula III or VI compound, at least one aryl sulfonyl halide in the presence of at least one base is added to the first reaction mixture to sulfonate the compound of Formula I, and Δ^8-isomer thereof, that is present in the first reaction mixture. Specifically, the aryl sulfonyl halide reacts with the compound of Formula I (and the Δ^8-isomer thereof) at the phenyl hydroxyl group, thereby producing aryl sulfonates.

[0048] Sulfonylation desirably occurs immediately upon completion of the condensation reaction to prevent further formation of Δ^8-isomers, and facilitates the separation of Δ^9- and Δ^8-isomers (using techniques generally known in the art, including for example reverse phase chromatography). As used herein, "immediate" sulfonylation generally means the sulfonylation reagents (i.e., aryl sulfonyl halide and base) are added to the first reaction (i.e., condensation reaction) mixture as soon as conversion of the Formula II and Formula III or VI compounds to the product compound of Formula I is deemed to be sufficiently complete. Completion of the condensation reaction may be monitored through use of techniques known in the art, including for example high performance liquid

chromatography (HPLC). Specifically, the condensation reaction produces an intermediate product having the following general Formula V:



Formula V

wherein R^1, R^2, R^3, R^c, R^d, and R^e are as defined above. Disappearance of intermediate Formula V compounds from the reaction mixture correlates directly to formation of the Formula I compound. As such, HPLC may be used to monitor the presence of the intermediate compounds in the reaction mixture, and thus the progress of the condensation reaction. The condensation reaction may be deemed complete upon sufficient disappearance of the intermediate Formula V compounds from the first reaction mixture. This typically occurs when the concentration of intermediate compound in the first reaction mixture is about 10 wt.% or less (e.g., about 8 wt.%, about 6 wt.%, about 4 wt.%, about 2 wt.%, or less).

[0049] Accordingly, the sulfonylation reagents (i.e., aryl sulfonyl halide and base) are added to the first reaction mixture immediately following completion of the condensation reaction. The aryl sulfonyl halide forms a sulfonate of both the compound of Formula I present in the first reaction mixture, as well as any Δ^8-isomers that may have formed during the condensation reaction. By adding the sulfonylation reagents immediately upon completion of the condensation reaction, formation of the product compound of Formula I is maximized, while also minimizing the presence of the corresponding Δ^8-isomers in the reaction mixture.

[0050] The base used in the sulfonylation reaction is added, at least in part, to neutralize the halide acid produced as a by-product during the reaction. Therefore, any suitable base that does not interfere with the sulfonylation reaction may be used. Exemplary bases include lower alkyl amines, especially tertiary amines such as triethyl amine, which provide inexpensive bases that are suitable for

the present invention. Primary and secondary amines may also be used, but may result in unwanted reactions with the sulfonyl halide. In particular, amines of the formula $R^5R^6R^7N$ may be used, wherein R^5, R^6, and R^7 may typically be lower alkyl substituents having from about one to about six carbon atoms.

[0051] The aryl group of the sulfonyl halide may be any aromatic system, substituted (including multiply substituted) or unsubstituted, that does not interfere with the sulfonylation reaction. Suitable aromatic systems include but are not limited to benzene, alkyl substituted benzene, halogen substituted benzene, nitrobenzene, alkyloxy substituted benzene and substituted and unsubstituted napthyl compounds. Particularly suitable alkyl substituents include an alkyl group directly attached to an aromatic ring carbon where the alkyl substituent may typically be from about one to about six carbon atoms. In one embodiment, the aryl sulfonyl halide is p-toluenesulfonyl chloride.

[0052] In a particular embodiment, the aryl sulfonyl halide and base are added to the first reaction mixture, and allowed to react at about room temperature (e.g., about 20°C to about 25°C) until sulfonylation is complete, forming a second reaction mixture. Typically, the sulfonylation reaction will be complete after from about 2 hours to about 16 hours, more typically after from about 4 hours to about 12 hours, and still more typically after about 6 or about 8 hours. In an alternative embodiment, the reaction may be run at increased temperatures, although doing so may result in minimal increase in reaction rate. Reaction temperatures in the range of from about room temperature to about 75°C, or about 35°C to about 55°C, may therefore alternatively be used.

IV. Product Isolation

[0053] Following sulfonylation, the reaction product may be separated or isolated from the second reaction mixture using essentially any means generally known in the art. For example, in one embodiment, the drying agent is removed from the second reaction mixture, such as by means of filtration, and then the filtrate is subject to a solvent extraction step (using for example sodium bicarbonate and brine solutions). The solvent is then removed from the second reaction mixture by any suitable method, such as evaporation (e.g., rotary evaporation), supercritical fluid chromatography, normal phase liquid chromatography, and the like, yielding an oily residue that contains the aryl sulfonates present in the second reaction mixture (including compounds of Formula IV). The crude aryl sulfonates may then be subjected to additional separation and purification steps generally known in the art, including for example reverse-phase chromatography, to remove sulfonated Δ^8-THC or related compounds, as well as additional reaction by-products. In one particular embodiment, the crude aryl

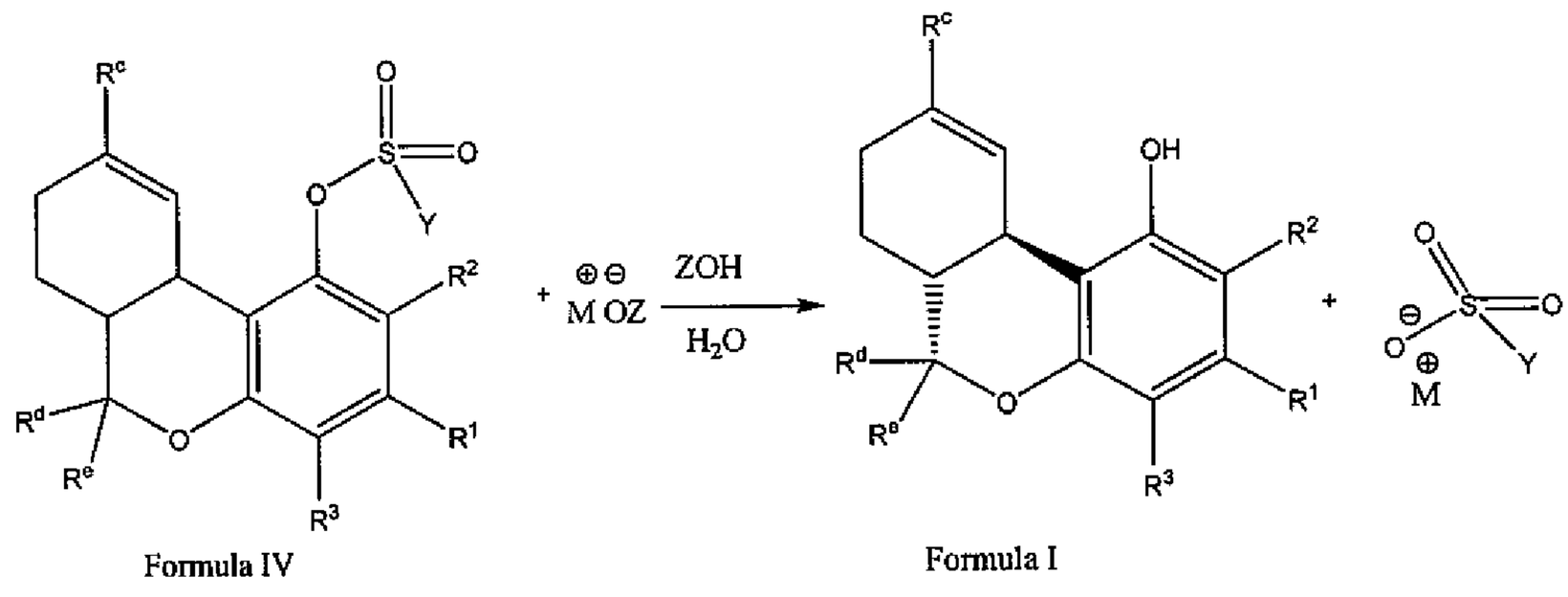
sulfonates are purified using reverse-phase chromatography using a Prodigy ODS-Prep 250 x 21.2 mm ID column; and an eluant comprising 77 volume percent methanol, 10 volume percent tetrahydrofuran, and 13 volume percent water, at a flow rate of 20 mL/minute, and UV detection at 255 nm.

[0054] The isolated fractions containing the aryl sulfates of Formula IV obtained from chromatographic purification may optionally comprise not more than about 2 wt.%, or not more than about 1 wt.%, or even not more than about 0.5 wt.%, of the sulfonated Δ8-isomers. If desired, however, isolated fractions of the Formula IV aryl sulfonates containing these amounts of sulfonated Δ^8-isomers may be further purified, alone or in combination, using recrystallization techniques generally known in the art to remove other impurities from the isolated fractions. Suitable solvents for recrystallization include, but are not limited to, heptane, hexane, t-butyl methyl ether, n-pentanol, n-butanol, isopropanol, isobutanol, ethanol, acetone, acetonitrile, and isopropyl acetate. In particular, alcohols, including methanol, may be used.

[0055] In general, the purity of the aryl sulfonates obtained, after separation and optional recrystallization, is typically greater than about 90 weight%, and more typically is great than about 95 weight%, and still more typically is greater than about 99 weight%. The resulting aryl sulfonates having Formula IV are highly crystalline and stable at room temperature.

[0056] In this regard it is to be noted that all percentages given herein are weight percentages unless otherwise noted.

[0057] The crystalline Formula IV aryl sulfonates can then be hydrolyzed to recover the purified compound of Formula I by, for example, base hydrolysis, as illustrated in the reaction below:



Formula IV Formula I

wherein R^1, R^2, R^3, R^c, R^d, R^e, and Y are as defined above; M is a metal; and Z is an alkyl group, typically having 1 to about 10 carbon atoms, or about 2 to about 8 carbon atoms.

[0058] The hydrolysis can be accomplished by any method known in the art. In a particular embodiment, the base comprises at least one metal salt of an alkyl oxide in at least one alkyl alcohol. Suitable bases include but are not limited to potassium methoxide, ethoxide, propoxide, isopropoxide, t-butoxide, and t-pentanoxide, with tertiary alkoxides being used in one or more embodiments. Suitable alcohols include, but are not limited to, methanol, ethanol, n-propanol, isopropanol, t-butanol, and t-pentanol, with tertiary alcohols being used in one or more embodiments. The use of the same alkyl group for both the oxide and the alcohol, such as for example potassium t-butoxide in t-butanol, optionally with several equivalents of water, may be desirably to, for example, prevent exchange of the alkyl groups present therein. The reaction may include about 2, about 3 or more equivalents of base, and about 3, about 4 or more equivalents of water, per equivalent of the sulfonated compound (i.e., the compound of Formula IV). The reaction is typically carried out at a temperature in excess of room temperature (e.g., a temperature in excess of about 20°C or about 25°C), and may optionally be carried out at a temperature of about 50°C, about 65°C or more.

[0059] A suitable method of hydrolysis comprises placing the crystalline Formula IV aryl sulfonates in a flask, or some other type of vessel, under an inert atmosphere. The flask is typically equipped for or with (i) magnetic stirring, or some other type of agitation, (ii) electronic temperature control, (iii) a condenser, (iv) an inert gas bubbler, and/or (v) a heating mantle. Deionized water and an alkyl oxide in alcohol are added to the flask. All solvents utilized are optionally deoxygenated by bubbling with an inert gas. In one embodiment, the resulting slurry is then heated (to for example about 65°C or more), to increase the reaction rate and to force the reaction to completion. While the reaction will proceed at lower temperatures, the reaction may optionally be heated to a temperature between about 40°C to about 80°C, with about 50°C to about 70°C being used in one or more embodiments, the maximum temperature being determined by the boiling point of the solvent being used. The reaction mixture is maintained at the desired temperature until the reaction is substantially complete, which is typically between about 2 to about 12 hours, more typically between about 2.5 to about 8 hours, and more typically about 3 hours. The reaction mixture is then cooled to room temperature.

[0060] After cooling, deionized water is added, and the reaction mixture is stirred or agitated. An organic solvent is added, and then resulting mixture is again stirred or agitated. The resulting mixture is then placed in a separatory funnel and then the phases are separated. The organic fraction containing the product compound of Formula I is then washed with at least one aliquot of deionized deoxygenated water. The organic fraction is then typically dried with a salt solution, filtered, and

evaporated under vacuum to form an oil. Distillation of the resulting oil under vacuum, using means generally known in the art, results in a highly purified cannabinoid product.

[0061] The purity of the recovered cannabinoid product typically is about 90 weight%, about 95 weight%, about 98 weight% or more. Additionally, the overall yield of the reaction sequence used to obtain this highly pure cannabinoid product is at least about 15 wt.%, about 20 wt.%, about 25 wt.%, about 30 wt.% or more.

[0062] The synthetic cannabinoid produced using the process of the present disclosure will, in at least one embodiment, advantageously comprise not more than about 2 wt.%, more typically not more than about 1 wt.%, and more typically not more than about 0.5 wt.% of the corresponding Δ^8-isomer, which is within the 2% USP limit for Δ^8-isomer levels for Δ^9-THC preparations.

[0063] The process of the present disclosure is applicable to both small scale and large, commercial scale production of synthetic Δ^9-THC or related compounds. For example, the process of the present disclosure is effective for the production of Δ^9-THC, or structurally similar or related compounds, using as little as about 1 g up to about 50 g, about 100 g, about 250 g, about 500 g, or more, of a Formula II compound as the starting material.

[0064] Having described the disclosure in detail, it will be apparent that modifications and variations are possible without departing from the scope of the disclosure defined in the appended claims.

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EXAMPLES

[0065] The following non-limiting examples are provided to further illustrate the present disclosure.

EXAMPLE 1

[0066] In this example, Δ^9-THC tosylate was synthesized.

[0067] To begin, 0.53 g olivetol and 0.50 g of p-mentha-2-en-1,8-diol were dissolved in 35 mL dichloromethane in a flask. 2.12 g magnesium sulfate was added to the flask. The resulting suspension was chilled to less than 5°C. A solution of 37 µL boron trifluoride etherate in 5 mL

dichloromethane was added dropwise to the suspension over a period of five minutes. The temperature of the reaction mixture was increased to 12°C, and maintained at that temperature for 6 hours to allow the reaction to occur.

[0068] 0.82 mL triethylamine and 1.12 g p-toluenesulfonyl chloride were added to the reaction mixture. The temperature of the reaction mixture was raised to room temperature, and the reaction was stirred overnight.

[0069] The resulting reaction mixture was filtered using vacuum filtration through Whatman 541 filter paper to remove the magnesium sulfate. Evaporation of the solvent produced an oily residue containing crude Δ^9-THC tosylate. The crude tosylate was purified using a single pass through of a reverse-phase preparative chromatography column under the following conditions: Column: 250 x 10 mm, packed with Develosil RP-Aqueous Phase; Eluant: 3/3/2/2 acetonitrile/methanol/THF/water isocratic; Flow Rate 4.7 mL/min.

[0070] The fractions of Δ^9-THC tosylate isolated using chromatography that contained less than 2% Δ^8-THC tosylate were identified using reverse-phase liquid chromatography with UV detection (255 nm), and were combined and recrystallized. Specifically, 0.48 grams of the isolated fractions of Δ^9-THC tosylate was dissolved in 7 mL of refluxing methanol. Upon cooling to room temperature, the Δ^9-THC tosylate began to precipitate. The crystals were collected by vacuum filtration and dried under high vacuum overnight. The purity of the resulting crystalline Δ^9-THC tosylate was determined using reverse-phase liquid chromatography with UV detection (255 nm). The crystalline Δ^9-THC tosylate was found to be 99.6% pure, and contained only 0.34% Δ^8-THC tosylate.

EXAMPLE 2

[0071] In this example, the Δ^9-THC tosylate prepared in Example 1 was hydrolyzed to obtain Δ^9-THC.

[0072] 0.28 g of the Δ^9-THC tosylate prepared in Example 1 was placed in a flask along with 1.64 mL t-butanol and 0.043 mL water. 0.02 g of potassium butoxide was then added, and the resulting slurry was stirred and heated at 65°C for 5 hours. 5 mL of water was then charged into the reactor, and the resulting solution was cooled to 25°C. 5 mL of hexane was then added, and the resulting biphasic solution was stirred for 10 minutes. The organic phase was then separated and washed twice with 5 mL of water and once with 5 mL of brine. The organic phase was then dried over magnesium sulfate and filtered through Whatman 541 filter paper. The solvent was evaporated to give 56 mg of pure Δ^9-

THC as a light yellow oil. The resulting Δ^9-THC was 95% pure Δ^9-THC, and contained only 0.44% Δ^8-THC.

EXAMPLE 3

[0073] In this example, Δ^9-tetrahydrocannabivarin (3-propyl-THC) is synthesized.

[0074] To begin, a 1L jacketed reaction vessel was charged with 14.31 g of 1R,4R-p-mentha-2-en-1,8-diol, 14.08 g of 5-propylresorcinol, and 990 mL of dichloromethane. The resulting mixture was stirred vigorously at room temperature until all solids were dissolved, approximately 10 minutes. The reaction vessel was then charged with 60.74 g of magnesium sulfate. The resulting suspension was stirred at room temperature for 10 minutes, then cooled to 3°C with a circulating chiller. A solution of 1.1 mL of boron trifluoride etherate in 10 mL of dichloromethane was then added drop-wise to the reaction mixture over a period of 5 minutes. Upon completion of the addition, the temperature was increased to 12°C, and the progress of the reaction was monitored by high performance liquid chromatography (HPLC). After 5 hours, 23.4 mL of triethylamine was added to the reaction mixture. This was followed immediately by the addition of 32.1 g of p-toluenesulfonyl chloride.

[0075] The resulting mixture was then allowed to warm to room temperature, and stirred overnight. The reaction mixture was then filtered through Whatman 541 filter paper, and extracted twice with 500 mL saturated sodium bicarbonate, and once with 500 mL brine. The resulting organic phase was evaporated to give a reddish-yellow oil.

[0076] The oil was purified using reversed phase preparative chromatography, as described in Example 1. Column fractions were combined and concentrated to give an oily residue. The 3-propyl-THC tosylate was obtained by dissolving the oil in a heated solution of 10:1 methanol:acetone, allowing the solution to cool to room temperature, and recovering the 3-propyl-THC tosylate crystals by vacuum filtration.

[0077] A 250 mL 3-necked round bottom flask, equipped with a stir bar, thermocouple, and nitrogen purge, was charged with 9.4 grams of the tetrahydrocannabivarin tosylate. The reaction flask was then charged with 55 mL t-butanol and 0.95 mL of degassed water. 6.90 g of potassium t-butoxide was then added, and the reaction mixture was heated at 65°C for 4.5 hours. After 4.5 hours, the heat was removed, and the reaction was allowed to cool to 50°C. The reaction mixture was then charged with 95 mL of degassed water, and the resulting mixture was allowed to cool to room temperature with stirring for 1 hour.

[0078] The resulting mixture was charged with 95 mL of degassed n-heptane, and stirred for 20 minutes. The mixture was transferred to a 500 mL separatory funnel, and the phases were allowed to separate under a nitrogen blanket. The aqueous (bottom) phase was then removed, and the extraction was repeated once more with 95 mL of degassed water. The organic phase was extracted with 95 mL of degassed brine solution. The organic phase was dried over magnesium sulfate, filtered as previously described, and concentrated. The resulting product was an amber-colored oil. The oil was dried under high vacuum overnight to give 6.24 grams of Δ^9-tetrahydrocannabivarin. The purity of the Δ^9-tetrahydrocannabivarin was determined using HPLC to be 97% pure.

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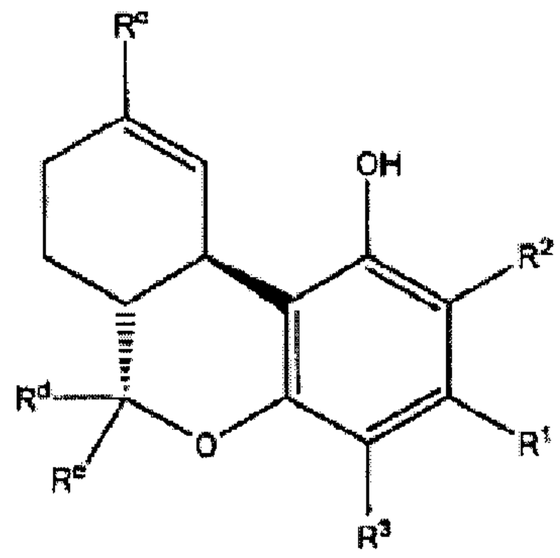
[0079] When introducing elements of the present disclosure or the embodiments(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[0080] In view of the above, it will be seen that the several objects of the disclosure are achieved and other advantageous results attained.

[0081] As various changes could be made in the above compositions, products, and methods without departing from the scope of the disclosure, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

CLAIMS:

1. A process for the synthesis of a cannabinoid having general Formula I:



(I)

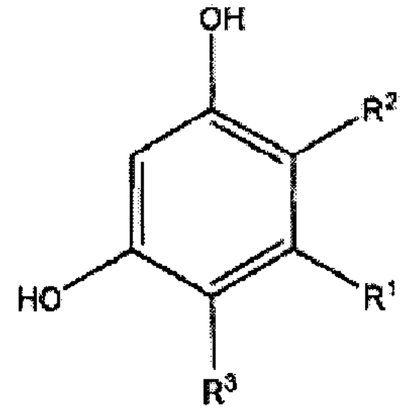
wherein:

R^1 to R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, OH, aryl, acyl, halide, nitrate, sulphonate, phosphate, and OR', wherein R' is alkyl, aryl, substituted alkyl, substituted aryl, silyl, acyl, or phosphonate; and

R^c, R^d, and R^e are independently selected from the group consisting of H, alkyl, or substituted alkyl;

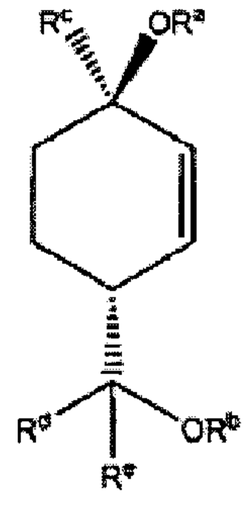
the process comprising:

reacting a substituted resorcinol having general Formula II:



(II)

wherein R^1, R^2, and R^3 are as defined above, with a compound having general Formula III:



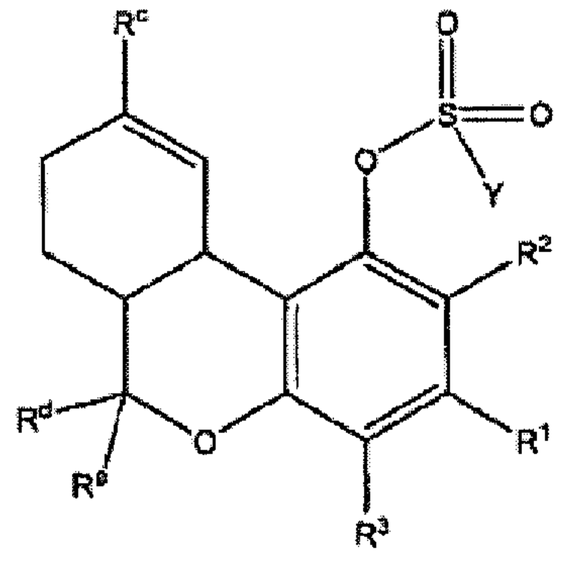
(III)

wherein R^a is H, alkyl, aryl, acyl, or silyl; R^b is H, alkyl aryl, or acyl; and R^c, R^d, and R^e are as defined above, in the presence of an acid catalyst and a non-alkaline dehydrating agent to form a first reaction mixture comprising a cannabinoid having general Formula I;

monitoring the ratio of delta9 isomer to the delta8 isomer in the first reaction mixture during the reaction of resorcinol (II) with compound (III);

quenching the reaction of resorcinol (II) with compound (III) by introduction of base when the ratio of the delta9 isomer to the delta8 isomer is about 49:1 or greater;

contacting the first reaction mixture containing the cannabinoid having general Formula I with an aryl sulfonyl halide and a base to produce a second reaction mixture comprising an aryl sulfonate having general Formula IV:



(IV)

wherein R^1, R^2, R^3, R^c, R^d, and R^e are as defined above, and Y is selected from the group consisting of a substituted aryl group, an unsubstituted aryl group, a substituted alkyl group, and an unsubstituted alkyl group;

isolating the aryl sulfonate from the second reaction mixture; and

hydrolyzing the aryl sulfonate to produce the cannabinoid having general Formula I.

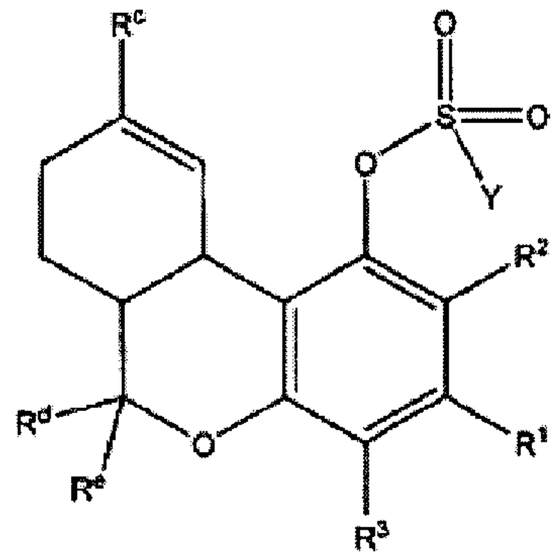
2. The process of claim 1, wherein the aryl sulfonate is isolated by subjecting the second reaction mixture to reverse phase chromatography, and collecting one or more fractions therefrom containing the aryl sulfonate.

3. The process of claim 1 or 2, wherein the isolated aryl sulfonate is purified by crystallization or recrystallization.

4. The process of any one of claims 1 to 3, wherein the step of quenching is conducted when the ratio of delta8 isomer is about 50:1, about 55:1, about 60:1, about 75:1, about 85:1, about 95:1 or about 99:1.

5. The process of of any one of claims 1 to 3, wherein the first reaction is quenched when the ratio of the delta9 isomer versus the delta8 isomer is about 49:1, and subsequently, the first reaction mixture is contacted with the aryl sulfonyl halide.

6. A process for the synthesis of an aryl sulfonate having general Formula IV:



(IV)

wherein:

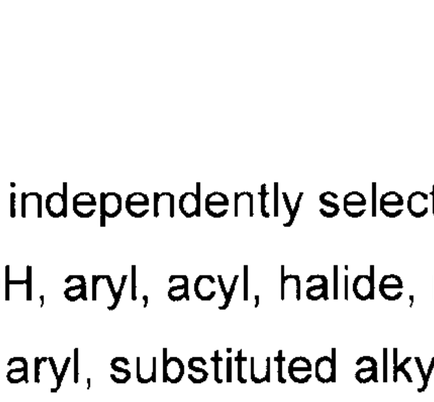
R^1 to R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, OH, aryl, acyl, halide, nitrate, sulphonate, phosphate, and OR', wherein R' is alkyl, aryl, substituted alkyl, substituted aryl, silyl, acyl, or phosphonate;

R^c, R^d, and R^e are independently selected from the group consisting of H, alkyl, or substituted alkyl; and

Y is selected from the group consisting of a substituted aryl group, an unsubstituted aryl group, a substituted alkyl group, and an unsubstituted alkyl group;

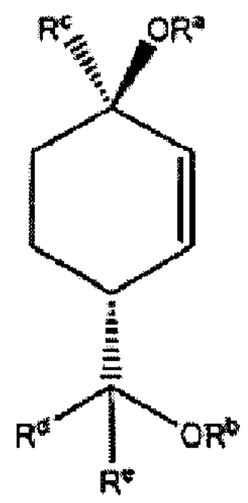
the process comprising:

reacting a substituted resorcinol having general Formula II:



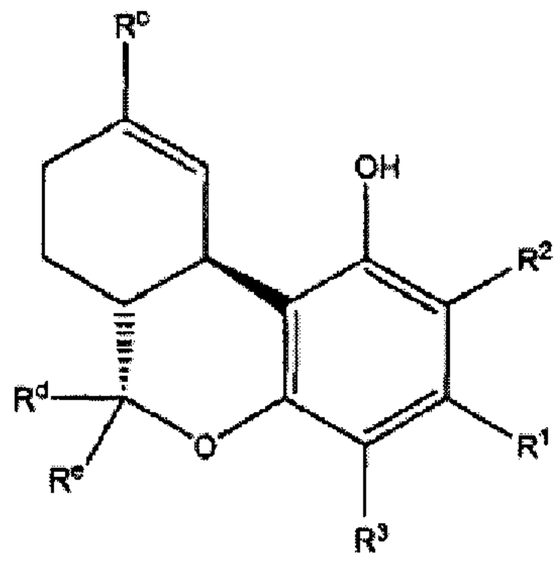
(II)

wherein R^1, R^2, and R^3 are as defined above, with a compound having general Formula III:



(III)

wherein R^a is H, alkyl, aryl, acyl or silyl; R^b is H, alkyl aryl, or acyl; and R^c, R^d, and R^e are as defined above, in the presence of an acid catalyst and a non-alkaline dehydrating agent to form a first reaction mixture comprising a cannabinoid having general Formula I:



(I)

wherein R^1, R^2, R^3, R^c, R^d, and R^e are as defined above; and

contacting the first reaction mixture containing the cannabinoid having general Formula I with an aryl sulfonyl halide and a base when the ratio of the delta9 isomer to the delta8 isomer is about 49:1 or greater; thereby producing a second reaction mixture comprising the aryl sulfonate having general Formula IV.

7. The process of any one of claims 1 to 6 wherein R^2 and R^3 are H.

8. The process of any one of claims 1 to 6 wherein R^1 is an alkyl having from 1 to 10 carbon atoms.

9. The process of claim 8 wherein R^1 is an alkyl having from 1 to 5 carbon atoms.

10. The process of any one of claims 1 to 6 wherein the substituted resorcinol is olivetol.

11. The process of any one of claims 1 to 6 wherein R^c, R^d, and R^e are $-CH_3$.

12. The process of any one of claims 1 to 6 wherein R^a and R^b are H.

13. The process of any one of claims 1 to 6 wherein the compound having general Formula III is p-mentha-2-en-1,8-diol.

14. The process of any one of claims 1 to 6 wherein the acid catalyst is selected from the group consisting of boron trifluoride, boron trifluoride etherate, aluminum chloride, stannic chloride, zinc chloride, antimony pentafluoride, iron chloride, indium (III) triflate, scandium (III) triflate, ytterbium (III) triflate, bismuth (III) triflate, and combinations thereof.

15. The process of any one of claims 1 to 6 wherein the non-alkaline dehydrating agent is selected from the group consisting of calcium sulfate, magnesium sulfate, sodium sulfate, calcium chloride, aluminum oxide, silica, and molecular sieves.

16. The process of any one of claims 1 to 6 wherein the aryl of the aryl sulfonyl halide is selected from the group consisting of benzene, alkyl substituted benzene,

halogen substituted benzene, nitrobenzene, alkyloxy substituted benzene, substituted napthyl compounds, and unsubstituted napthyl compounds.

17. The process of any one of claims 1 to 6 wherein the aryl sulfonyl halide is p-toluenesulfonyl chloride.

18. The process of any one of claims 1 to 6 wherein the base is a tertiary amine.

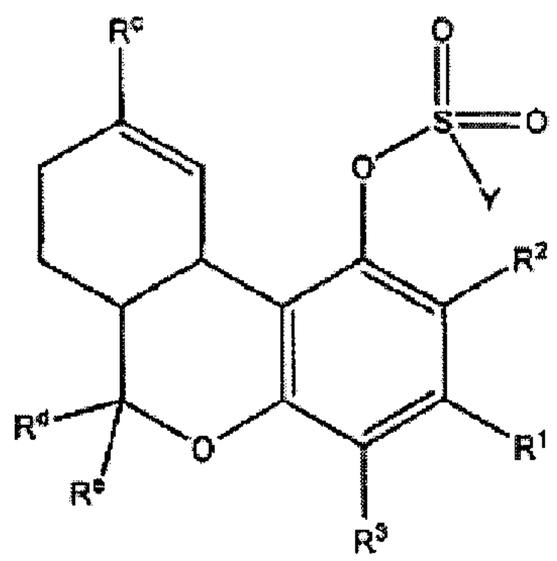
19. The process of claim 18 wherein the base is triethylamine.

20. The process of any one of claims 1 to 6 wherein the first reaction mixture further comprises an organic solvent.

21. The process of claim 20 wherein the organic solvent is selected from the group consisting of toluene, methylene chloride, chloroform, heptane, petroleum ether, diethyl benzene, tetrahydrofuran, dioxane, carbon tetrachloride, bromobenzene, and 2-methyl-THF.

22. The process of claim 20 further comprising removing the organic solvent from the second reaction mixture.

23. A process for the synthesis of an aryl sulfonate having general Formula IV:



(IV)

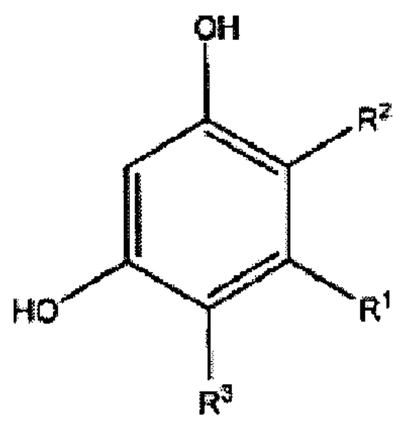
wherein R^1 to R^3 are independently selected from the group consisting of H, alkyl, substituted alkyl, OH, aryl, acyl, halide, nitrate, sulphonate, phosphate, and OR', wherein R' is alkyl, aryl, substituted alkyl, substituted aryl, silyl, acyl, or phosphonate;

R^c, R^d, and R^e are independently selected from the group consisting of H, alkyl, or substituted alkyl; and

Y is selected from the group consisting of a substituted aryl group, an unsubstituted aryl group, a substituted alkyl group, and an unsubstituted alkyl group;

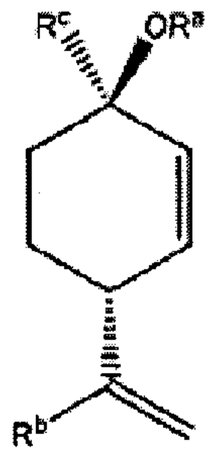
the process comprising:

reacting a substituted resorcinol having general Formula II:



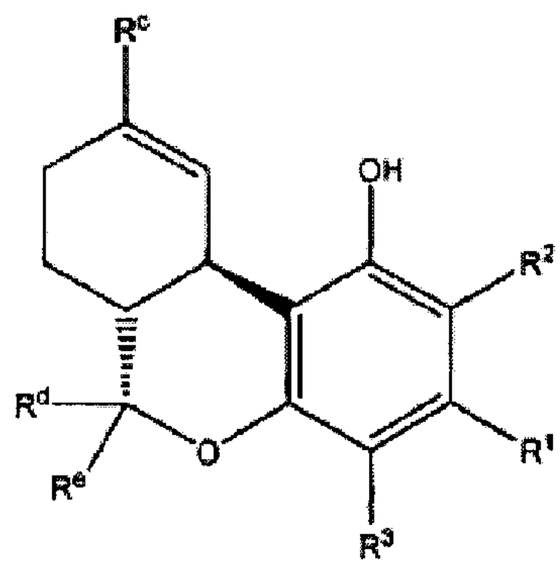
(II)

wherein R^1, R^2, and R^3 are as defined above; with a compound having general Formula VI:



(VI)

wherein R^a is H, alkyl, aryl, acyl, or silyl; R^b is H, alkyl, aryl, or acyl; and R^c is as defined above, in the presence of an acid catalyst and an excess of a non-alkaline dehydrating agent to form a first reaction mixture comprising a cannabinoid having general Formula I:



(I)

wherein R^1, R^2, R^3, and R^c are as defined above, and R^d and R^e are as defined above; and

reacting the cannabinoid having general Formula I present in the first reaction mixture with an aryl sulfonyl halide in the presence of a base when the ratio of the delta9 isomer to the delta8 isomer is about 49:1 or greater; to produce a second reaction mixture comprising the aryl sulfonate of Formula IV.

24. The process of claim 23 wherein the substituted resorcinol is olivetol.

25. The process of claim 23 wherein the compound of Formula VI is p-mentha-2,8-dien-1-ol.

26. The process of claim 23 wherein the first reaction mixture further comprises an organic solvent, and wherein the process further comprises:

removing the organic solvent from the second reaction mixture;

subjecting the second reaction mixture to reverse phase chromatography to obtain an isolated fraction comprising the aryl sulfonate;

allowing the aryl sulfonate to crystallize, and

hydrolyzing the aryl sulfonate to produce the cannabinoid having general Formula I.

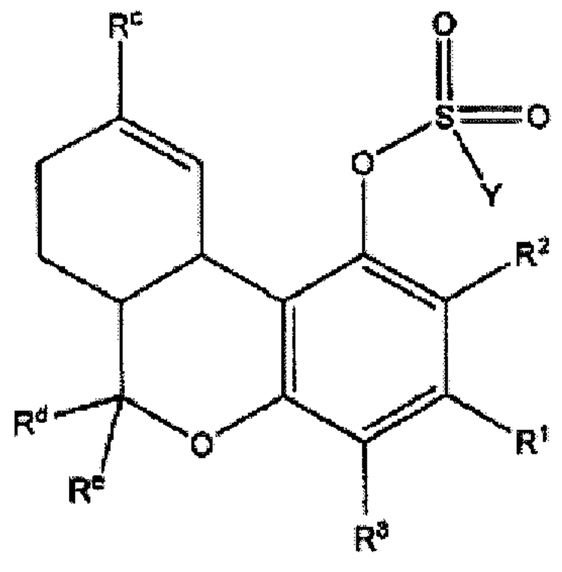
27. The process of claim 26 wherein the cannabinoid having general Formula I is (-)-delta9-tetrahydrocannabinol.

28. A process for the preparation of (-)-delta9-tetrahydrocannabinol aryl sulfonate, comprising:

reacting olivetol with a compound selected from the group consisting of p-mentha-2-en-1,8-diol and p-mentha-2,8-dien-1-ol in the presence of an acid catalyst and an excess of a non-alkaline dehydrating agent to form a first reaction mixture comprising (-)-delta9-tetrahydrocannabinol;

reacting the (-)-delta9-tetrahydrocannabinol in the first reaction mixture with an aryl sulfonyl halide;

quenching the first reaction mixture with a base when the ratio of the delta9 isomer to the delta8 isomer is about 49:1 or greater; thereby producing a second reaction mixture comprising an aryl sulfonate having general Formula IV:



(IV)

wherein R^1 is C_5H_{11}; R^2 and R^3 are H; R^c, R^d, and R^e are -CH_3; and Y is a substituted or unsubstituted aryl group.

29. The process of claim 28 wherein the acid catalyst is boron trifluoride etherate.

30. The process of claim 28 wherein the non-alkaline dehydrating agent is magnesium sulfate.

31. The process of claim 28 wherein the aryl sulfonyl halide is p-toluenesulfonyl chloride.

32. The process of claim 28 wherein the base is triethylamine.

33. The process of claim 28 wherein the first reaction mixture further comprises an organic solvent, and wherein the process further comprises:

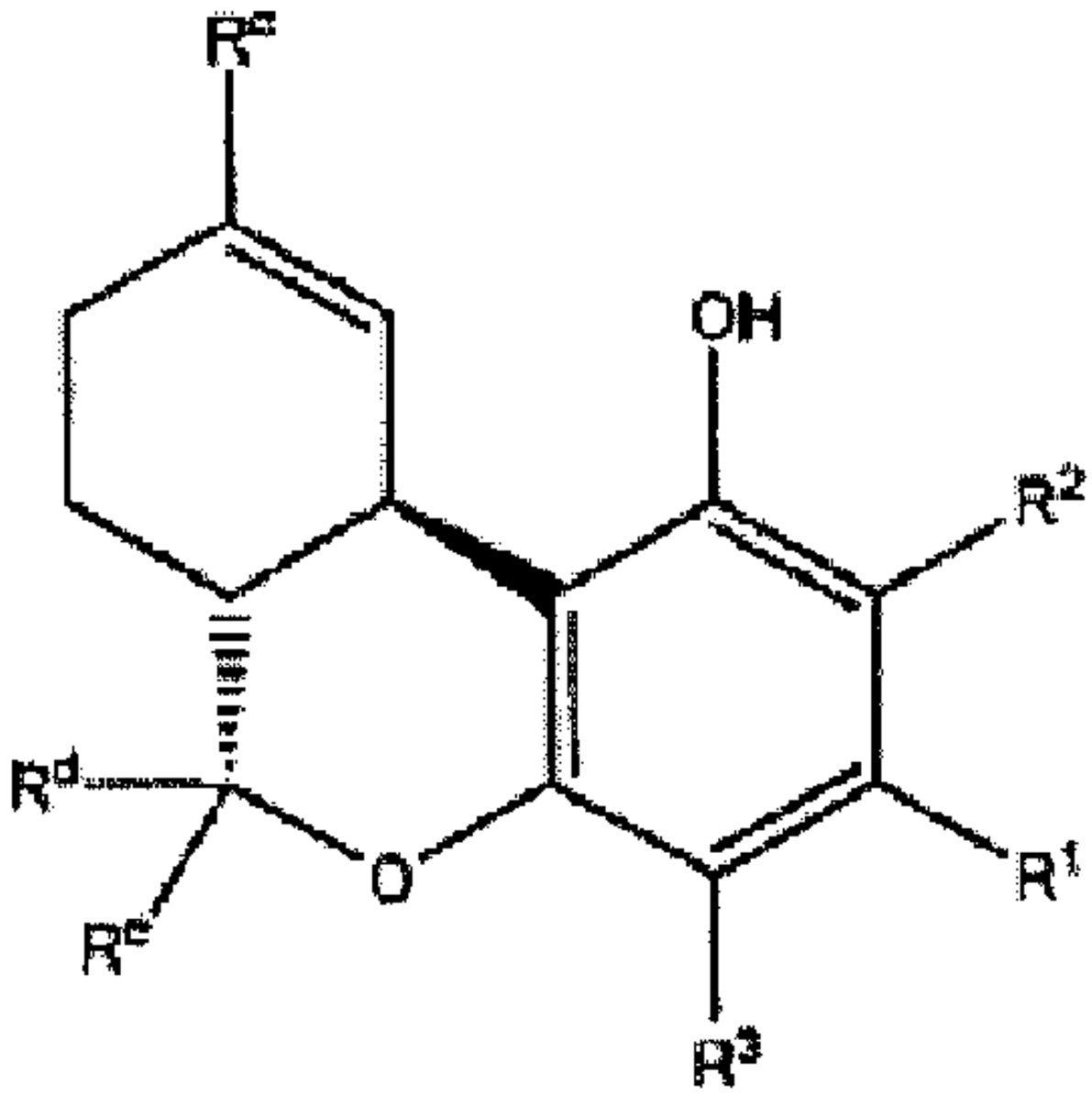
removing the organic solvent from the second reaction mixture;

subjecting the second reaction mixture to reverse phase chromatography to obtain an isolated fraction comprising the aryl sulfonate;

allowing the aryl sulfonate to crystallize, and

hydrolyzing the aryl sulfonate to produce the (-)-delta9-tetrahydrocannabinol.

34. The process according to claim 1, wherein the cannabinoid having general Formula I is delta9-tetrahydrocannabinol or delta9-tetrahydrocannabivarin.



(I)