

Tetrahydrocannabinol Isomerism

DTAB Meeting, December 7, 2021

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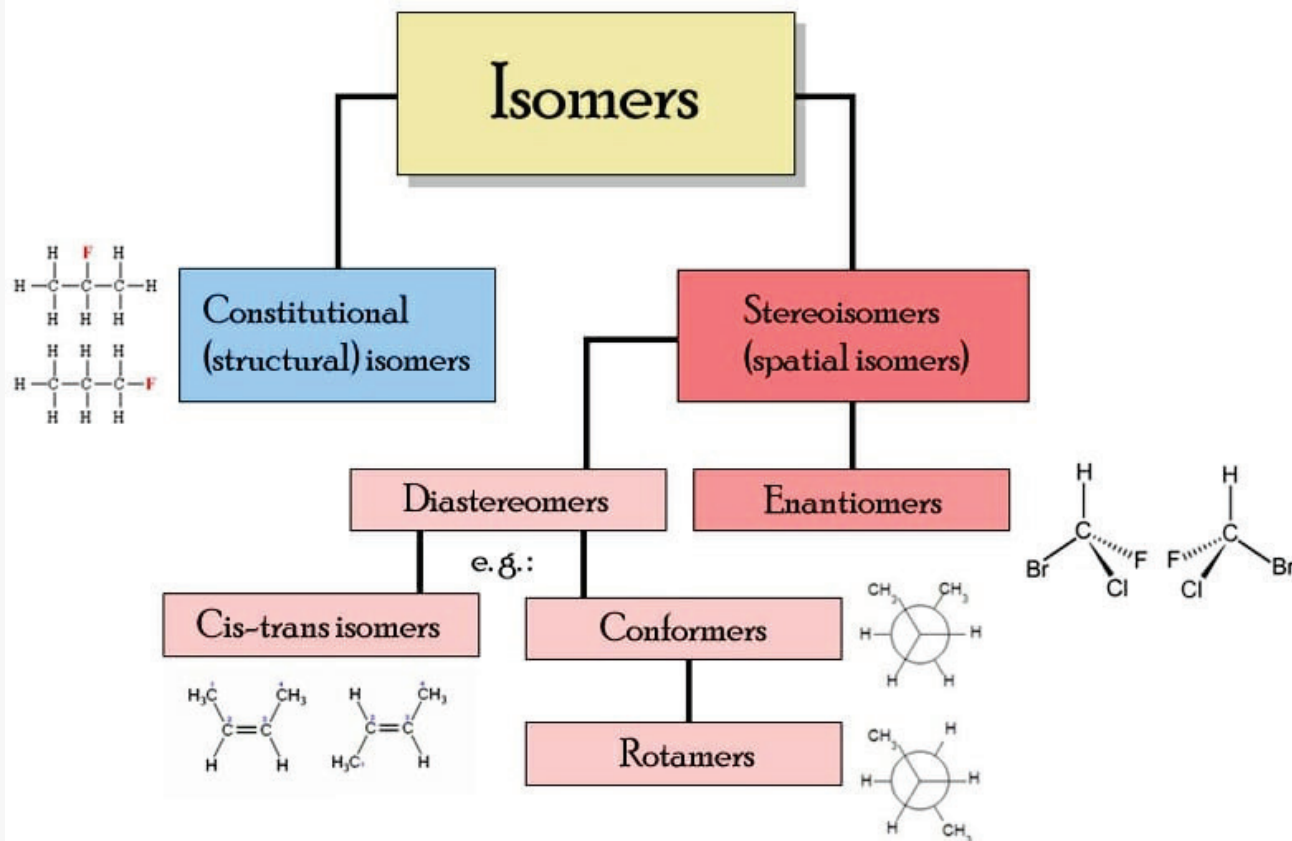
ConeChem Research, LLC &
Johns Hopkins School of Medicine

Outline

- Brief review of isomer nomenclature
- THC numbering systems
- THC isomers
- Conversion of CBD to THC

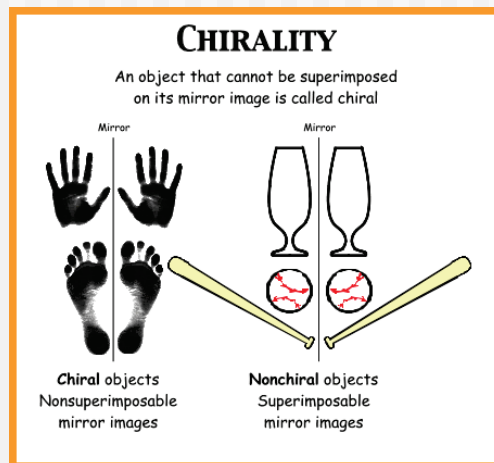
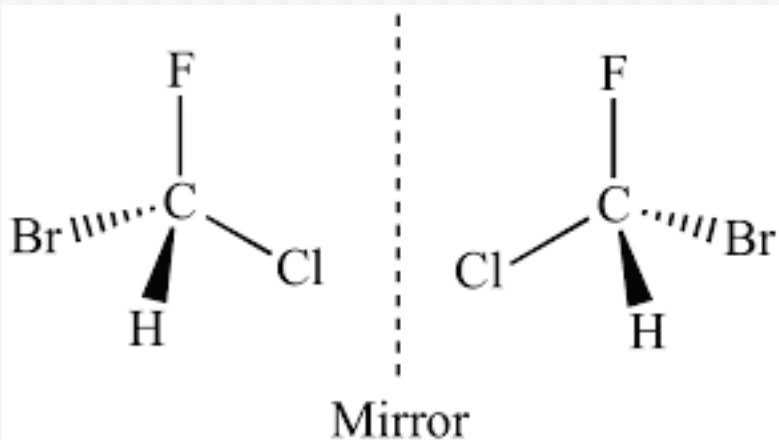
Isomers: Molecules with Same Molecular Formula but Differ Structurally

■ Isomers Come in Many Forms



Chiral Carbon

- A molecule containing a carbon atom with four different groups form a “chiral” molecule
 - Optically active, rotates polarized light (d-, l-)
- A molecule with a single chiral carbon can exist as two mirror images that can't be superimposed



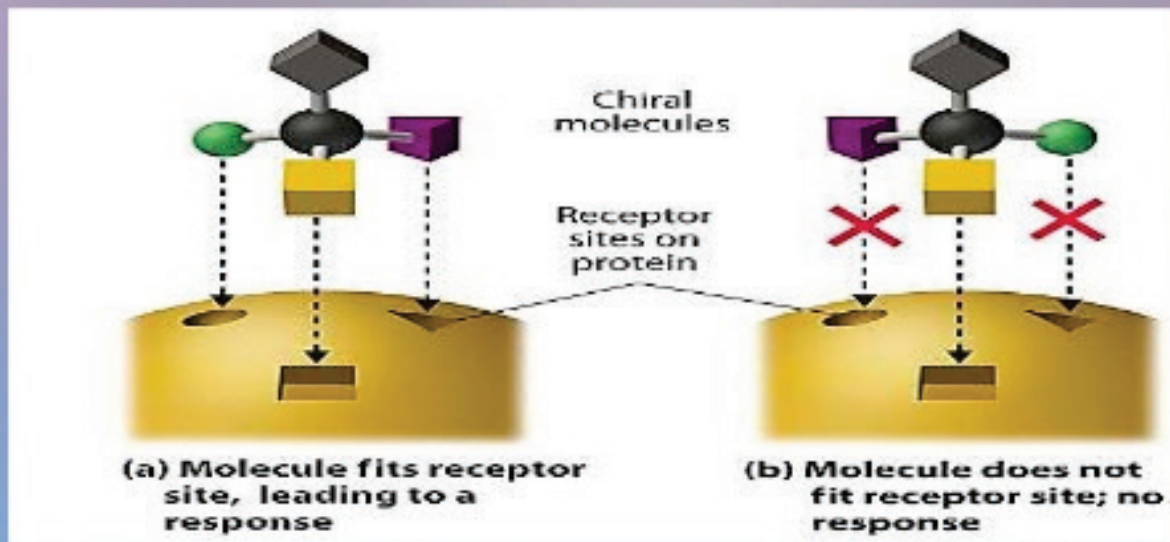
- Enantiomers have identical physical properties

Importance of Chirality

Biological importance-

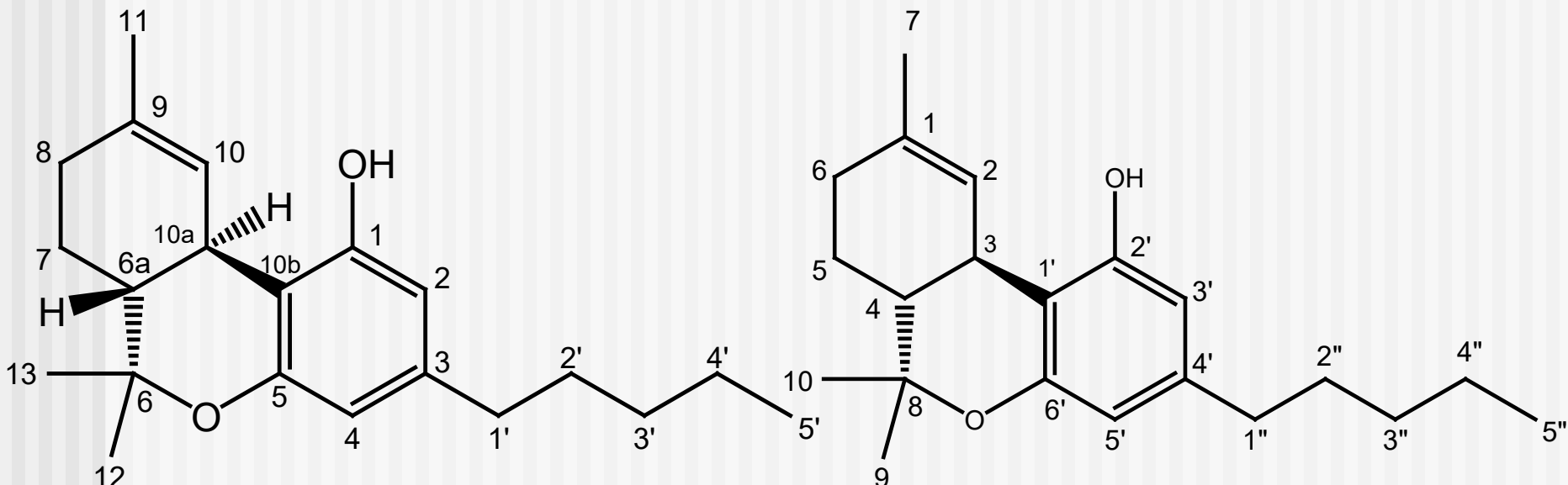
Active Molecule

Inactive Molecule



Tetrahydrocannabinol Numbering System Can Be Confusing

- Current literature generally uses "Dibenzopyran" system
- Older literature used "Monoterpenoid" system



Δ^9 -THC

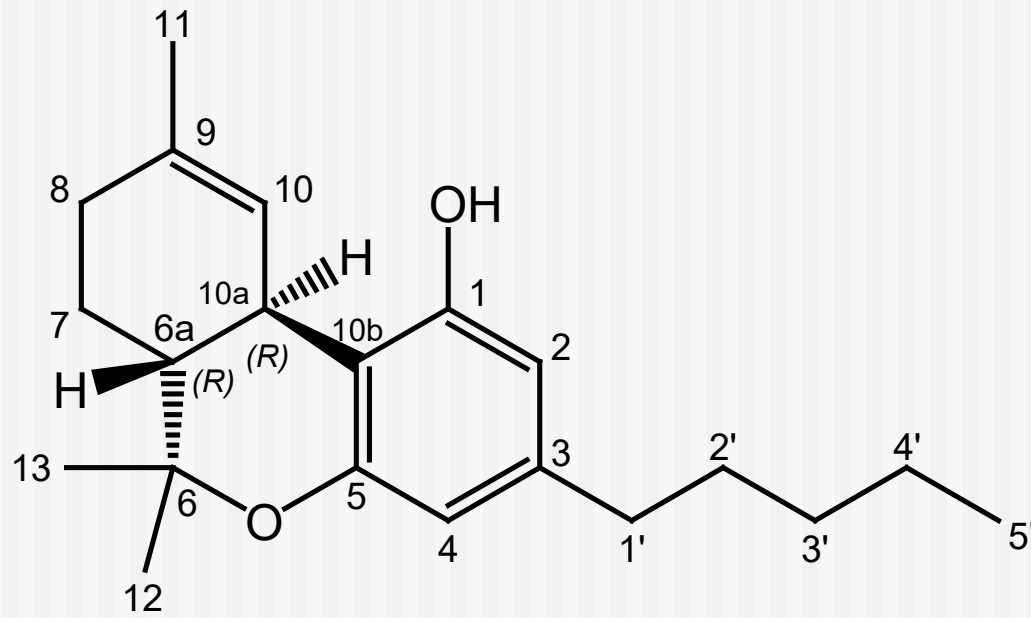
Dibenzopyran System

Δ^1 -THC

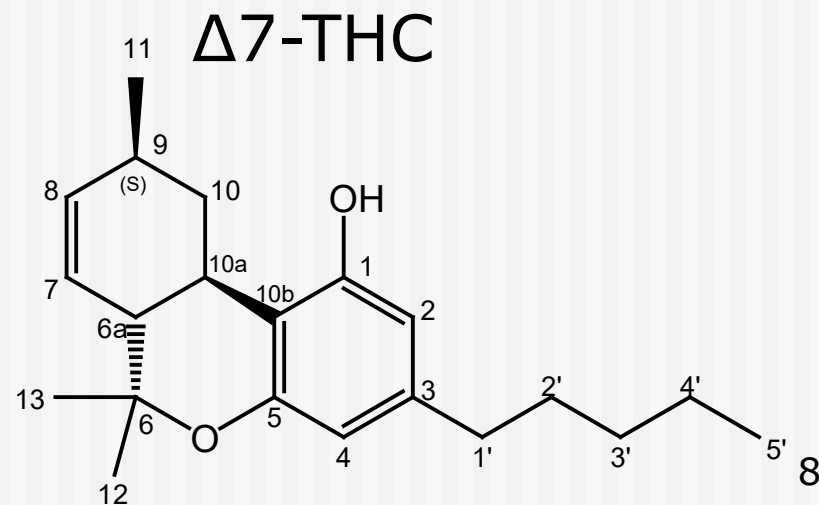
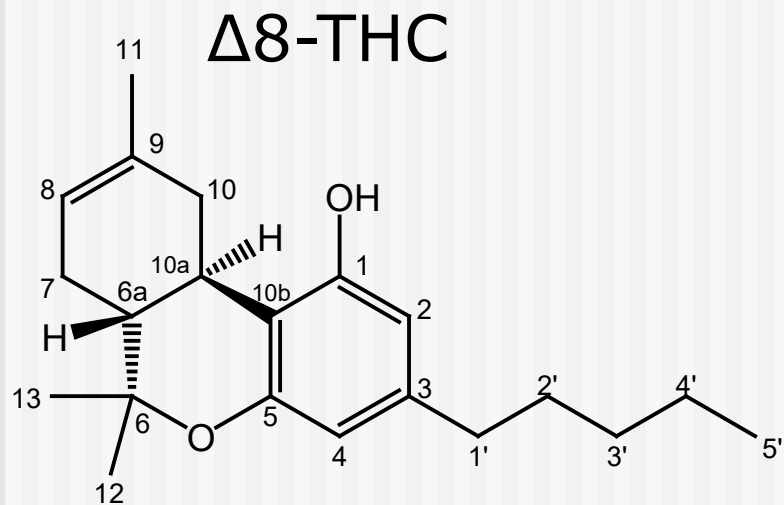
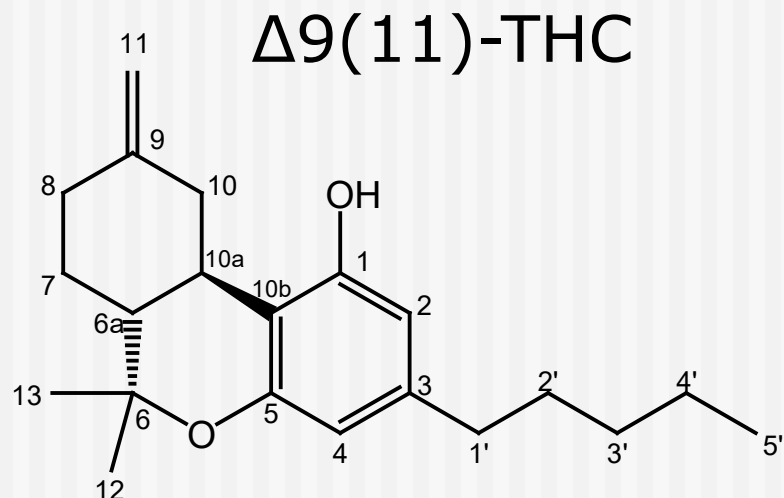
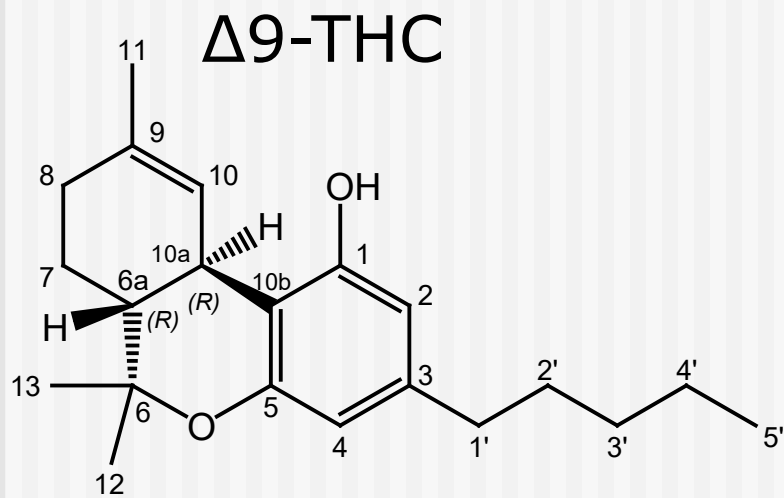
Monoterpenoid System ₆

Tetrahydrocannabinol Isomers

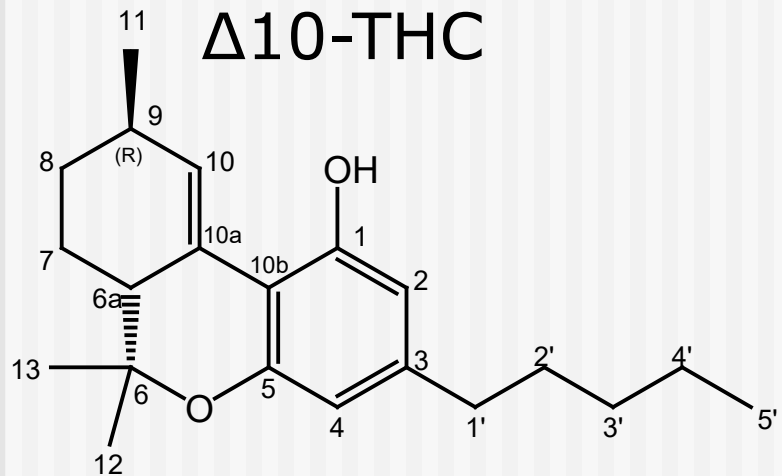
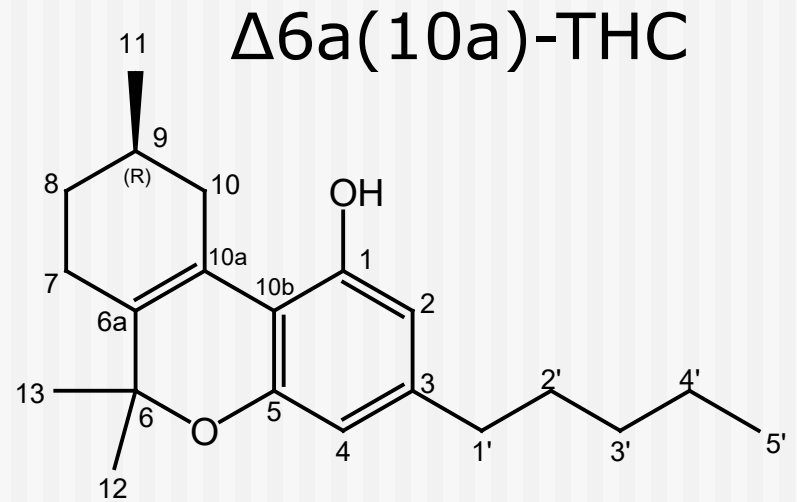
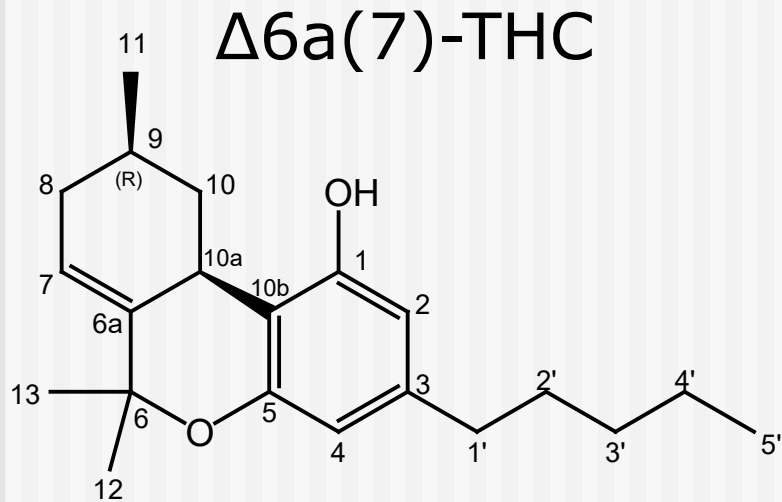
- Δ^9 -THC has a total of 4 stereoisomers at C6a and C10a (cis and trans)
- Seven double-bond isomers (six in addition to Δ^9 -THC)
- Only the R, R form of Δ^9 -THC and Δ^8 -THC at C6a and C10a occur naturally
- Thirty stereoisomers



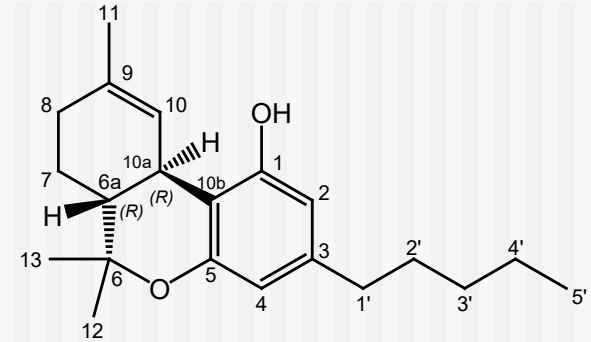
Double-Bond Isomers of THC



Double-Bond Isomers of THC

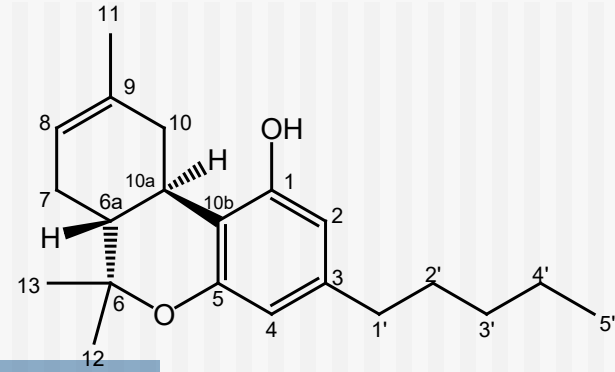


Δ9-THC



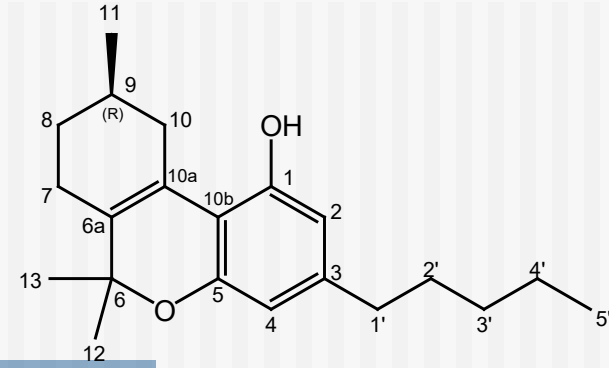
- Δ9-THC is a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
 - The natural active isomer is the R,R-isomer
- R,R-isomer tested extensively in humans

Δ8-THC



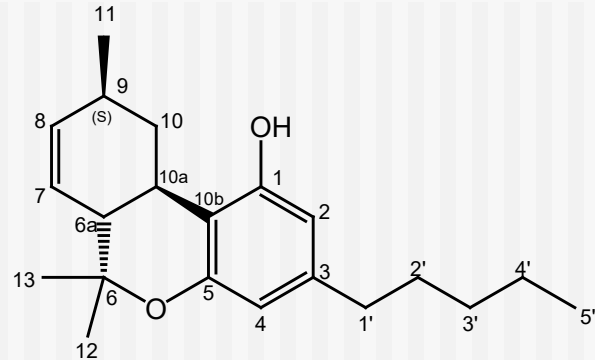
- Δ8-THC is a naturally occurring minor cannabinoid
- Two stereogenic centers; 4 stereoisomers (R/S-isomers)
 - Natural active isomer is R, R-isomer
- Tested in humans by oral and IV route (Hollister et al., 1973, Clin Pharmacol Ther)
 - Δ8-THC produced similar effects as Δ9-THC
 - Was approximately 75% as potent as Δ9-THC
- Tested in humans by smoked route (Karniol & Carlini, 1973, Pharmacol)
 - Δ8-THC produced similar effects as Δ9-THC
 - Was approximately 50% as potent as Δ9-THC

Δ 6a(10a)-THC



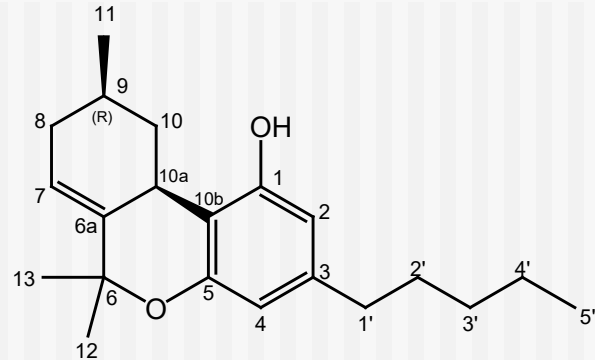
- Δ 6a(10a)-THC is not a naturally occurring cannabinoid
- One stereogenic center; two stereoisomers (R/S-isomers)
- R- and S- Δ 6a(10a)-THC tested in humans by IV route (Hollister et al., 1987, Psychopharmacol)
 - S-isomer produced psychic effects similar to Δ 9-THC and was 1:3 to 1:6 less potent
 - R-isomer was inactive at 8 mg
- Δ 6a(10a)-THC tested in humans by smoked route (Isbell et al., 1967, Psychopharmacologia [Berl.]
 - Inactive
- Can be synthesized by a condensation reaction between olivetol and pulegone

Δ7-THC



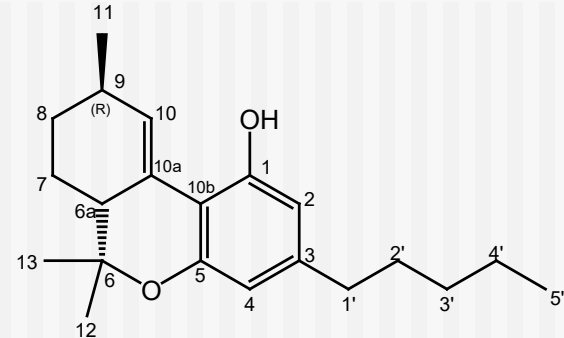
- Δ7-THC is not a naturally occurring cannabinoid
- Three stereogenic centers; eight stereoisomers (R/S-isomers)
- Activity of C9 R/S-epimers (Huffman, et al., Tetrahedron, 1995)
 - Molecular modeling studies predict activity in range of Δ9-THC for the C9S-epimer
 - Cannabinoid receptor binding studies show activity for C9S-epimer ($K_i=71.5\text{nM}$) compared to Δ9-THC ($K_i=41\text{nM}$). C9R was less active ($K_i=304\text{nM}$)
- Can be synthesized by condensation of olivetol with p-menth-4-en-3,8-diol in toluene-p-sulphonic acid (WHO, 2018)

$\Delta 6a(7)$ -THC



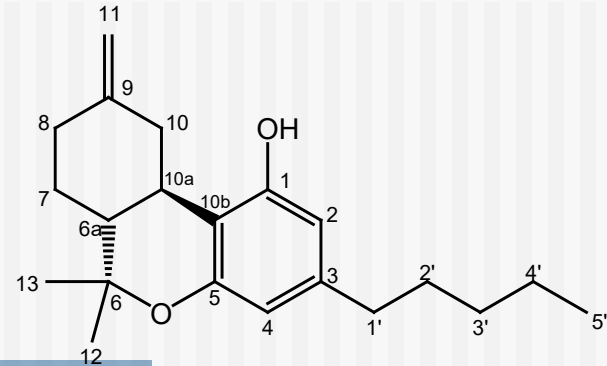
- $\Delta 6a(7)$ -THC is not a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
- Arnone et al. reported synthesis in 1975 (Tetrahedron, 31, 3093-3096) but did not test for biological activity
- Can be synthesized by condensation of olivetol with p-menth-4-en-3,8-diol in toluene-p-sulphonic acid (WHO, 2018)

Δ 10-THC



- Δ 10-THC is not a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
- Did not produce Δ 9-THC-like effects in pigeons (Jarbe et al., Eur. J. Pharmacol. 1988)
- Can be synthesized by base catalyzed isomerization of Δ 9-THC (Srebnik, et al. 1984, J Chem Soc Perkin Trans)

$\Delta^9(11)$ -THC



- $\Delta^9(11)$ -THC is not a naturally occurring cannabinoid
- Two stereogenic centers; four stereoisomers (R/S-isomers)
- $\Delta^9(11)$ -THC produces Δ^9 -THC-like effects in mice (iv)¹, rhesus monkeys (im)^{2,3}, and rats (ip).^{2,4} Can be synthesized by addition of HCl followed by a dichlorination procedure

¹Compton, D. R., Prescott, W. R., Jr., Martin, B. R., Siegel, C., Gordon, P. M., and Razdan, R. K. (1991) Synthesis and pharmacological evaluation of ether and related analogues of delta 8-, delta 9-, and delta 9,11-tetrahydrocannabinol. *J Med Chem* **34**, 3310-3316

²Wiley, J. L., Barrett, R. L., Britt, D. T., Balster, R. L., and Martin, B. R. (1993) Discriminative stimulus effects of delta-9-tetrahydrocannabinol and delta-9-11-tetrahydrocannabinol in rats and rhesus monkeys. *Neuropharmacology* **32(4)**, 359-363

³Wiley, J. L., Huffman, J. W., Balster, R. L., and Martin, B. R. (1995) Pharmacological specificity of the discriminative stimulus effects of delta 9-tetrahydrocannabinol in rhesus monkeys. *Drug Alcohol Depend* **40**, 81-86

⁴Järbe TU, Henriksson BG. Discriminative response control produced with hashish, tetrahydrocannabinols (delta 8-THC and delta 9-THC), and other drugs. *Psychopharmacologia*. 1974;40(1):1-16.

Number of Stereoisomers of THC

Isomer	# Optical Centers	# Stereoisomers
Δ 9-THC	2	4
Δ 10-THC	2	4
Δ 6a(10a)-THC	1	2
Δ 6a(7)-THC	2	4
Δ 7-THC	3	8
Δ 8-THC	2	4
Δ 9(11)-THC	2	4

Tabulation of Human Potencies of Cannabinoids

Cannabinoid	%Potency (Relative to Δ 9-THC)	Reference
Δ 9-THC	100	(1)
Δ 10-THC	Not Tested	
Δ 6a(10a)-THC	30, 0	(1,2)
Δ 6a(7)-THC	Not Tested	
Δ 7-THC	Not Tested	
Δ 8-THC	75, 50	(1,3)
Δ 9(11)-THC	Not Tested	
11-OH- Δ 9-THC	120	(1)
11-OH- Δ 8-THC	90	(1)
8-Alpha-OH- Δ 9-THC	25	(1)
8-Beta-OH- Δ 9-THC	20	(1)
Parahexyl (Synhexyl)	30	(1)
Δ 9-THCV	25	(1)
CBD	0	(1)
CBN	0	(1)

- Hollister, L. E. (1974) Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta9-tetrahydrocannabinol. *Pharmacology* **11**, 3-11
- Isbell, H., Gorodetzky, C. W., Jasinski, D., Claussen, U., Spulak, F. V., and Korte, F. (1967) Effects of (-)delta-9-trans-tetrahydrocannabinol in man. *Psychopharmacologia* **11**, 184-188
- Karniol, I. G., and Carlini, E. A. (1973) Comparative studies in man and in laboratory animals on 8 - and 9 -trans-tetrahydrocannabinol. *Pharmacology* **9**, 115-126

WHO Expert Committee on Drug Dependence, 40th Report, 2018

- The WHO Technical Report Series makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects.
- After reviewing the chemistry, pharmacology and toxicology of the seven isomers of THC, the committee concluded that
 - *"aside from Δ -9THC, there is no evidence that any of these listed isomers are being abused or are likely to be abused so as to constitute a public health or social problem."*

(WHO Expert Committee on Drug Dependence, fortieth report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1013). License: CC BY-NC-SA 3.0 IGO.)

C&EN Concerns About Safety and Purity of $\Delta 8$ -THC

- C&EN article (August 30, 2021) warns that $\Delta 8$ -THC products are not safe or pure

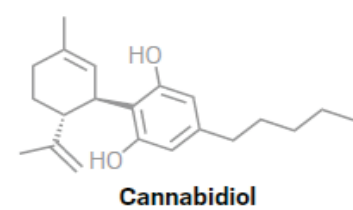
"The conversion of CBD into $\Delta 8$ -THC also produces small amounts of $\Delta 9$ -THC and $\Delta 10$ -THC"

unidentified compounds in products labeled as delta-8-THC.

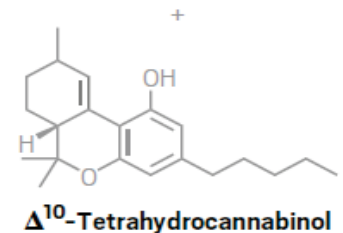
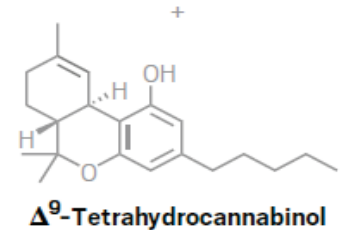
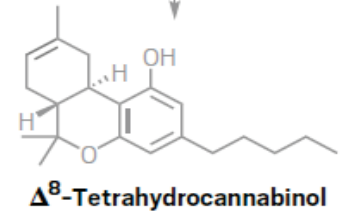
Safety concerns skyrocket

"My concern is that we have no idea what these products are," says Christopher Hudalla, president and chief scientific officer of ProVerde Laboratories, an analytical testing firm with facilities in Massachusetts and Maine. "Consumers are being used as guinea pigs. To me, that's horrific," he says.

Using chromatographic methods with ultraviolet or mass spectrometry detection, scientists at ProVerde have tested thousands of products labeled delta-8-THC. "So far, I have not seen one that I would consider a legitimate delta-8-THC product," Hudalla says. "There's some delta-8 in there, but there's very frequently up to 30 [chromatographic] peaks that I can't identify." There are often also peaks that correlate with delta-9-THC as well as another isomer, delta-10-THC, he notes. Little is known about the effects of delta-10-THC, but users have anecdotally reported feeling euphoric and more focused after consuming it.



Acid catalyst, solvent, heat



The conversion of cannabidiol into delta-8-tetrahydrocannabinol (delta-8-THC) also produces small amounts of delta-9-THC and delta-10-THC.

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Δ8-THC is Being Sold as a Legal Product

Delta 8 THC: Legal or Not

by [Bruce Hovland](#) in [CBD News August 3, 2020](#)

Delta-8 THC: Legal or Not

Backed by many scientific studies along with anecdotal proof, **Delta 8 THC** is enjoying the spotlight for being an amazing ingredient for medicinal and therapeutic benefits. The product is available in numerous forms, including [Delta 8 THC vape cartridges](#), [gummies](#), [oral tinctures](#), and even restaurant delicacies.

However, most people are still confused regarding the **legal status of Delta 8 THC**. So, the question is, **is Delta 8 THC legal?**

Is hemp illegal in the US

The short answer to the question is that a substance that matches the definition of "hemp" is legal under the federal controlled substances laws. Delta 8 THC is measured federally legal if it is extracted from hemp containing below 0.3% delta-9-THC, [according to the Agriculture Improvement Act of 2018](#).

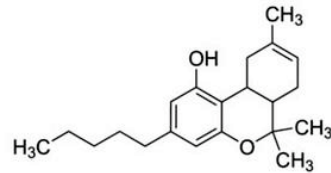
So, the answer is, YES, if it is [hemp-derived Delta 8](#).

However, **Delta 8 legal** status can vary state to state as each state has its individual regulations regarding the hemp plant.



D8 Fruit Slice 75mg each
“Max Strength” 5 per bag. 30
Bags FREE SHIPPING:
\$489.99





Delta 8 Tetrahydrocannabinol



Internet Article by Justin Cooke

“What is Delta 10 THC?”

<https://dailycbd.com/en/delta-10-thc/> Accessed 5/12/21

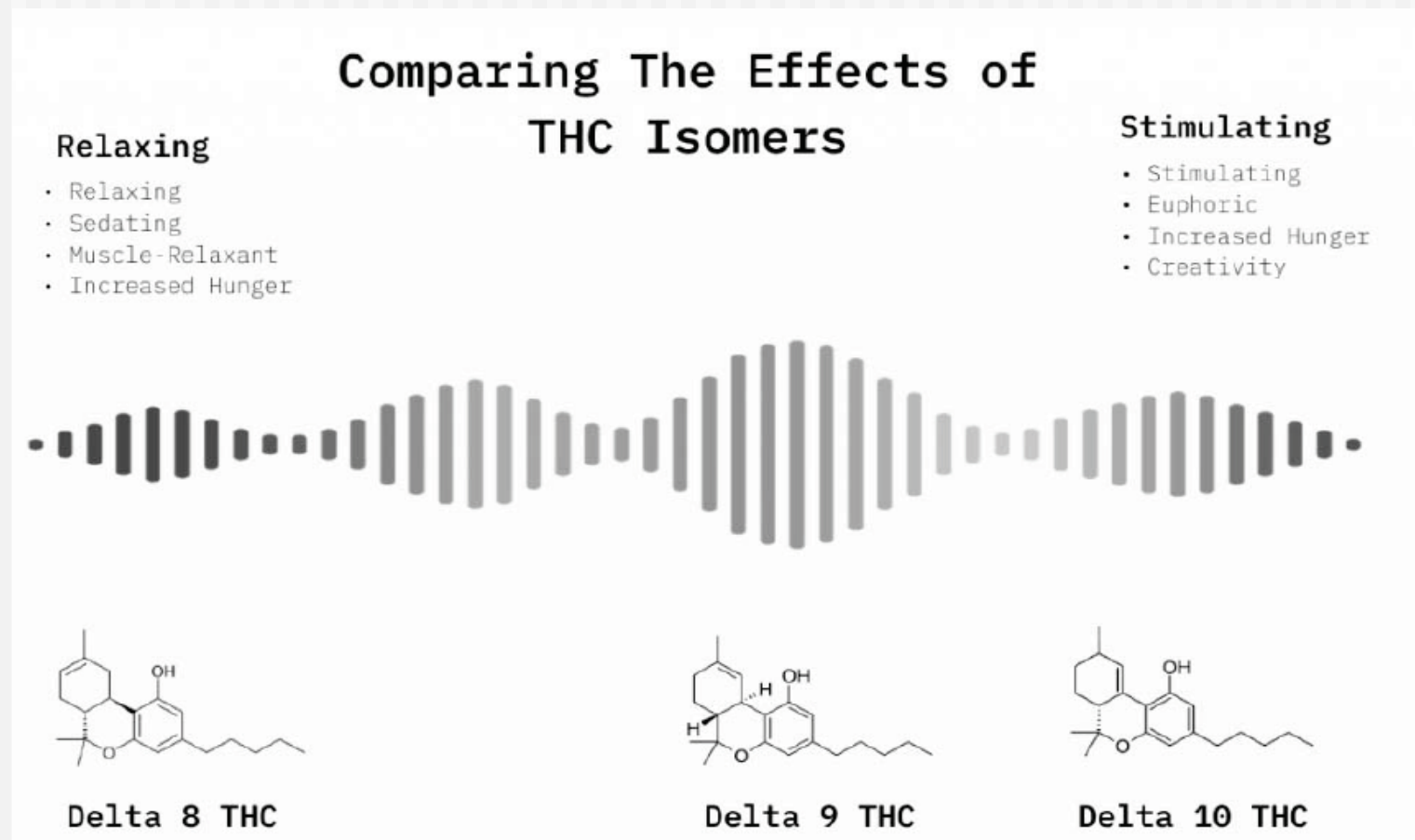
- Characteristics of Delta 10 THC
 - Δ 10 is roughly half as potent as Δ 9 THC
 - Δ 10 is more stimulating & nootropic
 - Δ 10 is better than Δ 9 for promoting flow states, creativity, euphoria, & focus
 - Δ 10 appears to have less side effects than Δ 9
- *“These effects are likely going to make delta 10 THC a staple in the cannabis industry over the next couple of years.”*

Internet Article by Justin Cooke

“What is Delta 10 THC”

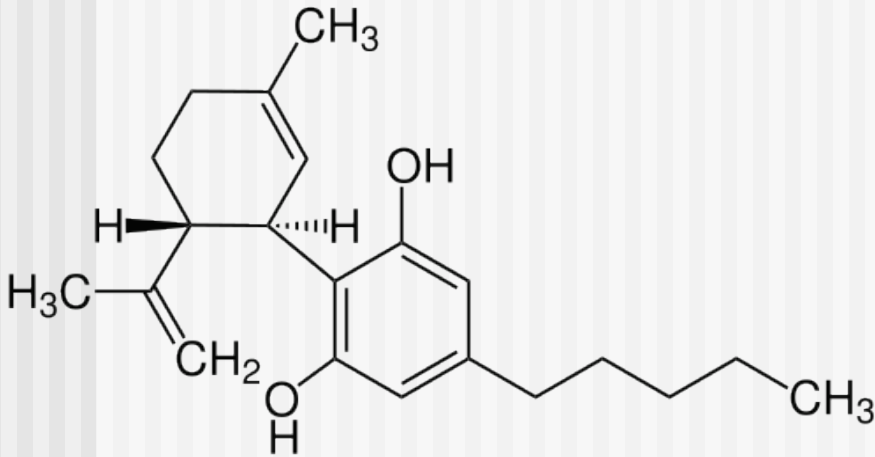
<https://dailycbd.com/en/delta-10-thc/> Accessed 5/12/21

“Delta 8, 9, and 10 THC are essentially different flavors of the THC molecule.”

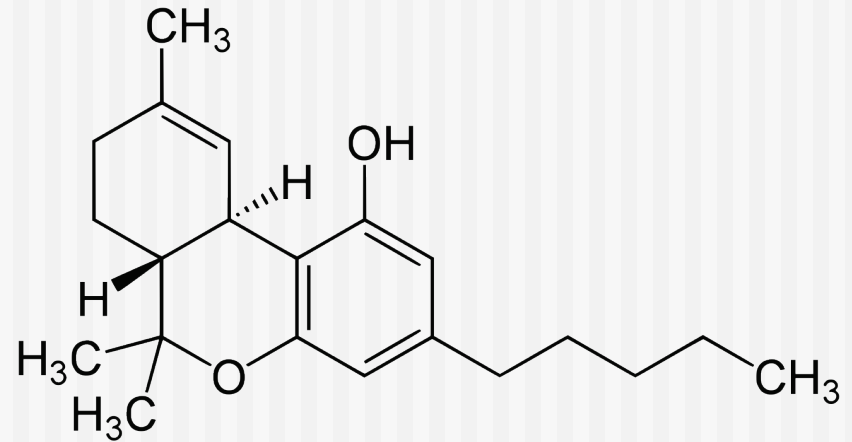
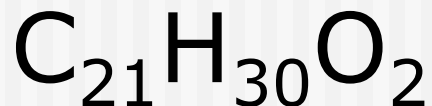


CBD is a Structural Isomer of $\Delta 9$ -THC

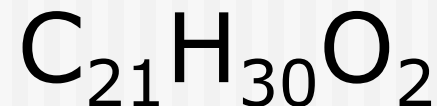
- Same molecular formula
- Same stereochemical configuration



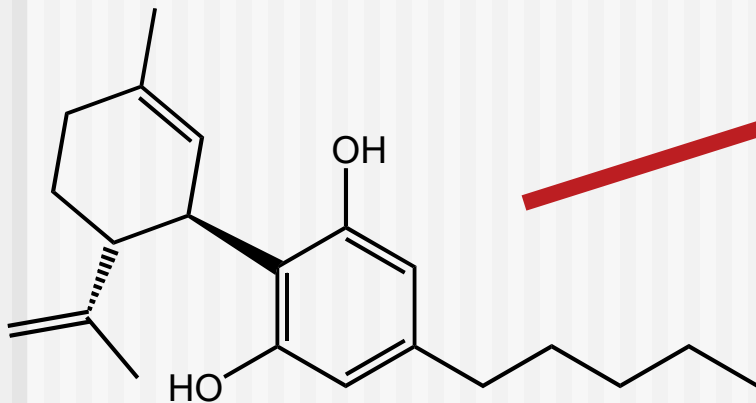
CBD



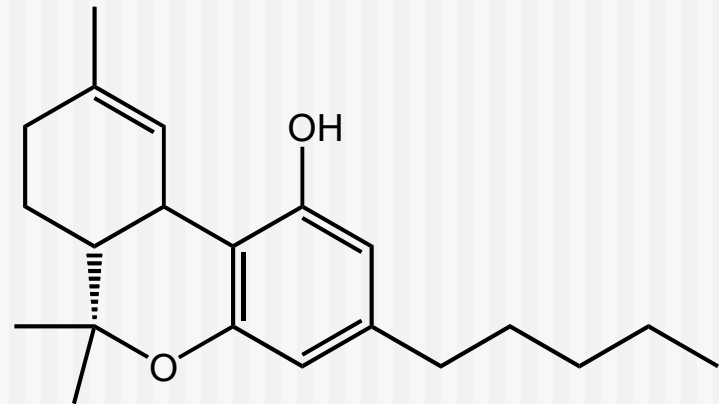
$\Delta 9$ -THC



CBD Conversion to THC



CBD



Δ^9 -THC



Δ^8 -THC

Conditions for CBD Conversion to THC

- Feasible under acidic conditions
 - Formation of $\Delta 8$ - or $\Delta 9$ -THC can be in low or high yield in the presence of acid (Golombek, et al. 2020, Toxics)
 - Assay artifact during derivatization with acidic derivatives (Andrews & Paterson, 2012, JAT)
 - Incubation with simulated gastric fluid (Merrick et al., 2016, Cannabis and Cannabinoid Research; Watanabe et al., 2007, Forensic Toxicol)
 - Possibly, when CBD is stored under acidic conditions (Golombek, et al. 2020, Toxics)
- Pyrolysis of CBD at e-cigarette (250-400°C) and higher temperature (500°C) produced $\Delta 9$ - and $\Delta 8$ -THC (Czegeny et al. 2021, Scientific Reports)
- Recent studies of low temperature vaping and oral ingestion found no conversion (Spindle et al. 2019, JAT)

Take Home Message

- Keep your eyes and minds open for the potential appearance of more cannabinoid isomers!

