WHO Expert Committee on Drug Dependence Pre-Review

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Isomers of THC

Section 1: Chemistry

World Health Organization

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Acknowledgments

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a preliminary review for the 40th Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge the contributions of the following individuals who authored this report:

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1. delta-6a(10a)-THC

1.1 Substance identification

7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

1.1.1 International Nonproprietary Name (INN)

N/A

1.1.2 Chemical Abstract Service (CAS) Registry Number

7663-50-5

1.1.3 Other Chemical Names[1]

- (±)-Δ^3-Tetrahydrocannabinol[2 (B)]
- (±)-$\Delta^{6a,10a}$-Tetrahydrocannabinol[2(A)]
- Cannabinol, Δ^3-tetrahydro- [2(B)]
- EA 1477
- Δ^3-Tetrahydrocannabinol[2(B)]
- $\Delta^{6a,10a}$-tetrahydrocannabinol[2(A)]

1.1.4 Trade names

N/A

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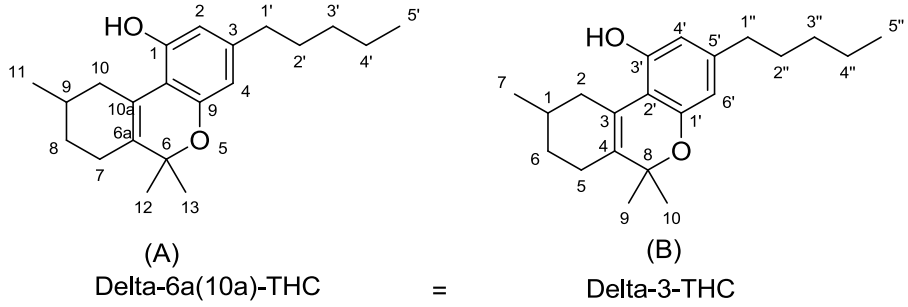
[1] Reported by Chemical Abstract Service (CAS).

[2] Alternate numbering systems: (A)"Dybenzopyran"; (B) "Monoterpenoid"



1.1.5 Street Names

N/A

1.1.6 Physical Appearance

The first description of the synthesis of (±)-$\Delta^{6a,10a}$-THC by Adams et al. in 1947 describes the compound as a viscous oil that solidifies on standing and may be purified by recrystallization from glacial acetic acid forming white crystals [1].

In 1984 Srebnik et al. synthetized each enantiomer of (±)-$\Delta^{6a,10a}$-THC described as an oil [2].

1.1.7 WHO Review History

The following isomers of Δ^{9}-THC and their stereochemical variants:

- 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or $\Delta^{6a,10a}$-THC)
- (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or $\Delta^{6a,7}$-THC)
- (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or Δ^{7}-THC)
- (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or Δ^{8}-THC)
- 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or Δ^{10}-THC)
- (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (or $\Delta^{9,11}$-THC)

were included in Schedule I of the 1971 Convention on Psychotropic Substances.

These constitutional isomers of delta-9-THC were never subject to a critical review and are still in schedule I of the 1971 Convention.

1.2 Chemistry

1.2.1 Chemical Name

IUPAC Name:

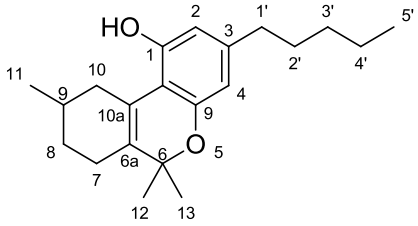
7,8,9,10-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-

1.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

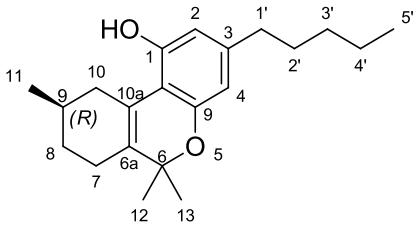
Molecular Weight:

314.46

1.2.3 Stereoisomers

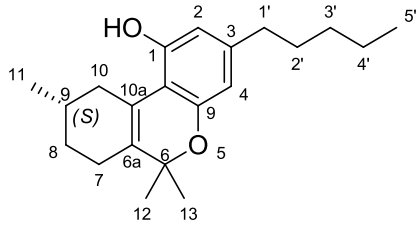
The compound has one stereogenic carbon atom and two stereoisomers can be present. Two stereoisomers are known:

1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol,7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-,(R)- (9CI) [CAS Registry Number: 95720-01-7]



(*R*)-$\Delta^{6a,10a}$-THC

2) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol,7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-,(S)- (9CI) [CAS Registry Number: 95720-02-8]

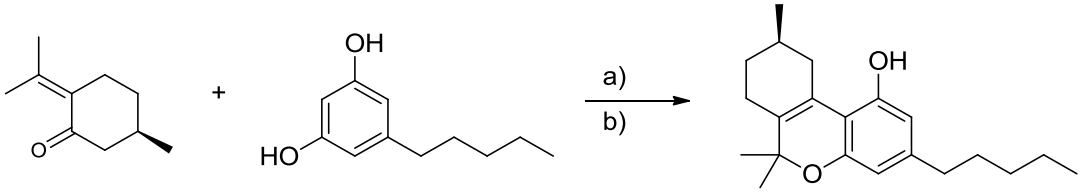


(*S*)-$\Delta^{6a,10a}$-THC

1.2.4 Methods and Ease of Illicit Manufacturing

$\Delta^{6a,10a}$-THC is not a naturally occurring cannabinoid and is generally obtained by chemical synthesis. The condensation between olivetol and pulegone under acid catalysis for the preparation of $\Delta^{6a,10a}$-THC in its racemic form was investigated in the early 1940s [3-6].

The synthesis and isolation of (R)-(+)-$\Delta^{6a,10a}$-THC and (S)-(−)-$\Delta^{6a,10a}$-THC was achieved in 1984 [2]. The method used the single enantiomers of Δ^{10}-THC[1], (9R,6aR)-Δ^{10}-THC and (9S,6aR)-Δ^{10}-THC, as starting material that isomerized in toluene-p-sulphonic acid in benzene to lead to (R)-(+)-$\Delta^{6a,10a}$-THC and (S)-(−)-$\Delta^{6a,10a}$-THC, respectively. More recently, Rosati et al. developed a one-pot microwave assisted synthesis of (R)-(+)-$\Delta^{6a,10a}$-THC and (S)-(−)-$\Delta^{6a,10a}$-THC starting from single enantiomers of pulegone condensed with olivetol (scheme1) under Ytterbium triflate-ascorbic acid catalysis [7].



(*R*)-(+)-Pulegone Olivetol (*R*)-(+)-Δ^{6a10a}-THC

[1] (±)-Δ^{10}-THC is in Schedule I of the 1971 Convention.

Scheme 1

Reagents and conditions: a) $POCl_3$ (33 mol %), benzene, reflux, 4h b) Ytterbium triflate-ascorbic acid [YTACA 1:10], $ClCH_2CH_2Cl$, 120 min, 150°C

Hollister et al. tested the two enantiomers (R)-(+)-$\Delta^{6a,10a}$-THC and (S)-(−)-$\Delta^{6a,10a}$-THC in man for psychoactivity. (S)-(−)- $\Delta^{6a,10a}$-THC in man had psychic actions similar to those of Δ^{9}-THC but quantitatively less potent (1:3 to 1:6), while the (R)-(+)- $\Delta^{6a,10a}$-THC was inactive [8].

1.2.5 *Chemical Properties*

Melting point

About 72-73 °C [1]

Boiling point

175-180 °C at 0.02 Torr [1]

1.2.6 Solubility

N/A

1.2.7 *Identification and Analysis*

Identification of pure enantiomers (R)-(+)-$\Delta^{6a,10a}$-THC and (S)-(−)-$\Delta^{6a,10a}$-THC was described by Srebnik et al. reporting optical rotations, UV, IR, NMR and MS spectra [2].

There are few analytical methods for the analysis of $\Delta^{6a,10a}$-THC reported in the literature:

1. A gas chromatographic method coupled to mass spectrometry detection (GC-MS) [9]
2. A gas chromatographic (GC) method [10]
3. A micro-analytical determination of $\Delta^{6a,10a}$-THC was effected by thin layer chromatography (TLC) (color former: Fast Blue salt B, H_2PtCl_6-KI or 1% $KMnO_4$ solution), GC (3 mm × 2 m column, silicone SE-30, OV-1, polyethylene glycol 20M, 130-270 °C), high performance liquid chromatography (styrene-divinylbenzene polymer, detection at 274 or 258 nm)

(HPLC-UV) and microcrystal test (crystallization from 3% AcOH solution and detection on polarization microscope) [11].

4. Nine different cannabinoids (including $\Delta^{6a,10a}$-THC) were converted to their 1-dimethylaminonaphthalene-5-sulfonates. Mixtures of the fluorescent-labeled cannabinoids were separated by TLC and individual spots were detectable at the 0.5 nanogram level. This sensitivity appeared adequate to develop an assay for biotransformation products of cannabinoids in human urine after the smoking of a single cigarette [12].

1.3 Ease of Convertibility Into Controlled Substances

N/A

2. delta-6a(7)-THC

2.1 Substance identification

(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

2.1.1 International Nonproprietary Name (INN)

N/A

2.1.2 Chemical Abstract Service (CAS) Registry Number

59042-44-3

2.1.3 Other Chemical Names

N/A

2.1.4 Trade names

N/A

2.1.5 Street Names

N/A

2.1.6 Physical Appearance

Viscous oil [13].

2.1.7 WHO Review History

See data reported for $\Delta^{6a,10a}$-THC.

2.2 Chemistry

2.2.1 Chemical Name

IUPAC Name:

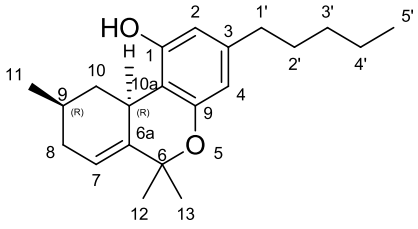
(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (9R-trans)- (9CI)

2.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

Molecular Weight:

314.46

2.2.3 Stereoisomers

The compound has two stereogenic carbon atoms and four stereoisomers can be present.

Only the (9R,10aR)- 8,9,10,10a-tetrahydro-6,6,9-trimethyl-1-pentyl-6H-Dibenzo[b,d]pyran-3-ol was described in the literature [13].

2.2.4 Methods and Ease of Illicit Manufacturing

Arnone et al reported the synthesis of (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol by condensation of olivetol with p-menth-4-en-3,8-diol in toluene-p-sulphonic acid at room temperature for two days [13].

2.2.5 Chemical Properties

Melting point

N/A

Boiling point

N/A

Solubility

N/A

2.2.6 Identification and Analysis

(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol was characterized for its UV, NMR, optical rotatory power and MS properties [13]. The analyses were carried out on the pure compound: neither sample pre-treatment nor chromatographic method were set up or developed [13].

2.3 Ease of Convertibility Into Controlled Substances

N/A

3. delta-7-THC

3.1 Substance identification

(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

3.1.1 International Nonproprietary Name (INN)

N/A

3.1.2 Chemical Abstract Service (CAS) Registry Number

42793-13-5

3.1.3 Other Chemical Names

N/A

3.1.4 Trade names

N/A

3.1.5 Street Names

N/A

3.1.6 Physical Appearance

Pale yellow oil [14, 15].

3.1.7 WHO Review History

See data reported for $\Delta^{6a,10a}$-THC.

3.2 Chemistry

3.2.1 Chemical Name

IUPAC Name:

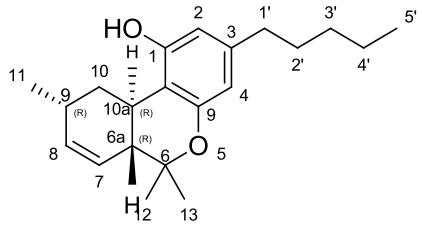
(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,[6aR-(6aα, 9β,10aβ)]- (9CI)

3.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

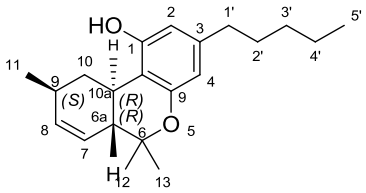
Molecular Weight:

314.46

3.2.3 Stereoisomers

The compound has three stereogenic carbon atoms and eight stereoisomers can be present. The (6aR,9S,10aR)- Δ^7-THC epimer is known:

1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, [6aR-(6aα,9α,10aβ)]- (9CI) [CAS Registry Number: 162678-94-6]



(6aR,9S,10aR)-Δ^7-THC

A stereoselective synthesis was described to obtain the two epimers. Only the (6aR,9S,10aR)- Δ^7-THC epimer was only slightly less active than delta-9-THC in vitro and in vivo [15].

3.3 Methods and Ease of Illicit Manufacturing

N/A

3.4 Chemical Properties

3.4.1 Melting point

N/A

3.4.2 Boiling point

N/A

3.4.3 Solubility

N/A

3.5 Identification and Analysis

N/A

3.6 Ease of Convertibility Into Controlled Substances

N/A

4. delta-8-THC

4.1 Substance identification

(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

4.1.1 International Nonproprietary Name (INN)

N/A

4.1.2 Chemical Abstract Service (CAS) Registry Number

5957-75-5

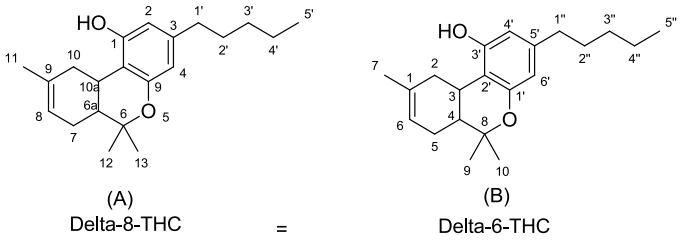
4.1.3 Other Chemical Names[1]

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-trans)-[2(A)]
- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, trans-(–)- (8CI) [2(A)]
- (6aR,10aR)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol[2(A)]
- (–)-trans-Δ^8-Tetrahydrocannabinol[2(A)]
- (–)-Δ^8-6a,10a-trans-Tetrahydrocannabinol[2(A)]
- (–)-Δ^8-THC[2(A)]
- (–)-Δ^8-Tetrahydrocannabinol[2(A)]
- (–)-Δ^8-trans-Tetrahydrocannabinol[2(A)]
- Δ^8-trans-Tetrahydrocannabinol[2(A)]
- Δ^8-THC[2(A)]
- Δ^8-Tetrahydrocannabinol[2(A)]
- Δ^8-l-Tetrahydrocannabinol[2(A)]
- D8-THC[2(A)]
- Delta-8-Tetrahydrocannabinol[2(A)]

[1] Reported by Chemical Abstract Service (CAS).

- l-Δ^{8}-Tetrahydrocannabinol[2(A)]
- trans-Δ^{8}-Tetrahydrocannabinol[2(A)]
- Cannabinol, Δ^{1}(6)-tetrahydro-[2(B)]
- Δ^{1}(6)-Tetrahydrocannabinol[2(B)]
- Δ^{1}(6)-trans-Tetrahydrocannabinol[2(B)]
- Δ^{6}-Tetrahydrocannabinol[2(B)]
- (–)-Δ^{6}-Tetrahydrocannabinol[2(B)]
- NSC 134453

[2] Alternate numbering systems: (A)"Dybenzopyran"; (B) "Monoterpenoid"



4.1.4 Trade names

N/A

4.1.5 Street Names

N/A

4.1.6 Physical Appearance

Gaoni et al. described the compound as an oil with an optical rotation value $[\alpha]^{25}_{D}$ −245 ($CHCl_3$) [16].

Ballerini et al. described the compound as a colorless oil with an $[\alpha]^{25}_{D}$ −245 (c. 0.78, $CHCl_3$) [17].

Rosenkrantz et al. described the pure compound (98-99 % purity by gas chromatography (GC)) as "highly viscous oils, virtually of a glue nature at room temperature" with an "optical rotation values from –254 to –268" [18].

4.1.7 WHO Review History

See data reported for $\Delta^{6a,10a}$-THC.

4.2 Chemistry

4.2.1 Chemical Name

4.2.1.1 IUPAC Name:

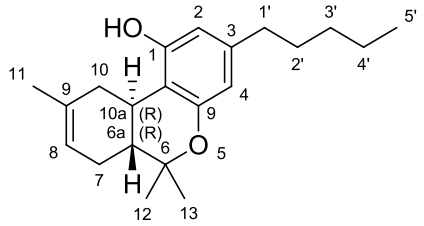
(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

4.2.1.2 CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR, 10aR)-

4.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

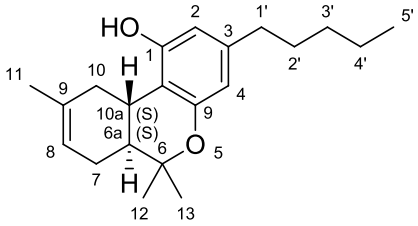
Molecular Weight:

314.46

4.2.3 Stereoisomers

The compound has two stereogenic carbon atoms and four stereoisomers can be present. The following stereoisomers are reported in the literature:

1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol,6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,(6aS,10aS)- [CAS Registry Number: 33029-18-4]



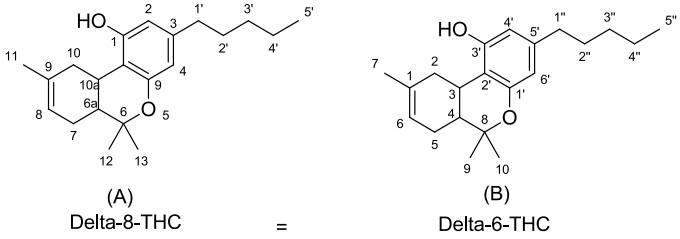
4.2.3.1 Other Names[1]

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,(6aS-trans) [2(A)]
- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,(6aS-trans)- [2(A)]

[1] Reported by Chemical Abstract Service (CAS).

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-,trans-(+)- (8CI) [2(A)]
- (6aS,10aS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol[2(A)]
- (+)-Δ^6-Tetrahydrocannabinol [2(B)]
- (+)-Δ^8-THC[2(A)]
- (+)-Δ^8-Tetrahydrocannabinol[2(A)]
- d-Δ^8-Tetrahydrocannabinol[2(A)]

[2] Alternate numbering systems: (A)"Dybenzopyran"; (B) "Monoterpenoid"

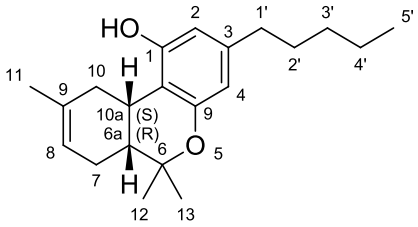


4.2.4 Methods and Ease of Illicit Manufacturing

In the literature are described few syntheses of (+)-trans-Δ^8-THC [17, 19-21].

The most feasible preparation is that reported in 1967 by Mechoulam et a1. [19], where (+)-trans-Δ^8-THC was obtained from the condensation of a pinane derivative, verbenol, with olivetol in the presence of acid catalysts. Hence, in the presence of toluene-p-sulphonic acid in methylene chloride, (+)-trans-verbenol condensed with olivetol to give 4-trans-(2-olivetyl)pinene that, after chromatographic purification, gave (+)-trans-Δ^8-THC (80% yield) upon treatment with boron trifluoride etherate in methylene chloride at room temperature.

2) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR,10aS)- [CAS Registry Number: 65634-24-4]

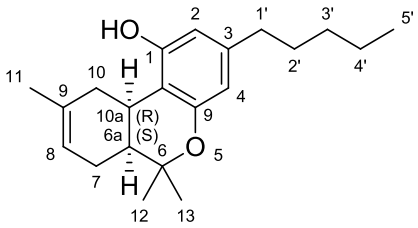


4.2.5 Other Names[1]

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-cis)-
- (6aR,10aS)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

3) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS,10aR)- [CAS Registry Number: 185752-04-9]

[1] Reported by Chemical Abstract Service (CAS).



4.2.6 Other Names[1]

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-cis)-
- (6aS,10aR)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

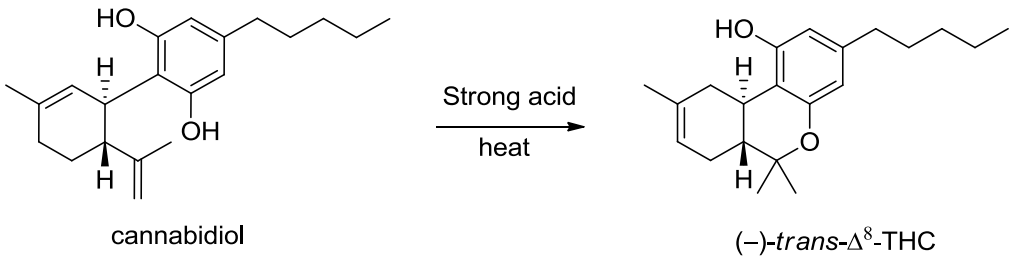
4.2.7 Methods and Ease of Illicit Manufacturing

(–)-trans-Δ^8-THC isomer is a minor active compound in cannabis occurring only in trace amounts, if at all (reported range of the ratio of (–)-trans-Δ^9-THC to (–)-trans- Δ^8-THC varied from 99.9:0.1 to 98.6:1.2) [22], although (–)-trans-Δ^8-THC isomer is notably more stable than its isomer (–)-trans- Δ^9-THC and persists in old material since it has even been found in a burial tomb dating from the fourth century B.C. [23, 24]. Concerns have been raised about the real natural origin of (–)-trans-Δ^8-THC suggesting that it should be artifacts resulting from (–)-trans-Δ^9-THC by acid- or oxidatively promoted shift of the endocyclic double bond [24].

Since (–)-trans-Δ^8-THC occurs in cannabis only in traces, it is generally obtained by chemical synthesis. Several synthetic methods to obtain (–)-trans-Δ^8-THC have been reported until now and they are well reviewed by Schafroth and Carreira [25].

The most feasible methods involve the electrophilic cyclization under acidic conditions of cannabidiol (CBD) and the condensation of olivetol with an optically pure monoterpene. The electrophilic cyclization of CBD affords the Δ^8-THC isomer upon treatment with a strong acid, while the Δ^9-THC isomer is obtained with mild acids [26-32].

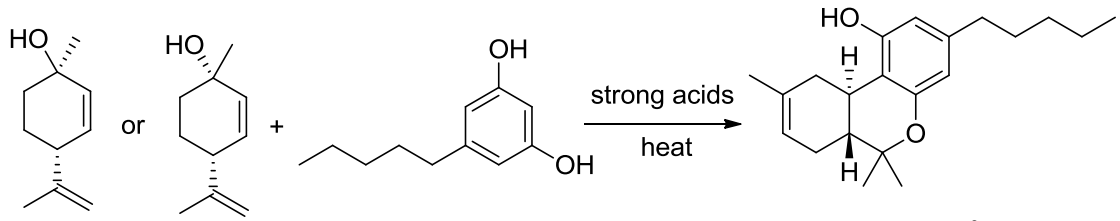
[1] Reported by Chemical Abstract Service (CAS).



cannabidiol (–)-*trans*-Δ^8-THC

The most common strategy for the synthesis of (–)-trans-Δ^8-THC is based on the condensation of olivetol with an optically pure monoterpene [33-36].

Condensation of olivetol with readily available (+)-cis/trans-p-mentha-2,8-dien-1-ol in strong acids (e.g. toluene-p-sulphonic acid or hydrochloride acid) led to (–)-trans-Δ^8-THC in 53% yield [37-39].

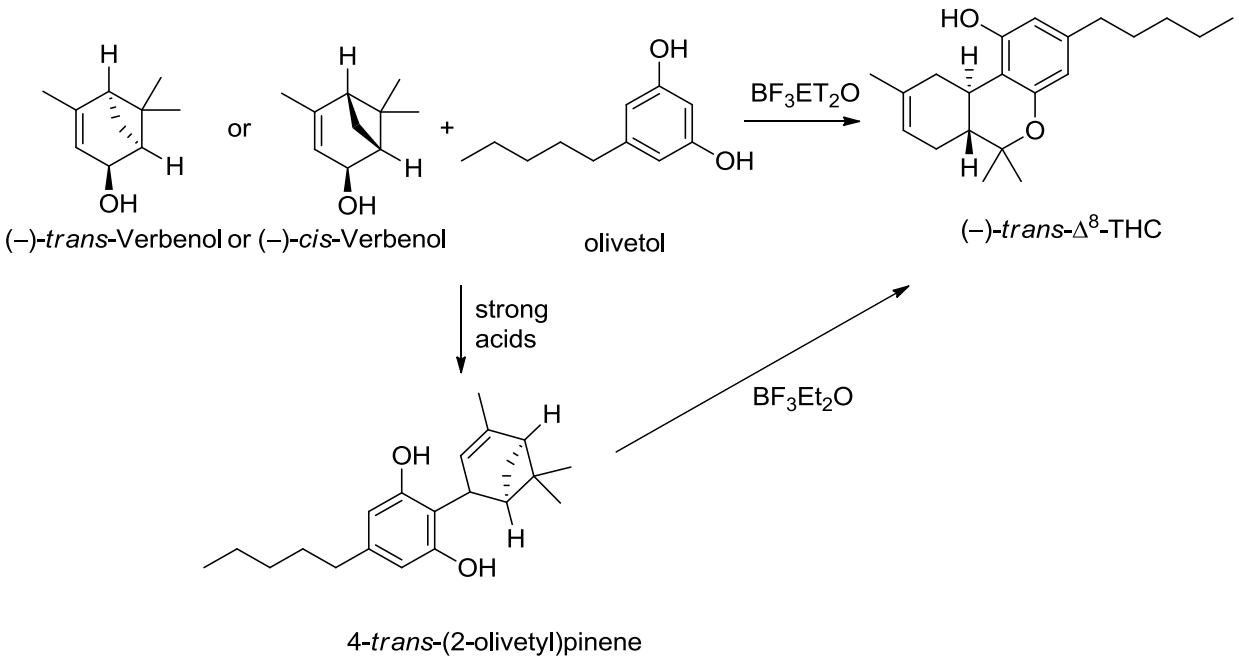


(+)-*cis*-*p*-mentha-2,8-dien-1-ol
or
(+)-*trans*-*p*-mentha-2,8-dien-1-ol

olivetol

(–)-*trans*-Δ^8-THC

In 1967 Mechoulam et al. [19] described a synthesis of (–)-trans-Δ^8-THC from a pinane derivative, verbenol, and olivetol in the presence of acid catalysts. Thus, in the presence of toluene-p-sulphonic acid in methylene chloride, (–)-cis- or (–)-trans-verbenol condensed with olivetol to give 4-trans-(2-olivetyl)pinene that after chromatographic purification, gave (–)-trans-Δ^8-THC (80% yield) upon treatment with boron trifluoride etherate in methylene chloride at room temperature.



4.2.8 *Chemical Properties*

4.2.8.1 Melting point

N/A

4.2.8.2 Boiling point

175-178 °C at atmospheric pressure (760 mmHg) [40, 41].

4.2.8.3 Solubility

n-Octanol/water partition coefficients (Po/w)

Brian et al. calculated n-octanol/water partition coefficients (Po/w) of (–)-trans-Δ^9-THC and (–)-trans-Δ^8-THC by two procedures: reverse-phase high performance liquid chromatography (HPLC) and computer calculation. As expected, the position of the double bond in either position 8 or 9 had only a poor effect on the Po/w. Based on the molecular structure, the log Po/w obtained for (–)-trans-Δ^8-THC by computer calculation was 7.18, which is in close agreement with the log Po/w of 7.41 as determined by HPLC. This very high value of log Po/w indicated an extreme lipophilicity [42].

Solvent solubility

Rosenkrantz et al. conducted solubility studies of (–)-trans-Δ^9-THC, (–)-trans-Δ^8-THC and pure cannabis extract in several solvents like ethanol, acetone, dimethyl sulfoxide (DMSO), chloroform, benzyl alcohol and sesame oil to obtain suitable oral and parenteral formulations of cannabinoids. Similar solubility values were obtained for (–)-trans-Δ^9-THC, (–)-trans-Δ^8-THC and crude cannabis extract in polar solvents. The solubility of (–)-trans-Δ^8-THC was in ethanol and acetone greater than 1 g/mL, 0.91 g/mL in benzyl alcohol, 0.30 g/mL in sesame oil, 0.62 g/mL in DMSO, 0.89 g/mL in propylene glycol, 0.38 g/mL in glycerol and 0.22 g/mL in polyoxyethylene monooleate (Tween 80) [18].

4.2.9 Identification and Analysis

Synthetic (–)-trans-Δ^8-THC was characterized and ^{1}H NMR properties [43-46], ^{13}C NMR properties [43, 44, 47], hetero NMR properties [46], IR properties [43], mass spectrometry properties [43, 48] and UV and visible properties are reported [48, 49].

Several analytical methods are reported regarding (–)-trans-Δ^8-THC qualitative and quantitative determination in different matrices such as cannabis inflorescence, cannabis extracts and biological fluid. Chromatographic methods are the most employed coupled to several detection modes such as ultraviolet and mass spectrometry [50]. They can be divided into:

4.2.9.1 Thin-layer chromatography (TLC)

It is quite difficult separate (–)-trans-Δ^8-THC from (–)-trans-Δ^9-THC employing a normal- and polar- stationary phase [48]. A two dimensional thin-layer chromatographic (2D TLC) method has been developed with the advantage to obtain a better resolution between the two isomers [51].

4.2.9.2 Gas chromatographic method with mass spectrometry or flame ionization detection (GC-MS or GC-FID)

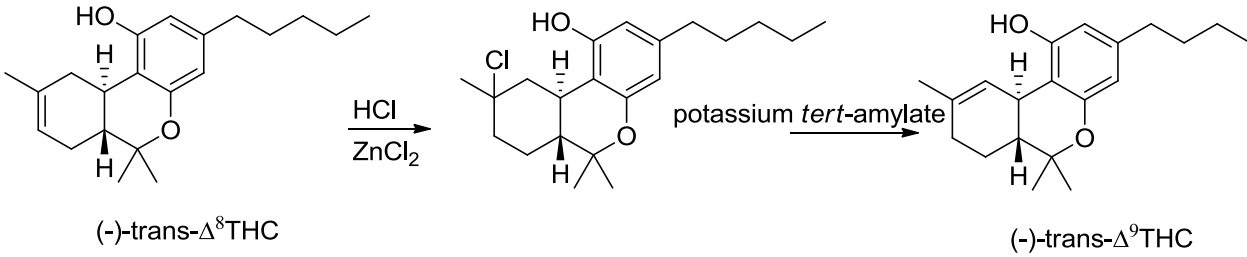
These methods are wide employed in several laboratories and permits to analyse (–)-trans-Δ^8-THC with or without previous derivatization needed for plant matrices [48, 52].

4.2.9.3 Liquid chromatography (LC)

LC methods are generally coupled to ultraviolet and/or mass spectrometry detection. They offer the advantage of a very high sensitivity without derivatization step [53-57].

4.3 Ease of Convertibility Into Controlled Substances

It is possible to convert (–)-trans-Δ^8-THC into (–)-trans-Δ^9-THC. Gaseous hydrochloric acid can be added in a quantitative yield to the double bond of (–)-trans-Δ^8-THC at low temperature with zinc chloride as catalyst. The unstable tertiary chloride obtained can be subsequently dehydrochlorinated by the use of potassium tert-amylate, which led to a quantitative formation of (–)-trans-Δ^9-THC [19, 38].



(-)-trans-Δ^8THC (-)-trans-Δ^9THC

5. delta-10-THC

5.1 Substance identification

6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

5.1.1 International Nonproprietary Name (INN)

N/A

5.1.2 Chemical Abstract Service (CAS) Registry Number

7663-51-6

5.1.3 Other Chemical Names[1]

6a,7,8,9-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

Δ^{10}-Tetrahydrocannabinol

5.1.4 Trade names

N/A

5.1.5 Street Names

N/A

5.1.6 Physical Appearance

N/A

5.1.7 WHO Review History

See data reported for $\Delta^{6a(10a)}$-THC.

[1] Reported by Chemical Abstract Service (CAS).

5.2 Chemistry

5.2.1 Chemical Name

IUPAC Name:

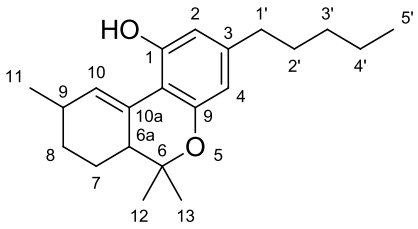
6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-

5.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

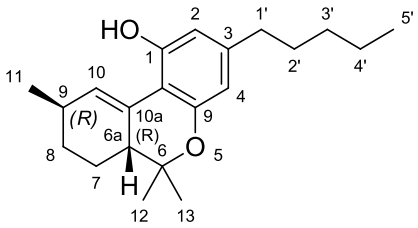
Molecular Weight:

314.46

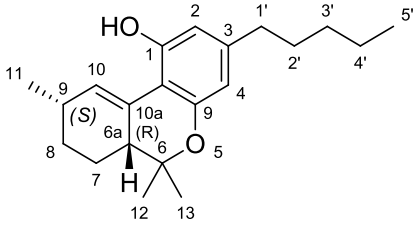
5.2.3 Stereoisomers

The compound has two stereogenic carbon atoms and four stereoisomers can be present. Two stereoisomers are reported in the literature:

1) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR-cis)- (9CI) [CAS Registry Number: 95543-62-7]



2) CA Index Name: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9-tetrahydro-6,6,9- trimethyl-3-pentyl-, (6aR-trans)- (9CI) [CAS Registry Number: 95588-87-7]



5.2.4 *Methods and Ease of Illicit Manufacturing*

In the literature is reported a synthesis of the two stereoisomers obtained by base catalyzed isomerization of (–)-trans-Δ^9-THC by Srebnik in 1984 [2]. Treatment of (–)-trans-Δ^9-THC with base gave a mixture of (6aR-trans)-Δ^{10}-THC (m.p. 153-154 °C; α –133°) and (6aR-cis)- Δ^{10}-THC (m.p. 54-55 °C; α –70°), that are further separated by chromatography [2].

5.2.5 *Chemical Properties*

5.2.5.1 Melting point

N/A

5.2.5.2 Boiling point

N/A

5.2.5.3 Solubility

N/A

5.2.6 *Identification and Analysis*

N/A

5.3 Ease of Convertibility Into Controlled Substances

N/A

6. delta-9(11)-THC

6.1 Substance identification

(6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene3-pentyl-6Hdibenzo[b,d]pyran-1-ol

6.1.1 International Nonproprietary Name (INN)

N/A

6.1.2 Chemical Abstract Service (CAS) Registry Number

27179-28-8

6.1.3 Other Chemical Names[1]

- 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-, (6aR-trans)- (8CI)
- (6aR,10aR)-6a,7,8,9,10,10a-Hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
- (–)-$\Delta^{9,11}$-THC
- Δ^{11}-THC
- Δ^{11}-Tetrahydrocannabinol

6.1.4 Trade names

N/A

6.1.5 Street Names

N/A

6.1.6 Physical Appearance

N/A

[1] Reported by Chemical Abstract Service (CAS).

6.1.7 WHO Review History

See data reported for $\Delta^{6a,10a}$-THC.

6.2 Chemistry

6.2.1 Chemical Name

IUPAC Name:

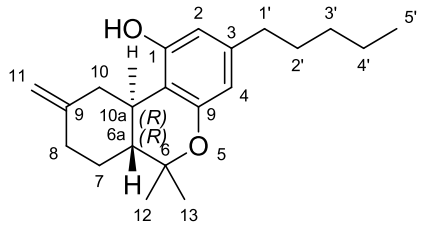
(6aR,10aR)-6a,7,8,9,10,10a-Hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

CA Index Name:

6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-, (6aR,10aR)-

6.2.2 Chemical Structure

Free base:



Molecular Formula:

$C_{21}H_{30}O_2$

Molecular Weight:

314.46

6.2.3 Stereoisomers

The compound has two stereogenic carbon atoms and four stereoisomers can be present. No stereoisomers are reported in the literature.

6.2.4 Methods and Ease of Illicit Manufacturing

Few methods of preparation are reported in the literature [59]. A method for the preparation of this compound involves ultraviolet irradiation of the corresponding (–)-trans-Δ^8-THC (yield 30%) [60]. Another commonly used method involves the addition of hydrogen chloride gas to (–)-trans-Δ^8-THC followed by treatment with potassium tert-amylate under anhydrous conditions [59, 61, 62].

6.2.5 Chemical Properties

Melting point

N/A

Boiling point

N/A

Solubility

N/A

6.2.6 Identification and Analysis

N/A

6.3 Ease of Convertibility Into Controlled Substances

N/A

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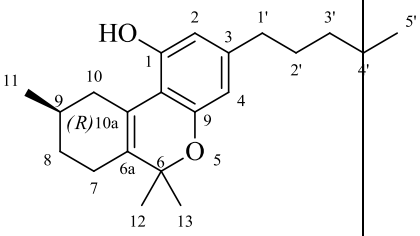
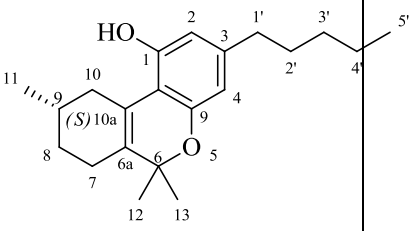
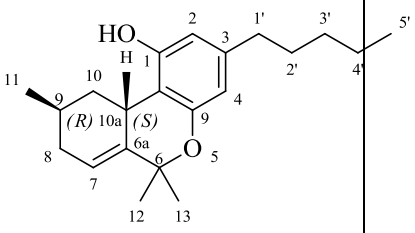
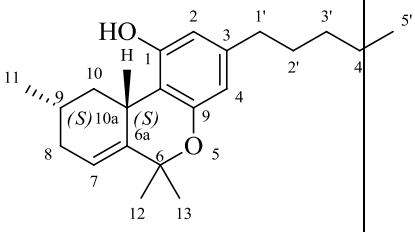
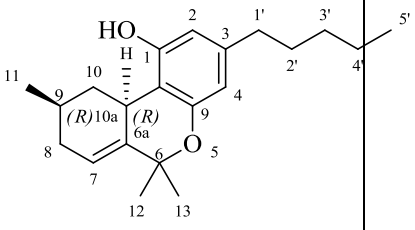
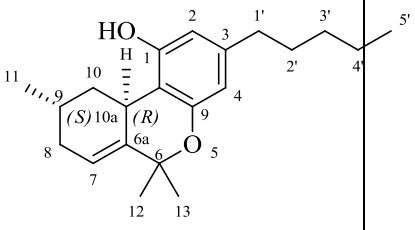
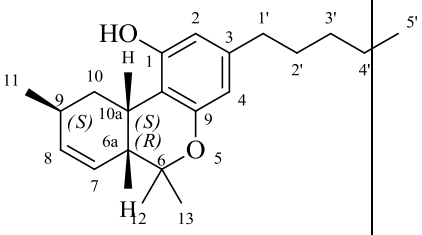
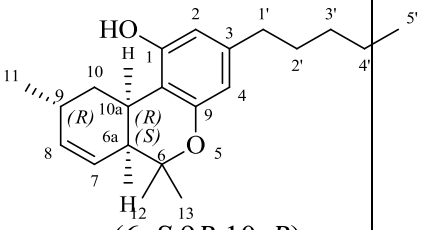
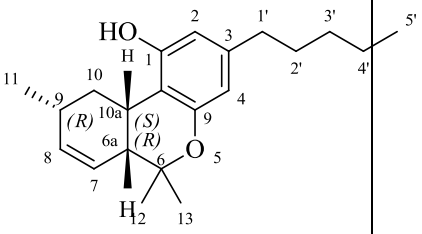
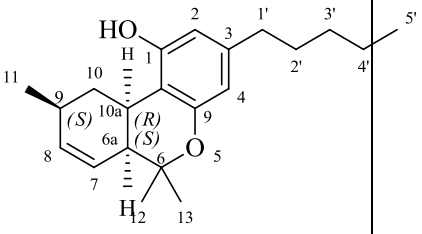
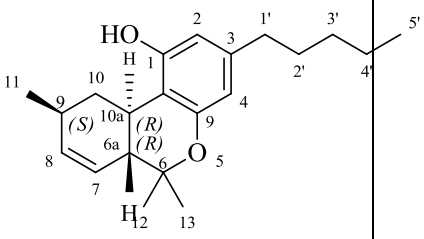
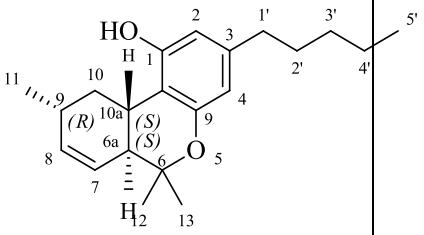
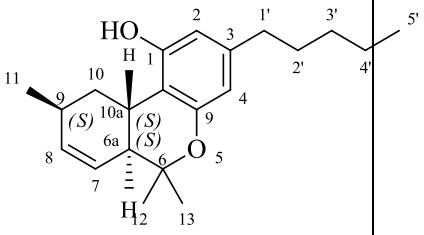
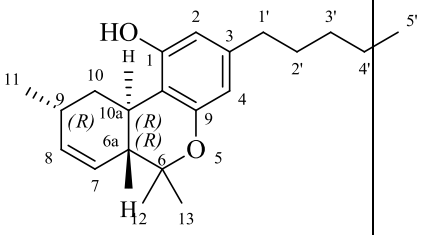
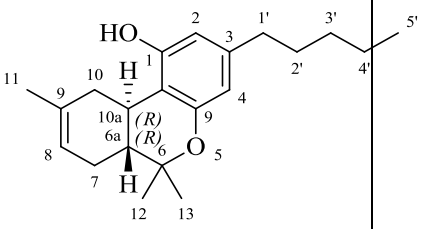
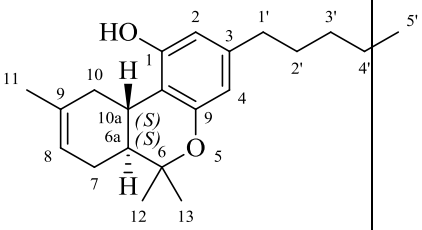
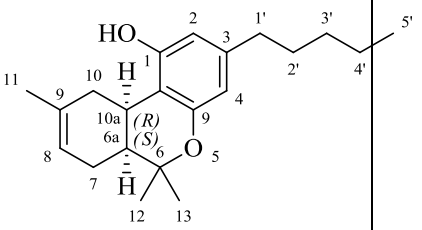
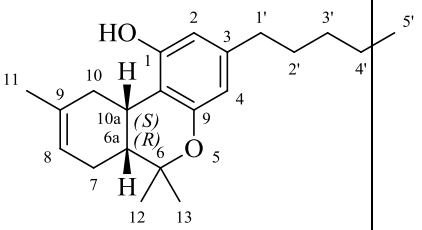
Annex 1: Isomers of THC

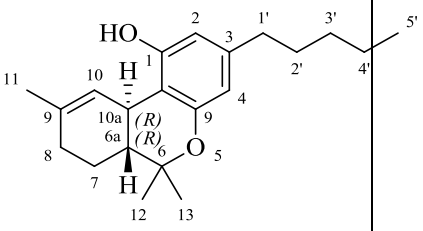
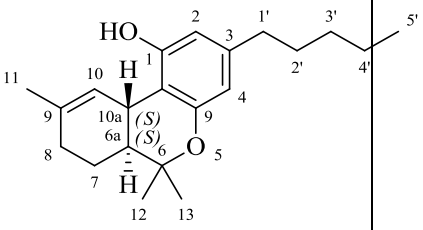
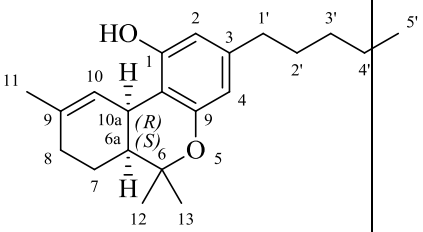
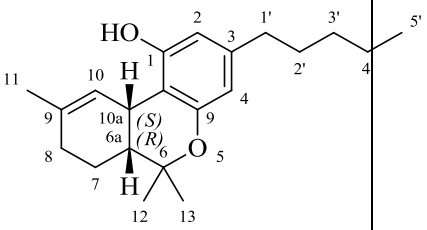
7 double bond isomers and their 30 stereoisomers						
Formal numbering			**Number of stereoisomers**	**Natural occurrence**	**CAS Registry Number**	**Structure**
Short name	**Chiral centers**	**Full name**				
$\Delta^{6a,10a}$-THC	C9	7,8,9,10-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	2	No	95720-01-7	 (*R*)-
				No	95720-02-8	 (*S*)-

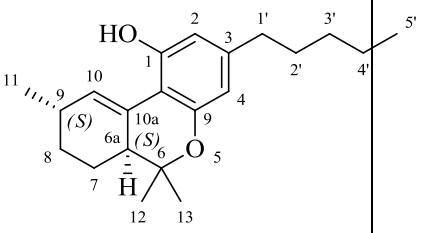
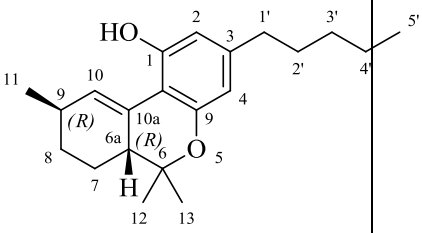
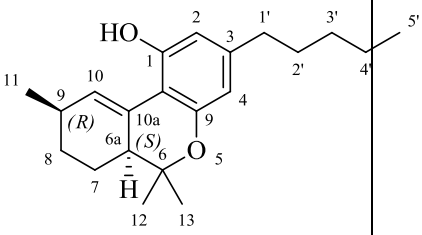
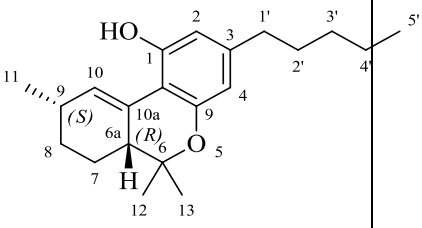
$\Delta^{6a,7}$-THC	C9 and C10a	8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	4	No	unknown	 (9*R*,10a*S*)-
				No	unknown	 (9*S*,10a*S*)-
				No	59042-44-3	 (9*R*,10a*R*)-
				No	unknown	 (9*S*,10a*R*)-

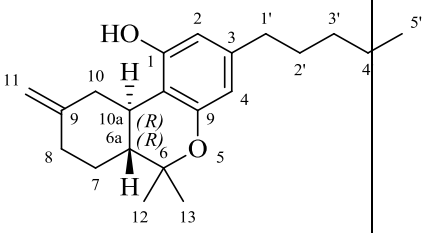
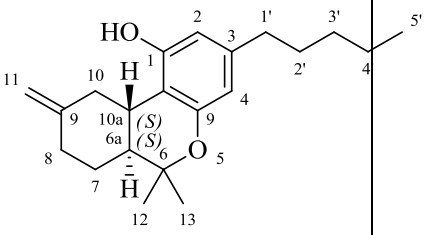
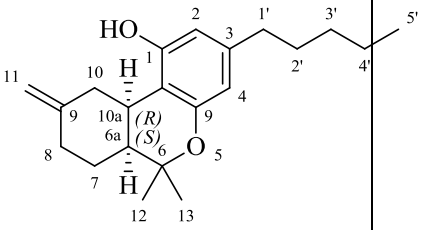
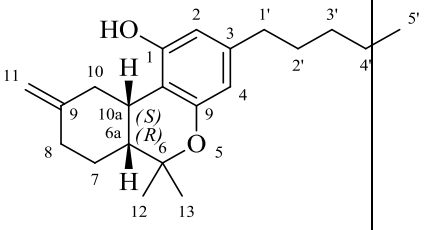
Δ^7-THC	C6a, C9 and C10a	6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol	8	No	unknown	 (6a*R*,9*S*,10a*S*)-
				No	unknown	 (6a*S*,9*R*,10a*R*)-
				No	unknown	 (6a*R*,9*R*,10a*S*)-
				No	unknown	 (6a*S*,9*S*,10a*R*)-

				No	16267 8-94-6	 (6a*R*,9*S*,10a*R*)-
				No	unkno wn	 (6a*S*,9*R*,10a*S*)-
				No	unkno wn	 (6a*S*,9*S*,10a*S*)-
				No	42793-13-5	 (6a*R*,9*R*,10a*R*)-

Δ^8-THC	C6a and C10a	6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6Hdibenzo[b,d]pyran-1-ol	4	Yes	5957-75-5	 (6a*R*,10a*R*)-
				No	33029-18-4	 (6a*S*,10a*S*)-
				No	18575 2-04-9	 (6a*S*,10a*R*)-
				No	65634-24-4	 (6a*R*,10a*S*)-

Δ^9-THC	C6a and C10a	6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	4	Yes	1972-08-3	 (6a*R*,10a*R*)-
				No	17766-02-8	 (6a*S*,10a*S*)-
				No	43009-38-7	 (6a*S*,10a*R*)-
				No	69855-10-3	 (6a*R*,10a*S*)-

Δ^{10}-THC	C6a and C9	6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	4	No	unknown	 (6a*S*,9*S*)-
				No	95543-62-7	 (6a*R*,9*R*)-
				No	unknown	 (6a*S*,9*R*)-
				No	95588-87-7	 (6a*R*,9*S*)-

$\Delta^{9,11}$ - THC	C6a and C10a		4	No	27179-28-8	 (6a*R*,10a*R*)-
				No	unknown	 (6a*S*,10a*S*)-
				No	unknown	 (6a*S*,10a*R*)-
				No	unknown	 (6a*R*,10a*S*)-