WHO Expert Committee on Drug Dependence Pre-Review

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Delta-9-tetrahydrocannibinol

Section 1: Chemistry

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

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Contents

1. Substance identification

Delta-9-tetrahydrocannabinol refers to the four stereoisomers:[1]

a. (–)-*trans*-delta-9-tetrahydrocannabinol (also known as dronabinol)[2]
b. (+)-*trans*-delta-9-tetrahydrocannabinol
c. (–)-*cis*-delta-9-tetrahydrocannabinol
d. (+)-*cis*-delta-9-tetrahydrocannabinol

1.1 International Nonproprietary Name (INN)

Dronabinol[2]

1.2 Chemical Abstract Service (CAS) Registry Number

- (–)-*trans*-delta-9-tetrahydrocannabinol (dronabinol): 1972-08-3
- (+)-*trans*-delta-9-tetrahydrocannabinol: 17766-02-8
- (–)-*cis*-delta-9-tetrahydrocannabinol: 43009-38-7
- (+)-*cis*-delta-9-tetrahydrocannabinol: 69855-10-3

1.3 Other Chemical Names[3]

1.3.1 delta-9-tetrahydrocannabinol:

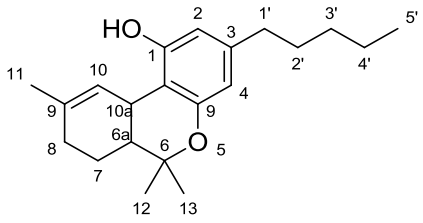
- 6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol[4(A)]

[1] Delta-9-tetrahydrocannabinol chemically comprises the four stereoisomers listed, as described in the report of "dronabinol" of the 34th meeting of the ECDD (34thECDD_dronabinol).
[2] Dronabinol refers to primary psychoactive compound in botanical cannabis (*Cannabis sativa* L.) (–)-*trans*-delta-9-tetrahydrocannabinol.
[3] Reported by Chemical Abstract Service (CAS).
[4] Alternate numbering systems: (A)"Dybenzopyran"; (B) "Monoterpenoid"

1.3.2 (–)-trans-delta-9-tetrahydrocannabinol (dronabinol):

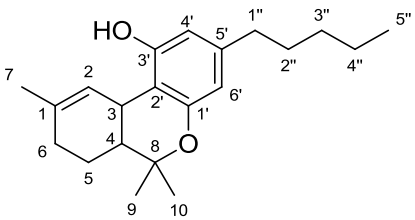
- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR-trans*)- [4(A)]

- Cannabinol, tetrahydro- (6CI)
- (6*aR*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4(A)]
- (–)-*trans*-Δ^9-THC [4(A)]
- (–)-*trans*-Δ^9-Tetrahydrocannabino[4(A)]
- (–)-Δ^9-Tetrahydrocannabinol [4(A)]
- (–)-Δ^9-*trans*-Tetrahydrocannabinol [4(A)]
- (6*aR*,10*aR*)-6,6,9-trimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol [4(A)]
- Abbott 40566
- Cannabinoids, THC
- Dronabinol
- Marinol
- NSC 134454
- Namisol
- QCD 84924
- SP 104
- THC
- Tetrahydrocannabinol
- *trans*-(–)-Δ^9-Tetrahydrocannabinol [4(A)]



(A)
Delta-9-THC

=



(B)
Delta-1-THC

- *trans*-Δ^9-Tetrahydrocannabinol [4(A)]
- Δ^9-THC [4(A)]
- Δ^9-Tetrahydrocannabinol [4(A)]
- Δ^9-*trans*-Tetrahydrocannabinol [4(A)]
- Cannabinol, Δ^1-tetrahydro- (7CI) [4(B)]
- (–)-3,4-*trans*-Δ^1-Tetrahydrocannabinol [4(B)]
- (–)-*trans*-Δ^1-Tetrahydrocannabinol [4(B)]
- (–)-Δ^1-Tetrahydrocannabinol [4(B)]
- (l)-Δ^1-Tetrahydrocannabinol [4(B)]
- l-*trans*-Δ^9-Tetrahydrocannabinol [4(B)]
- l-Δ^1-*trans*-Tetrahydrocannabinol [4(B)]
- Δ^1-THC [4(B)]
- Δ^1-Tetrahydrocannabinol [4(B)]

1.3.3 (+)-trans-delta-9-tetrahydrocannabinol:

- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (+)- (8CI) [4(A)]
- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-*trans*)- [4(A)]
- (6*aS*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4(A)]
- (+)-*trans*-Δ^9-Tetrahydrocannabinol [4(A)]
- (+)-Δ^1-Tetrahydrocannabinol [4(B)]
- (+)-Δ^9-THC [4(A)]
- (+)-Δ^9-Tetrahydrocannabinol [4(A)]
- *d*-Δ^9-Tetrahydrocannabinol [4(A)]
- *trans*-(+)-Δ^9-Tetrahydrocannabinol [4(A)]

1.3.4 (–)-cis-delta-9-tetrahydrocannabinol:

- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS-cis*)- [4(A)]
- (6*aS*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4(A)]
- *cis*-Δ^9-Tetrahydrocannabinol [4(A)]

1.3.5 (+)-cis-delta-9-tetrahydrocannabinol:

- 6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR*-*cis*)- [4(A)]
- (6*aR*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol [4(A)]

1.4 Trade names [1]

1.4.1 (–)-trans-delta-9-tetrahydrocannabinol (dronabinol or (–)-trans-Δ^9-THC):

Canada: **Marinol** (preparation discontinued or no longer actively marketed);

Israel: **Ronabin** (preparation discontinued or no longer actively marketed);

South Africa: **Elevat** (preparation discontinued or no longer actively marketed);

United States: **Marinol**[1]; **Syndros**[2];

United States Pharmacopeia USP 40: **Dronabinol Capsules**[3]

- (+)-*trans*-delta-9-tetrahydrocannabinol ((+)-*trans*-Δ^9-THC): N/A
- (–)-*cis*-delta-9-tetrahydrocannabinol ((–)-*cis*-Δ^9-THC): N/A
- (+)-*cis*-delta-9-tetrahydrocannabinol ((+)-*cis*-Δ^9-THC): N/A

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[1] MARINOL is supplied as round, soft gelatin capsules for oral use as follows: • 2.5 mg white capsules • 5 mg dark brown capsules • 10 mg orange capsules. Each MARINOL capsule strength is formulated with the following inactive ingredients: 2.5 mg capsule contains gelatin, glycerin, sesame oil, and titanium dioxide; 5 mg capsule contains iron oxide red and iron oxide black, gelatin, glycerin, sesame oil, and titanium dioxide; 10 mg capsule contains iron oxide red and iron oxide yellow, gelatin, glycerin, sesame oil, and titanium dioxide

[2] SYNDROS (dronabinol) oral solution, 5 mg/mL is a clear, pale yellow to brown solution. Each milliliter of SYNDROS contains 5 mg of dronabinol as an active ingredient and the following inactive ingredients: 50 % (w/w) dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole, and water.

[3] Dronabinol in sesame oil.

1.5 Street Names

N/A

1.6 Physical Appearance

1.6.1 (–)-trans-delta-9-tetrahydrocannabinol (or (–)-trans-Δ^9-THC):

Colourless to light yellow resinous oil at room temperature, which tends to solidify at lower temperature [2-6]

1.6.2 (+)-trans-delta-9-tetrahydrocannabinol (or (+)-trans-Δ^9-THC):

Colorless oil [5]

1.6.3 (–)-cis-delta-9-tetrahydrocannabinol (or (–)-cis-Δ^9-THC):

Colorless oil [5]

1.6.4 (+)-cis-delta-9-tetrahydrocannabinol (or (+)-cis-Δ^9-THC):

Colorless oil [5]

1.7 WHO Review History

Dronabinol was included in Schedule I of the 1971 Convention on Psychotropic Substances at the time of its adoption as delta-9-tetrahydrocannabinol together with several other isomers of tetrahydrocannabinol. At its 26th meeting, the Expert Committee on Drug Dependence (ECDD) recommended that dronabinol, which is the (–)-*trans* isomer of delta-9-tetrahydrocannabinol ((–)-*trans*-Δ^9-THC), be moved to Schedule II, while keeping the other stereoisomer in Schedule I. This proposal was rejected by the Commission on Narcotic Drugs and ECDD reviewed the question again at its 27th meeting in 1990, which recommended that all the stereochemical variants of delta-9-tetrahydrocannabinol be rescheduled to Schedule II. This recommendation was adopted by the Commission on Narcotic Drugs (CND).

At the 32nd meeting, ECDD pre-reviewed dronabinol and recommended its critical review on the grounds that the rate of abuse of dronabinol was extremely low.

Dronabinol was critically reviewed by the 33rd ECDD in September 2002. On the basis of the available data the Committee considered that dronabinol should be rescheduled to Schedule IV of the 1971 Convention. However, the procedure was not completed and the Committee's advice was not sent to the CND at that time.

2. Chemistry

2.1 Chemical Name

2.1.1 IUPAC Name:

2.1.1.1 (–)-trans-Δ^9-THC:

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

2.1.1.2 (+)-trans-Δ^9-THC:

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

2.1.1.3 (–)-cis-Δ^9-THC:

(6*aS*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol

2.1.1.4 (+)-cis-Δ^9-THC:

(6*aR*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol

2.1.2 CA Index Name:

2.1.2.1 (–)-trans-Δ^9-THC:

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

2.1.2.2 (+)-trans-Δ^9-THC:

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

2.1.2.3 (–)-cis-Δ^9-THC:

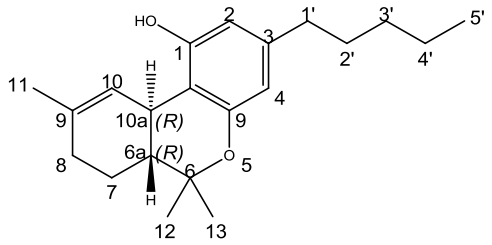
6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS*,10*aR*)-

2.1.2.4 (+)-cis-Δ^9-THC:

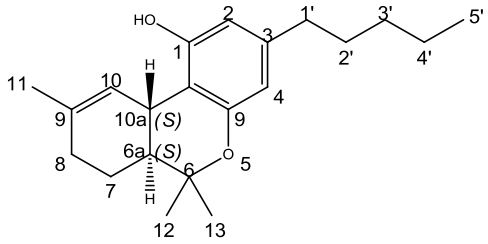
6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR*,10*aS*)-

2.2 Chemical Structure

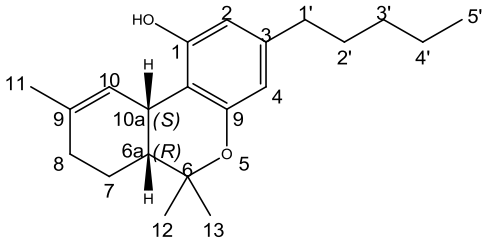
Free base:



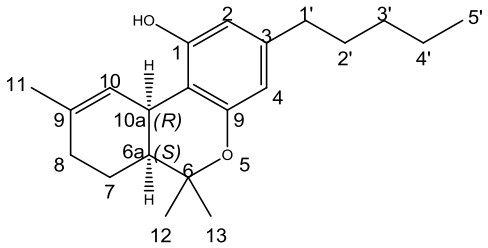
(6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(-)-trans-delta-9-tetrahydrocannabinol



(6aS,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(+)-trans-delta-9-tetrahydrocannabinol



(6aR,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(+)-cis-delta-9-tetrahydrocannabinol



(6aS,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(-)-cis-delta-9-tetrahydrocannabinol

Molecular Formula: $C_{21}H_{30}O_2$

Molecular Weight: 314.46

2.3 Stereoisomers

Δ^9-THC has two chiral carbon atoms C6*a* and C10*a*, which generate four stereoisomers:

(–)-*trans*-Δ^9-THC and (+)-*trans*-Δ^9-THC, (–)-*cis*-Δ^9-THC and (+)-*cis*-Δ^9-THC.

Naturally occurring in cannabis is the (–)-*trans*-Δ^9-THC. The other three stereoisomers have been recently synthetized [5].

2.4 Methods and Ease of Illicit Manufacturing

(–)-*trans*-Δ^9-THC can be obtained mainly by four methods:

1. Natural source: extraction of Δ^9-tetrahydrocannabinolic acid (THCA), decarboxylation and purification
2. Decarboxylation of THCA and purification
3. Semi-synthesis: extraction of cannabidiolic acid (CBDA), decarboxylation and conversion into THC
4. Total synthesis from terpene and olivetol

2.4.1 Natural source

(–)-*trans*-Δ^9-THC does not occur at significant concentration in Cannabis. The plant synthesizes primarily the carboxylic acid form of (–)-*trans*-Δ^9-THC, namely, Δ^9-tetrahydrocannabinolic acid (THCA)[7] from cannabigerolic acid and accumulates in the glandular trichomes of flowers and leaves where it represents up to 90% of the total THC samples [7, 8].

Contrary to (–)-*trans*-Δ^9-THC, THCA does not elicit intoxicating effects in humans [7].[1]

[1] THCA is not a scheduled substance.

This acidic cannabinoid is thermally unstable and can be quickly decarboxylated when exposed to heat via smoking or baking [9].

In order to obtain Δ^9-THC from cannabis plant it is possible to follow two strategies:

- Decarboxylation of cannabis inflorescence prior to extraction
- Extraction and decarboxylation of THCA into (–)-*trans*-Δ^9-THC.

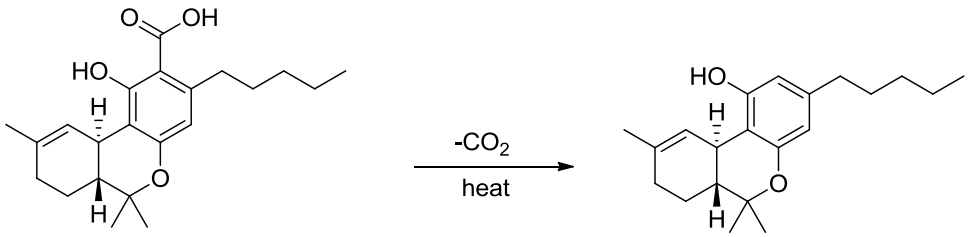
Both processes are described in the literature. As an example, the method of extraction of (–)-*trans*-Δ^9-THC and THCA is reported in the patent US8846409B2 [10].

The extraction of (–)-*trans*-Δ^9-THC involves the heating of cannabis inflorescence, which is preliminarily shredded in 2 mm particles in two phases, the first at 105 °C for 15 minutes and the second at 120 °C for 2 hours in order to decarboxylate at least 95% of THCA. Subsequently, the plant material is extracted with either supercritical carbon dioxide (CO_2) or an organic solvent, such as alcohol or hexane, which is evaporated to obtain a solid residue. The latter is dissolved into hot ethyl alcohol and left at –20 °C for two days in order to precipitate wax and other impurities, which are removed by filtration. The filtrate is dried and (–)-*trans*-Δ^9-THC is separated from the other components by chromatography through a column packed with Sephadex LH20, eluting with 2:1 chloroform/dichloromethane. (–)-*trans*-Δ^9-THC is then purified from methanol and pentane.

2.4.2 Decarboxylation of THCA and purification

THCA is extracted as a crystalline solid following a procedure similar to that employed for neutral (–)-*trans*-Δ^9-THC but without the heating step. If heated up (i.e. smoked or baked), THCA decarboxylates to give neutral (–)-*trans*-Δ^9-THC.[1]

[1] For forensic analysis the total THC is required, that is the sum of neutral THC and THCA. A gas chromatographic method is generally employed, thus the non-derivatized sample is heated up in the injector and THCA converts into neutral THC. The yield of decarboxylation is strictly dependent from the temperature and geometry of the injector.



(6aR,10aR)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-2-carboxylic acid
(-)-*trans*-delta-9-tetrahydrocannabinolic acid

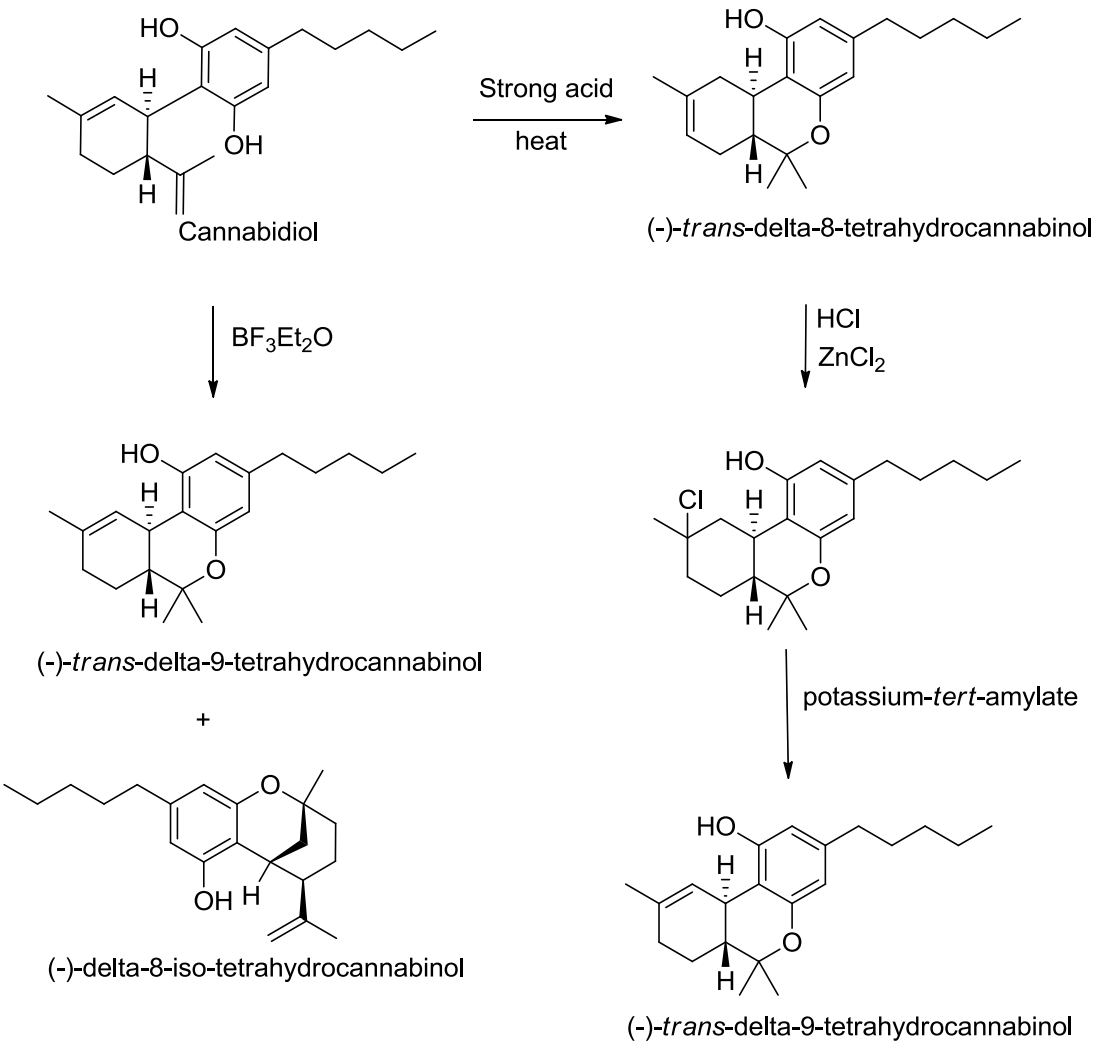
(6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
(-)-*trans*-delta-9-tetrahydrocannabinol

2.4.3 Semi-synthesis

(–)-*trans*-Δ^9-THC can be obtained by partial synthesis from cannabidiol (CBD) [6, 11].

Mechoulam *et al.* described that CBD, in the presence of boron trifluoride etherate in methylene chloride, rapidly isomerized to (–)-*trans*-Δ^9-THC (60% yield) and Δ^8-iso-THC (13%) [12].

Alternatively cannabidiol can be converted quantitatively into delta-8-tetrahydrocannabinol by strong acid and then into (–)-*trans*-Δ^9-THC by hydrochlorination and dehydrochlorination [12-17].

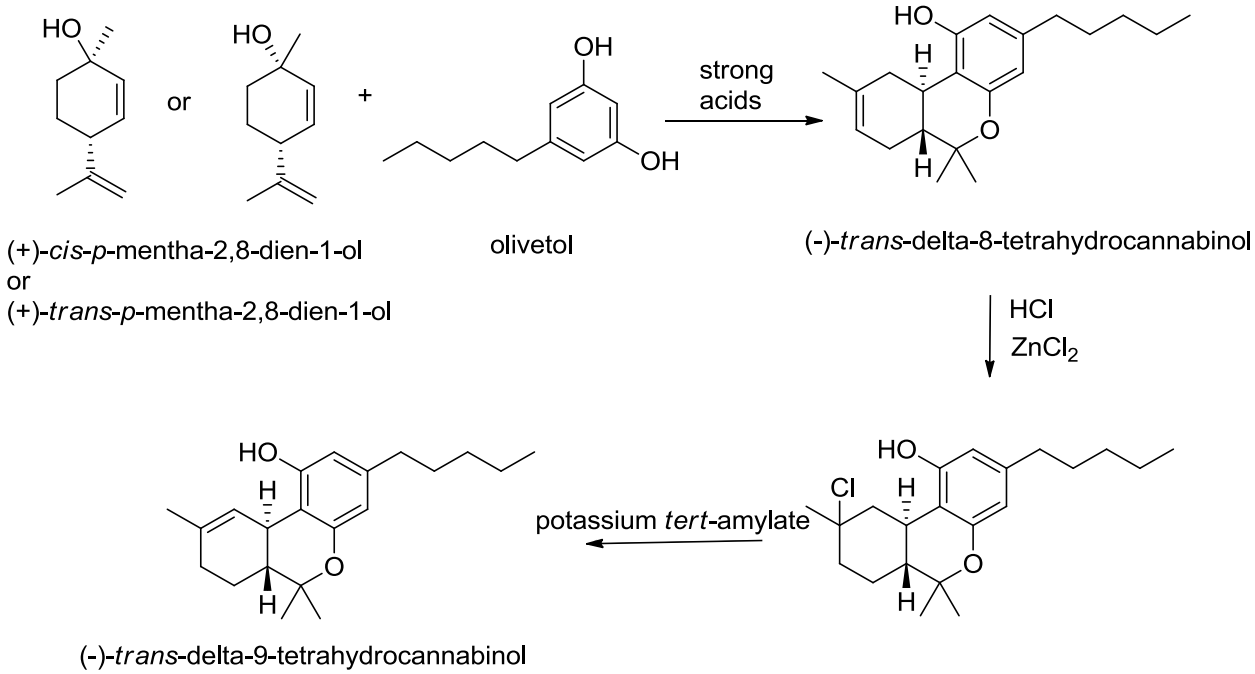


2.4.4 Total synthesis of (–)-trans-Δ^9-THC

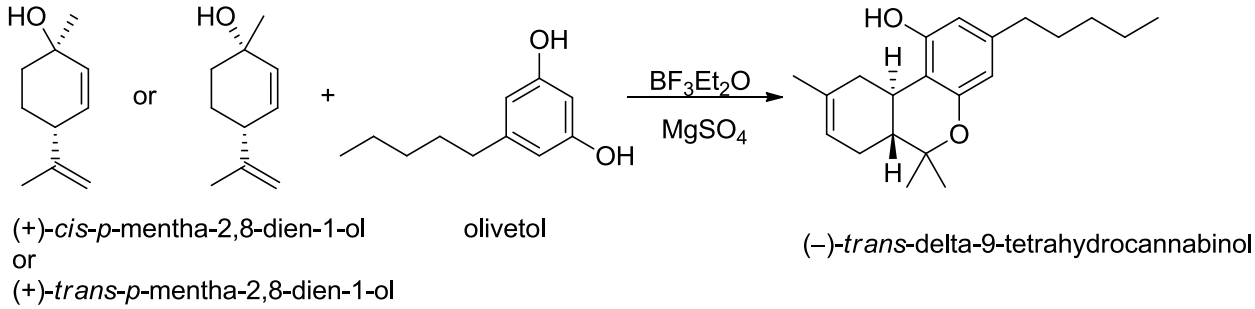
After the first synthesis of (±)-*trans*-Δ^9-THC, published by Mechoulam and co-workers [18], a number of stereospecific syntheses were published, such as those by Petrzilka *et al.* [19, 20], by Razdan and Handrick [21], and Gaoni and Mechoulam [6, 11] that are based on the same principle, the condensation of olivetol with an optically pure monoterpene [22-25].

The synthesis of Petrzilka *et al.* demonstrated a facile entry into cannabinoids utilizing (+)-*cis*- or *trans*-*p*-mentha-2,8-dien-l-ol. By condensing with olivetol in the presence of weak and strong acids they obtained (–)-CBD and (–)-Δ^8-THC, respectively. The yield of cannabidiol was 25%, but with a strong

acid, no cannabidiol was isolated and delta-8-tetrahydrocannabinol was obtained in 53% yield. The conversion to (–)-*trans*-Δ^9-THC was carried out by addition of hydrochloric acid (HCl) and dehydrochlorination using potassium *tert*-amylate in benzene obtaining a 100% yield.



Because of the commercial availability of the starting terpene *cis*/*trans*-*p*-mentha-2,8-dien-l-ol, this route was further developed by Razdan and co-workers for the preparation of (-)-*trans*-Δ^9-THC employing boron trifluoride diethyl etherate (BF_3Et_2O) in the presence of magnesium sulfate ($MgSO_4$) as the dehydrating agent [26]. By this process (–)-*trans*-Δ^9-THC of very high optical purity was formed in a simple one-step synthesis in 50% yield.



Recently, a stereoselective total synthesis of all isomeric forms of Δ^9-THC has been developed by Schafroth *et al.* [5].

2.5 Chemical Properties

i. (–)-*trans*-Δ^9-THC:

2.5.1 Melting point

<25 °C [27]

2.5.2 Boiling point

200 °C at 0.02 Torr[1]

2.5.3 Solubility

Yalkowsky *et al.* measured a pKa of 10.6 and a solubility in water of 2.8 mg/L at 23 °C [28]. (-)-*trans*-Δ^9-THC is also soluble in alcohol (1 part in 1 part of alcohol); 1 part in 1 part of acetone; 1 part in 3 parts of glycerol. It is also soluble in 0.15 M sodium chloride (0.77 mg/L at 23 °C) and in fixed oils [29].

(-)-*trans*-Δ^9-THC binds to glass (20% at 0.1 µg/mL). Polycarbonate, polypropylene, Teflon and stainless steel containers showed more extensive binding than glass. Degraded rapidly in acidic solution ($t_{1/2}$=1 h at pH 1 and at 55 °C) [30].

Rosenkrantz *et al.* conducted studies of solubility 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 in order 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^9-THC was in ethanol and acetone greater than 1 g/mL, 0.90 g/mL in benzyl alcohol, 0.30 g/mL in sesame oil, 0.54 g/mL in DMSO, 0.58 g/mL in propylene glycol, 0.39 g/mL in glycerol and 0.28 g/mL in polyoxyethylene monooleate (Tween 80) [31].

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

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

n-Octanol/water partition coefficients (Po/w) of (–)-*trans*-Δ^9-THC, as measured by shake-flask methods, span from 6,000 [32] to 60,000, as estimated by Roth and Williams [30].

Brian *et al.* calculated the Po/w of (–)-*trans*-Δ^9-THC and (–)-*trans*-Δ^8-THC by two procedures: reverse-phase high-pressure liquid chromatographic (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^9-THC by computer calculation was 7.18, which is in close agreement with the log Po/w of 6.93 as determined by HPLC. This very high value of log Po/w indicated an extreme lipophilicity [33].

2.5.3.2 *Optical Rotatory Power*

Reports vary from –148 to –161.8:

- –148: (*c.* 0.35,$CHCl_3$, wavelength: 589.3 nm) [34]
- –150.5: ($CHCl_3$, Temp: 20 °C)[10]
- –161.8: (*c.* 1.0, $CHCl_3$) [5]

2.5.3.3 *Stability*

When stored, (–)-*trans*-Δ^9-THC decomposes and becomes reddish [4]. It is unstable in air, light, and acidic media and at high temperatures. (–)-*trans*-Δ^9-THC is more stable in ethanol than in carbon tetrachloride or hexane. Thin films of (–)-*trans*-Δ^9-THC are less stable than (–)-*trans*-Δ^9-THC in solutions. Stability is not improved by adding antioxidants. The major product of (–)-*trans*-Δ^9-THC decomposition is cannabinol (CBN) and the minor product is (–)-*trans*-Δ^8-THC. Due to its high lipid/aqueous partition coefficient, (–)-*trans*-Δ^9-THC has a higher affinity for biomembranes than for aqueous media [3, 6, 35].

2.5.3.4 *Chemical characterization*

^{1}H NMR (400 MHz, $CDCl_3$)

δ = 6.32 – 6.28 (m, 1H), 6.27 (d, J = 1.6 Hz, 1H), 6.14 (d, J =1.6 Hz, 1H), 4.71 (s, 1H), 3.25 – 3.15 (m, 1H), 2.48 – 2.38 (m, 2H), 2.21 – 2.11 (m, 2H), 1.95– 1.85 (m, 1H), 1.71 – 1.67 (m, 4H), 1.60 – 1.51 (m, 2H), 1.41 (m, 4H), 1.33 – 1.24 (m, 4H), 1.09 (s, 3H), 0.91 – 0.84 (m, 3H)

^{13}C NMR (101 MHz, $CDCl_3$)

δ = 154.9, 154.3, 143.0, 134.6, 123.8, 110.3, 109.2, 107.7, 77.4, 46.0, 35.6, 33.7, 31.7, 31.3, 30.8, 27.7, 25.2, 23.5, 22.7, 19.4, 14.2

IR (neat, ν_{max}/cm^{-1})

3392, 2927, 2858, 1624, 1578, 1425, 1365, 1331, 1268, 1234, 1183, 1129, 1113, 1038, 878

$[\alpha]^{25}_D$ = –161.8 (*c.* 1.0, $CHCl_3$) [5]

ii. (+)-*trans*-Δ^9-THC:

Melting point: N/A

Boiling point: N/A

Solubility: N/A

Stability: N/A

2.5.3.5 Chemical characterization

^{1}H NMR (400 MHz, $CDCl_3$)

δ = 6.32 – 6.28 (m, 1H), 6.27 (d, J = 1.6 Hz, 1H), 6.14 (d, J =1.6 Hz, 1H), 4.71 (s, 1H), 3.25 – 3.15 (m, 1H), 2.48 – 2.38 (m, 2H), 2.21 – 2.11 (m, 2H), 1.95– 1.85 (m, 1H), 1.71 – 1.67 (m, 4H), 1.60 – 1.51 (m, 2H), 1.41 (m, 4H), 1.33 – 1.24 (m, 4H), 1.09 (s, 3H), 0.91 – 0.84 (m, 3H)

^{13}C NMR (101 MHz, $CDCl_3$)

δ = 154.9, 154.3, 143.0, 134.6, 123.8, 110.3, 109.2, 107.7, 77.4, 46.0, 35.6, 33.7, 31.7, 31.3, 30.8, 27.7, 25.2, 23.5, 22.7, 19.4, 14.2

IR (neat, ν_{max}/cm^{-1})

3392, 2927, 2858, 1624, 1578, 1425, 1365, 1331, 1268, 1234, 1183, 1129, 1113, 1038, 878

$[\alpha]^{25}_{D}$ = +159.1 (*c*. 1, $CHCl_3$) [5]

iii. (–)-*cis*-Δ^9-THC:

Melting point: N/A

Boiling point: N/A

Solubility: N/A

Stability: N/A

Chemical characterization

^{1}H NMR, ^{13}C NMR and IR data were identical with that of the (+)-*trans*-Δ^9-THC.

$[\alpha]^{25}_{D}$ = –95.0 (*c*. 1.0, $CHCl_3$) [5]

iv. (+)-*cis*-Δ^9-THC:

Melting point: N/A

Boiling point: N/A

Solubility: N/A

Stability: N/A

2.5.3.6 Chemical characterization

^{1}H NMR (400 MHz, $CDCl_3$)

δ = 6.25 (d, J = 1.6 Hz, 1H), 6.23 – 6.19 (m, 1H), 6.13 (d, J = 1.6 Hz, 1H), 4.75 (s, 1H), 3.56 (t, J = 5.6 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.06 – 1.88 (m, 3H), 1.75 – 1.70 (m, 1H), 1.70 – 1.67 (bs, 3H), 1.59 – 1.52 (m, 2H), 1.5 - 1.42 (m, 1H), 1.39 (s, 3H), 1.34 – 1.28 (m, 4H), 1.27 (s, 3H), 0.90 – 0.86 (m, 3H)

^{13}C NMR (101 MHz, $CDCl_3$)

δ = 154.9, 154.0, 142.6, 135.2, 122.1, 110.2, 109.6, 108.1, 76.3, 40.2, 35.6, 31.7, 31.7, 30.7, 29.9, 26.1, 25.5, 23.8, 22.7, 20.8, 14.2

IR (neat, νmax /cm-1) 3395, 2927, 2856, 1622, 1577, 1425, 1379, 1366, 1263, 1236, 1157, 1136, 1112, 1035, 889

$[\alpha]^{25}_{D}$ = +91.7 (*c.* 1.0, $CHCl_3$) [5]

2.6 Identification and Analysis

Synthetic (–)-*trans*-Δ^9-THC was characterized and ^{1}H NMR properties [36, 37], ^{13}C NMR properties [36-39], mass properties [36, 40-57] and ultraviolet (UV) and visible properties [56, 58] are reported.

Recently, Schafroth *et al.* synthesized all stereoisomeric forms of Δ^9-THC and optical rotatory power, ^{1}H NMR, ^{13}C NMR, IR and chromatographic enantioseparation of each stereoisomer was reported [5].

Color tests are described in "Recommended methods for the identification and analysis of cannabis and cannabis products" edited by United Nations office on drug and crime [59]. They are the Fast Corinth V salt test, Fast Blue B salt test and Rapid Duquenois test (Duquenois-Levine test) [59]. The positive results to color tests are only presumptive test and it is therefore mandatory for the analyst to confirm such results using additional analysis like chromatographic analysis.

Several analytical methods are reported regarding (–)-*trans*-Δ^9-THC qualitative and quantitative determination in different matrices such as cannabis inflorescence, cannabis extracts and biological fluids. Chromatographic methods are the most employed coupled to several detection techniques such as UV

and mass spectrometry (MS) [60]. Based on the specific matrix available, specific sample pre-treatment and chromatographic method should be followed. In general, the chromatographic techniques can be divided into:

2.6.1 Thin-layer chromatography (TLC)

It is quite difficult to separate (–)-*trans*-Δ^8-THC from (–)-*trans*-Δ^9-THC employing a normal and polar stationary phases [56]. A two dimensional TLC method has been developed with the advantage to obtain a better resolution between the two isomers [61].

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

These methods are widely employed in several laboratories and permit to analyse (–)-*trans*- Δ^9-THC with or without preliminary derivatization [56, 62]. Hazekamp *et al.* also developed a GC-MS method that easily distinguished (–)-*trans*-Δ^9-THC from its isomer (–)-*trans*-Δ^8-THC [56]. GC methods are generally employed for both plant material and biological matrices with an appropriate sample pre-treatment [60].

2.6.3 Liquid chromatography (LC)

LC methods are generally coupled to ultraviolet (LC-UV) and/or mass spectrometry (LC-MS) detection. They offer the advantage of a very high sensitivity without a derivatization step [63-67]. LC methods are widely employed for both plant material and biological matrices with an appropriate sample pre-treatment [60]. As for GC-MS, (–)-*trans*-Δ^9-THC from its isomer (–)-*trans*-Δ^8-THC can be easily separated by LC-UV [56].

3. Ease of Convertibility Into Controlled Substances

The only controlled substance that (–)-*trans*-Δ^9-THC can be converted into is its isomer (–)-*trans*-Δ^8-THC, which is in Schedule I of the 1971 Convention. The conversion reaction is reported in the literature and involves the treatment of (–)-*trans*-Δ^9-THC with an acid resulting in an equilibrium mixture containing approximately 3% of the (–)-*trans*-Δ^9- and 97% of the more thermodynamically stable (–)-*trans*-Δ^8-THC isomer [68, 69].

4. References

[1] Dronabinol Monograph, Martindale: The Complete Drug Reference, Pharmaceutical Press, London, 2018 Available from: https://www.medicinescomplete.com/mc/martindale/current/search.htm?q=dronabinol

[2] Cannabisblüten Cannabis flos, Bundesinstitut für Arzneimittel und Medizinprodukte, Bekanntmachung einer Mitteilung zum Deutschen Arzneibuch (Empfehlungen der Fachausschüsse der Deutschen Arzneibuch-Kommission) from: 30.05.2017 Bundesinstitut für Arzneimittel und Medizinprodukte BAnz AT 21.06.2017 B6, 2017.

[3] M.J. O'Neil, The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals, NJ: Merck and Co., Inc., Whitehouse Station, 2006.

[4] Toxicology and carcinogenesis studies of 1-trans-delta-9-tetrahydrocannabinol in F344/N rats and B6c3f, mice (Gavage Studies), NTP TR 446, US Department of Health and Human Services, Public Health Service, NIH, Research Triangle Park, NC 27709, 1996. Available from:
https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr446.pdf

[5] M.A. Schafroth, G. Zuccarello, S. Krautwald, D. Sarlah, E.M. Carreira, Stereodivergent total synthesis of Δ^9-tetrahydrocannabinols, Angewandte Chemie International Edition 53(50) (2014) 13898-13901.

[6] Y. Gaoni, R. Mechoulam, The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish, Journal of American Chemical Society 93(1) (1971) 217-224.

[7] G. Moreno-Sanz, Can you pass the acid test? critical review and novel therapeutic perspectives of Δ^9-tetrahydrocannabinolic acid, Cannabis and Cannabinoid Research 1(1) (2016) 124-130.

[8] M. Taschwer, M.G. Schmid, Determination of the relative percentage distribution of THCA and Delta(9)-THC in herbal cannabis seized in Austria - Impact of different storage temperatures on stability, Forensic Science International 254 (2015) 167-171.

[9] M. Wang, Y.H. Wang, B. Avula, M.M. Radwan, A.S. Wanas, J. van Antwerp, J.F. Parcher, M.A. ElSohly, I.A. Khan, Decarboxylation study of acidic cannabinoids: a novel approach using ultra-high-performance supercritical fluid chromatography/photodiode array-mass spectrometry, Cannabis and Cannabinoid Research 1(1) (2016) 262-271.

[10] I.R. Flockhart, G.W. Wheatley, S. Dring, L. Archer, Methods of preparing cannabinoids from plant material, GW Pharmaceuticals (2002) US patent US8846409B2.

[11] R. Mechoulam, P. Braun, Y. Gaoni, Syntheses of delta-1-tetrahydrocannabinol and related cannabinoids, Journal of the American Chemical Society 94(17) (1972) 6159-6165.

[12] Y. Gaoni, R. Mechoulam, Isolation, structure and partial synthesis of an active constituent of hashish, Journal of the American Chemical Society 86(8) (1964) 1646-1647.

[13] R. Adams, Marihuana: Harvey Lecture, February 19, 1942, Bulletin of the New York Academy of Medicine 18(11) (1942) 705-730.

[14] R. Adams, D.C. Pease, C.K. Cain, J.H. Clark, Structure of cannabidiol. VI. Isomerization of cannabidiol to tetrahydrocannabinol, a physiologically active product. Conversion of cannabidiol to cannabinol, Journal of the American Chemical Society 62(9) (1940) 2402-2405.

[15] R. Adams, B.R. Baker, Structure of cannabidiol. VII. A method of synthesis of a tetrahydrocannabinol which possesses marihuana activity, Journal of the American Chemical Society 62(9) (1940) 2405-2408.

[16] R. Adams, S. Loewe, D.C. Pease, C.K. Cain, R.B. Wearn, R.B. Baker, H. Wolff, Structure of cannabidiol. VIII. Position of the double bonds in cannabidiol. Marihuana activity of tetrahydrocannabinols, Journal of the American Chemical Society 62(9) (1940) 2566-2567.

[17] Y. Gaoni, R. Mechoulam, Hashish-VII: The isomerization of cannabidiol to tetrahydrocannabinols, Tetrahedron 22(4) (1966) 1481-1488.

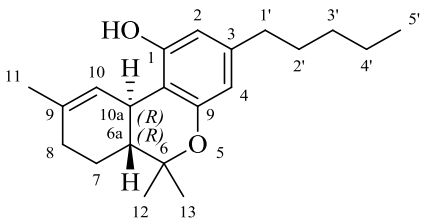
[18] R. Mechoulam, Y. Gaoni, A Total Synthesis of *dl*-Δ^1-tetrahydrocannabinol, the active constituent of hashish, Journal of the American Chemical Society 87(14) (1965) 3273-3275.
[19] T. Petrzilka, C. Sikemeier, Über inhaltsstoffe des haschisch. 3., vorläufige mitteilung umwandlung von (–)-$\Delta^{6,1}$-3,4-trans-tetrahydrocannabinol in (–)-$\Delta^{1,2}$-3,4-trans tetrahydrocannabinol, Helvetica Chimica Acta 50(7) (1967) 2111-2113.
[20] T. Petrzilka, W. Haefliger, C. Sikemeier, Synthese von haschisch-inhaltsstoffen. 4. Mitteilung, Helvetica Chimica Acta 52(4) (1969) 1102-1134.
[21] R.K. Razdan, G.R. Handrick, Hashish. A stereospecific synthesis of (-)-Δ^1- and (-)-$\Delta^{1(6)}$-tetrahydrocannabinols, Journal of the American Chemical Society 92(20) (1970) 6061-6062.
[22] R. Mechoulam, Cannabinoid chemistry, Marijuana: chemistry, pharmacology, metabolism and clinical effects, Academic Press, New York, 1973, p. 2.
[23] R. Mechoulam, N.K. McCallum, S. Burstein, Recent advances in the chemistry and biochemistry of cannabis, Chemical Reviews 76(1) (1976) 75-112.
[24] R.K. Razdan, The total synthesis of cannabinoids, in The total synthesis of natural products, J. ApSimon ed., Wiley, New York, 1981, p. 185.
[25] M.A. Tius, Stereospecific cannabinoid synthesis: the application of new techniques to a classical problem, in Studies in natural product chemistry, Structure and Chemistry (Part E), vol.19, Atta-ur-Rahman ed., Elsevier, Amsterdam, 1996, p. 185.
[26] G.R. Handrick, D.B. Uliss, H.C. Dalzell, R.K. Razdan, Hashish: synthesis of (–)-Δ^9-tetrahydrocannabinol (THC) and its biologically potent metabolite 3′-hydroxy-Δ^9-THC, 1979.
[27] H. Perrotin-Brunel, M.C. Kroon, M.J.E. van Roosmalen, J. van Spronsen, C.J. Peters, G.-J. Witkamp, Solubility of non-psychoactive cannabinoids in supercritical carbon dioxide and comparison with psychoactive cannabinoids, The Journal of Supercritical Fluids 55(2) (2010) 603-608.
[28] S.H. Yalkowsky, Y. He, P. Jain, Handbook of aqueous solubility data, Second ed., CRC Press, Boca Raton, FL, 2010.
[29] Martindale, The Extra Pharmacopoeia, 28th ed., The Pharmaceutical Press, London, 1982.
[30] S.H. Roth, P.J. Williams, The non-specific membrane binding properties of Δ^9-tetrahydrocannabinol and the effects of various solubilizers, Journal of Pharmacy and Pharmacology 31(1) (1979) 224-230.
[31] H. Rosenkrantz, G.R. Thompson, M.C. Braude, Oral and parenteral formulations of marijuana constituents, Journal of Pharmaceutical Science 61(7) (1972) 1106-12.
[32] E.W. Gill, G. Jones, Brain levels of Δ^1-tetrahydrocannabinol and its metabolites in mice - correlation with behaviour, and the effect of the metabolic inhibitors SKF 525A and piperonyl butoxide, Biochemical Pharmacology 21(16) (1972) 2237-2248.
[33] B.F. Thomas, D.R. Compton, B.R. Martin, Characterization of the lipophilicity of natural and synthetic analogs of delta-9-tetrahydrocannabinol and its relationship to pharmacological potency, Journal of Pharmacology and Experimental Therapeutics 255(2) (1990) 624-30.
[34] L. Minuti, E. Ballerini, High-pressure access to the Δ^9-cis- and Δ^9-trans-tetrahydrocannabinols family, The Journal of Organic Chemistry 76(13) (2011) 5392-5403.
[35] R. Mechoulam, P. Braun, Y. Gaoni, Stereospecific synthesis of (–)-delta-1- and (–)-delta-1(6)-tetrahydrocannabinols, Journal of the American Chemical Society 89(17) (1967) 4552-4554.
[36] L. Qi, N. Yamamoto, M.M. Meijler, L.J. Altobell, G.F. Koob, P. Wirsching, K.D. Janda, Δ^9-Tetrahydrocannabinol immunochemical studies: haptens, monoclonal antibodies, and a convenient synthesis of radiolabeled Δ^9-tetrahydrocannabinol, Journal of Medicinal Chemistry 48(23) (2005) 7389-7399.
[37] Y.H. Choi, A. Hazekamp, A.M. Peltenburg-Looman, M. Frédérich, C. Erkelens, A.W. Lefeber, R. Verpoorte, NMR assignments of the major cannabinoids and cannabiflavonoids isolated from flowers of Cannabis sativa, Phytochemical Analysis 15(6) (2004) 345-354.

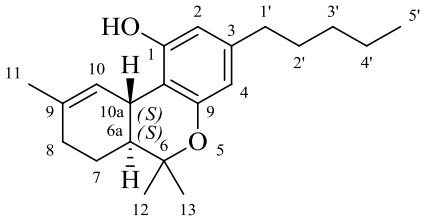
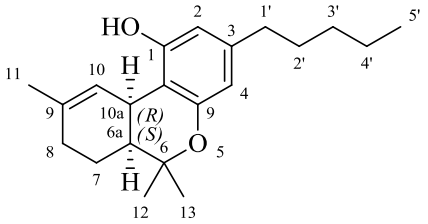
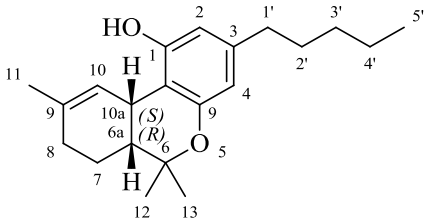
[38] R.A. Archer, D.W. Johnson, E.W. Hagaman, L.N. Moreno, E. Wenkert, Carbon-13 nuclear magnetic resonance spectroscopy of naturally occurring substances. 47. Cannabinoid compounds, Journal of Organic Chemistry 42(3) (1977) 490-495.
[39] L.J. Silverberg, Synthesis of cannabinoids, Johnson Matthey Public Limited Company, 2002.
[40] E.W. Schwilke, E.L. Karschner, R.H. Lowe, A.M. Gordon, J.L. Cadet, R.I. Herning, M.A. Huestis, Intra- and intersubject whole blood/plasma cannabinoid ratios determined by 2-dimensional, electron impact GC-MS with cryofocusing, Clinical Chemistry 55(6) (2009) 1188-1195.
[41] N. Badawi, K.W. Simonsen, A. Steentoft, I.M. Bernhoft, K. Linnet, Simultaneous screening and quantification of 29 drugs of abuse in oral fluid by solid-phase extraction and ultraperformance LC-MS/MS, Clinical Chemistry 55(11) (2009) 2004-2018.
[42] M.J. Welch, L.T. Sniegoski, S. Tai, Two new standard reference materials for the determination of drugs of abuse in human hair, Analytical and Bioanalytical Chemistry 376(8) (2003) 1205-1211
[43] M. Gergov, I. Ojanperä, E. Vuori, Simultaneous screening for 238 drugs in blood by liquid chromatography-ionspray tandem mass spectrometry with multiple-reaction monitoring, Journal of Chromatography B 795(1) (2003) 41-53.
[44] T. Saito, A. Wtsadik, K.B. Scheidweiler, N. Fortner, S. Takeichi, M.A. Huestis, Validated gas chromatographic-negative ion chemical ionization mass spectrometric method for Δ^9-tetrahydrocannabinol in sweat patches, Clinical Chemistry 50(11) (2004) 2083-2090.
[45] A.A.M. Stolker, J. van Schoonhoven, A.J. de Vries, I. Bobeldijk-Pastorova, W.H.J. Vaes, R. van den Berg, Determination of cannabinoids in cannabis products using liquid chromatography–ion trap mass spectrometry, Journal of Chromatography A 1058(1-2) (2004) 143-151.
[46] N. Fucci, N. De Giovanni, M. Chiarotti, Simultaneous detection of some drugs of abuse in saliva samples by SPME technique, Forensic Science International 134(1) (2003) 40-45.
[47] M. Pellegrini, E. Marchei, R. Pacifici, S. Pichini, A rapid and simple procedure for the determination of cannabinoids in hemp food products by gas chromatography-mass spectrometry, Journal of Pharmaceutical and Biomedical Analysis 36(5) (2005) 939-946.
[48] A.K. Hewavitharana, G. Golding, G. Tempany, G. King, N. Holling, Quantitative GC-MS analysis of Δ^9-tetrahydrocannabinol in fiber hemp varieties, Journal of Analytical Toxicology 29(4) (2005) 258-261.
[49] C. Gambelunghe, R. Rossi, C. Ferranti, R. Rossi, M. Bacci, Hair analysis by GC-MS-MS to verify abuse of drugs, Journal of Applied Toxicology 25(3) (2005) 205-211.
[50] C.A. Mueller, W. Weinmann, S. Dresen, A. Schreiber, M. Gergov, Development of a multi-target screening analysis for 301 drugs using a QTrap liquid chromatography/tandem mass spectrometry system and automated library searching, Rapid Communications in Mass Spectrometry 19(10) (2005) 1332-1338.
[51] M. Laloup, M. del Mar Ramirez Fernandez, M. Wood, G. De Boeck, C. Henquet, V. Maes, N. Samyn, Quantitative analysis of Δ^9-tetrahydrocannabinol in preserved oral fluid by liquid chromatography–tandem mass spectrometry, Journal of Chromatography A 1082(1) (2005) 15-24.
[52] C. Balducci, G. Nervegna, A. Cecinato, Evaluation of principal cannabinoids in airborne particulates, Analytica Chimica Acta 641(1) (2009) 89-94.
[53] E.S. Emídio, V. de Menezes Prata, F.J.M. de Santana, H.S. Dórea, Hollow fiber-based liquid phase microextraction with factorial design optimization and gas chromatography–tandem mass spectrometry for determination of cannabinoids in human hair, Journal of Chromatography B 878(24) (2010) 2175-2183.
[54] J.C. Domínguez-Romero, J.F. García-Reyes, A. Molina-Díaz, Screening and quantitation of multiclass drugs of abuse and pharmaceuticals in hair by fast liquid chromatography electrospray time-of-flight mass spectrometry, Journal of Chromatography B 879(22) (2011) 2034-2042.
[55] F. Hernández, L. Bijlsma, J.V. Sancho, R. Díaz, M. Ibáñez, Rapid wide-scope screening of drugs of abuse, prescription drugs with potential for abuse and their metabolites in influent and effluent urban

wastewater by ultrahigh pressure liquid chromatography–quadrupole-time-of-flight-mass spectrometry, Analytica Chimica Acta 684(1) (2011) 96-106.
[56] A. Hazekamp, A. Peltenburg, R. Verpoorte, C. Giroud, Chromatographic and spectroscopic data of cannabinoids from Cannabis sativa L., Journal of Liquid Chromatography & Related Technologies 28(15) (2005) 2361-2382.
[57] X. Wang, X. Zhou, Z. Ouyang, Direct analysis of nonvolatile chemical compounds on surfaces using a hand-held mass spectrometer with synchronized discharge ionization function, Analytical Chemistry 88(1) (2016) 826-831.
[58] B. De Backer, B. Debrus, P. Lebrun, L. Theunis, N. Dubois, L. Decock, A. Verstraete, P. Hubert, C. Charlier, Innovative development and validation of an HPLC/DAD method for the qualitative and quantitative determination of major cannabinoids in cannabis plant material, Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Science 877(32) (2009) 4115-24.
[59] Recommended methods for the identification and analysis of cannabis and cannabis products, Laboratory and Scientific Section, United Nations Office on Drugs and Crime, Vienna, 2009, pp. 30-32.
[60] C. Citti, D. Braghiroli, M.A. Vandelli, G. Cannazza, Pharmaceutical and biomedical analysis of cannabinoids: A critical review, Journal of pharmaceutical and biomedical analysis 147 (2018) 565-579.
[61] S.N. Tewari, J.D. Sharma, Two dimensional thin-layer chromatography of ganja (Cannabis sativa L.), Bulletin on narcotics 35(1) (1983) 63-67.
[62] A. Leghissa, Z.L. Hildenbrand, F.W. Foss, K.A. Schug, Determination of cannabinoids from a surrogate hops matrix using multiple reaction monitoring gas chromatography with triple quadrupole mass spectrometry, 41(2) (2018) 459-468.
[63] W. Gul, S.W. Gul, M.M. Radwan, A.S. Wanas, Z. Mehmedic, I.I. Khan, M.H. Sharaf, M.A. ElSohly, Determination of 11 cannabinoids in biomass and extracts of different varieties of cannabis using high-performance liquid chromatography, Journal of AOAC International 98(6) (2015) 1523-1528.
[64] T. Van der Linden, P. Silverans, A.G. Verstraete, Comparison between self-report of cannabis use and toxicological detection of THC/THCCOOH in blood and THC in oral fluid in drivers in a roadside survey, Drug Testing and Analysis 6(1-2) (2014) 137-42.
[65] D. Andersen, B. Rasmussen, K. Linnet, Validation of a fully automated robotic setup for preparation of whole blood samples for LC-MS toxicology analysis, Journal of Analytical Toxicology 36(4) (2012) 280-287.
[66] A. Petroczi, E.V. Aidman, I. Hussain, N. Deshmukh, T. Nepusz, M. Uvacsek, M. Toth, J. Barker, D.P. Naughton, Virtue or pretense? Looking behind self-declared innocence in doping, PLoS One 5(5) (2010) e10457.
[67] S. Valiveti, D.C. Hammell, D.C. Earles, A.L. Stinchcomb, LC-MS method for the estimation of Δ^8-THC and 11-nor-Δ^8-THC-9-COOH in plasma, Journal of Pharmaceutical and Biomedical Analysis 38(1) (2005) 112-118.
[68] R. Mechoulam, Marijuana Chemistry, Pharmacology, Metabolism and Clinical Effects, Academic Press, New York, 1973.
[69] R.K. Razdan, The Total Synthesis of Natural Products, Wiley-Interscience, New York, 1981.

Table 1: Stereoisomers of delta-9-THC

Short name	**Full name** **(***have IUPAC name and add the CA index names*	**Alternative names (***add footnotes from man text)which are normally lettered in table but as a largely a text table numbers perhaps better*	**Natural occurrence**	**CAS Registry Number**	**Structure**

(–)-*trans*-Δ^9-THC	***IUPAC name***: (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol ***CA index name***: 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR,10aR)-	6*H*-Dibenzo[*b,d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR-trans*)- Cannabinol, tetrahydro- (6CI) (6*aR*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol (–)-*trans*-Δ^9-THC (–)-*trans*-Δ^9-Tetrahydrocannabino (–)-Δ^9-Tetrahydrocannabinol (–)-Δ^9-*trans*-Tetrahydrocannabinol (6*aR*,10*aR*)-6,6,9-trimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol Abbott 40566 Cannabinoids, THC Dronabinol Marinol NSC 134454 Namisol QCD 84924 SP 104 THC Tetrahydrocannabinol *trans*-(–)-Δ^9-Tetrahydrocannabinol *trans*- Δ^9-Tetrahydrocannabinol Δ^9-THC [4] Δ^9-Tetrahydrocannabinol [4] Δ^9-*trans*-Tetrahydrocannabinol [4] Cannabinol, Δ^1-tetrahydro- (7CI) [4] (–)-3,4-*trans*-Δ^1-Tetrahydrocannabinol [4] (–)-*trans*-Δ^1-Tetrahydrocannabinol [4] (–)-Δ^1-Tetrahydrocannabinol [4] (l)-Δ^1-Tetrahydrocannabinol l-*trans*-Δ^9-Tetrahydrocannabinol l-Δ^1-*trans*-Tetrahydrocannabinol Δ^1-THC Δ^1-Tetrahydrocannabinol	Yes	1972-08-3	 (6a*R*,10a*R*)-

(+)-*trans*-Δ^9-THC	***IUPAC name***: (6aS,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol ***CA index name*:** 6*H*-Dibenzo[*b*,*d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS*,10*aS*)-	6*H*-Dibenzo[*b*,*d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (+)- (8CI)[4] 6*H*-Dibenzo[*b*,*d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aS-*trans*)-[4] (6*aS*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol [4] (+)-*trans*-Δ^9-Tetrahydrocannabinol[4] (+)-Δ^1-Tetrahydrocannabinol[4] (+)-Δ^9-THC[4] (+)-Δ^9-Tetrahydrocannabinol[4] *d*-Δ^9-Tetrahydrocannabinol[4] *trans*-(+)-Δ^9-Tetrahydrocannabinol [4]	No	17766-02-8	 (6a*S*,10a*S*)-
(–)-*cis*-Δ^9-THC	***IUPAC name***: (6aS,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol ***CA index name*:** 6*H*-Dibenzo[*b*,*d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS*, 10*aR*)-	6*H*-Dibenzo[*b*,*d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aS*-*cis*)-[4] (6*aS*,10*aR*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol [4] *cis*-Δ^9-Tetrahydrocannabinol [4]	No	43009-38-7	 (6a*S*,10a*R*)-
(+)-*cis*-Δ^9-THC	***IUPAC name***: (6aR,10aS)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol ***CA index name*:** 6*H*-Dibenzo[*b*,*d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,	6*H*-Dibenzo[*b*,*d*]pyran-1-ol, 6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6*aR*-*cis*)-[4] (6*aR*,10*aS*)-6*a*,7,8,10*a*-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol [4]	No	69855-10-3	 (6a*R*,10a*S*)-

	9-trimethyl-3-pentyl-, (6*aR*, 10*aS*)-				