From CBD gummies to gray-market highs: exploring the chemistry of semi-synthetic cannabinoids.

Inspired by: Ujváry I. Hexahydrocannabinol and closely related semi-synthetic cannabinoids: A comprehensive review. *Drug Test Anal*. 2024; 16(2): 127-161. doi:10.1002/dta.3519

Introduction

Figure 1. Gas station hemp products

Cannabis sativa is one of humanity's oldest plant companions—cultivated long before the wheel, fermented drink, or even written history. Across millennia, people have turned this plant into rope, medicine, incense, and food, shaping it through selective breeding just as it shaped them in turn. Modern society is no different – we've simply traded the stone mortars of alchemists for chemistry labs (of nerds). Advances in biochemistry and cultural acceptance have opened the door to an explosion of new cannabis-derived products that our forefathers could not have imagined to be possible; at the same time, decades of criminalization left a thriving gray and black market, where producers push right up to the edge of regulation—and often past it.

Figure 2. HHC cartridge, with a very ironic name

In the US, cannabis is legal for recreational use in 24 states, and for medical use in 40; the remaining 10 states have limits on the amount of THC, allowing only CBD products. It is illegal at the federal level, which creates a plethora of legal nuances even in states with full legalization. However, even in the states without legalization, gas stations and smoke shops often sell "hemp-derived" products that many customers reasonably assume are intoxicating.

But what's actually in them? How strong are they? What risks come with buying chemically tweaked cannabinoids that sit in a loophole rather than on a label?

A chemistry student weighs in.

History

The history of *Cannabis sativa* L., or hemp, usage by humans is fascinatingly long, dating back up to 10,000 years according to some estimates. Archaeological evidence suggests that the plant was first cultivated for its use as a fiber in ropes, beginning between 8000 and 3000 BC in various regions of east Asia, with ritual and recreational use beginning in the early antiquity: cannabis residue has even been found on two altars dating back to the Kingdom of Judah, and our first accounts of recreational use of the plant, in the form of smoking, come from Ancient Greek historians describing the Scythians. Medical applications emerged just as early, with medical uses being documented throughout most of the ancient world; by the medieval period, many Islamic physicians made use of the plant's known diuretic, antiemetic, antiepileptic, anti-inflammatory, analgesic and antipyretic effects. The first restrictions on cannabis, naturally, date back to the Islamic world of 14th century AD.

Figure 3. Holy of holies of the Tel Arad Temple: two altars found to have cannabis residue

The plant was only introduced to Europe in the 19th century, where it quickly gained a modicum of popularity among physicians and intellectuals. Of course, following the introduction of cannabis to Europe, criminalization followed suit along racial and class lines. By 1925 the import of cannabis was restricted to serve only medical and scientific uses, while the 1961 Convention of Narcotic Drugs declared cannabis a Schedule IV substance, the highest schedule a drug could receive; the designation was only removed from the treaty in 2020.

Where does that leave us today? As is readily apparent, the years of criminalization did not eliminate the use of cannabis. In fact, advances in synthetic chemistry and biochemistry,

combined with increasing social acceptance set against the backdrop of lagging legislation, led to the "Spice phenomenon" of the first decade of the 21st century. The first synthetic cannabinoids (SCs), commonly known as "Spice" or "K2", were introduced to the market in 2008, when their popularity skyrocketed due to low price, potency, and legal ambiguity; by 2021, 330 novel SCs have been reported by 84 countries to the UNODC Early Warning Advisory committee, dominating the new psychoactive substances (NPS) lists globally.

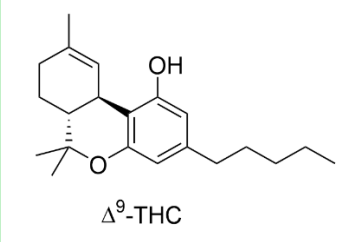
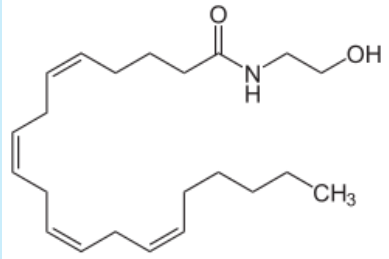
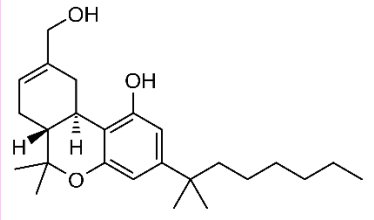
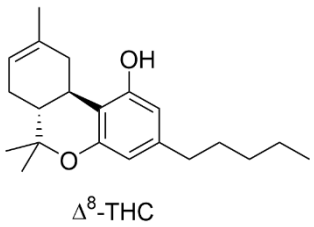
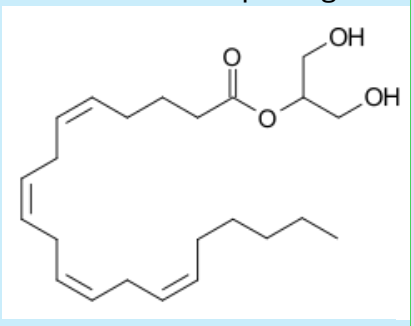
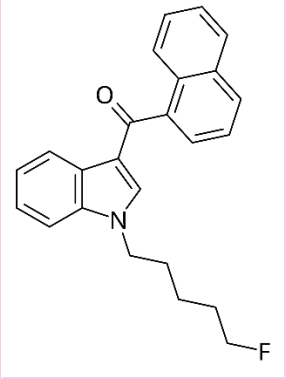
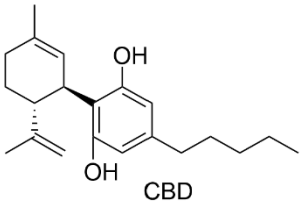
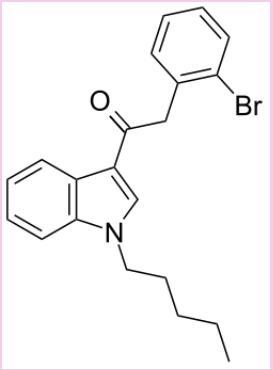
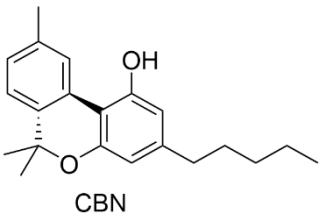
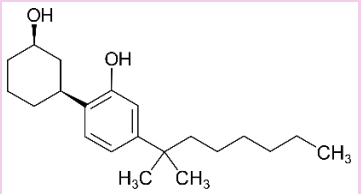
By mid-2021, a new player had entered the market in the US: semi-synthetic cannabinoids. These compounds are prepared from hemp extracts of cannabidiol (CBD) via simple chemical transformations. Though CBD products have been proliferating in the US and globally for several years prior to this, largely due to the 2018 Farm Bill which restarted industrial cultivation of "low-THC" cannabis in the US, its transformation from a "product" into a "precursor" is worth a closer look, particularly given all that we learned from the social consequences of criminalization, legalization, and the medical consequences of Spice.

A foreword on terminology: genealogy of cannabinoids

Early scientific research into cannabinoids was pioneered by William B. O'Shaughnessy, an Irish physician, in the 19th century; it was only a century later, in the 1960s, that the exact structure of CBD and the main psychoactive component, Δ^9-tetrahydrocannabinol (Δ^9-THC), were elucidated. Note that the term cannabinoid includes in itself several *structural* classes of compounds found in the cannabis plant: to date, over 290 different cannabinoids have been isolated from cannabis plants, though many of those may be artifacts of chemical processing. The plant itself contains around 500 different compounds, as could be expected for a living organism which needs its biosynthetic products for survival.

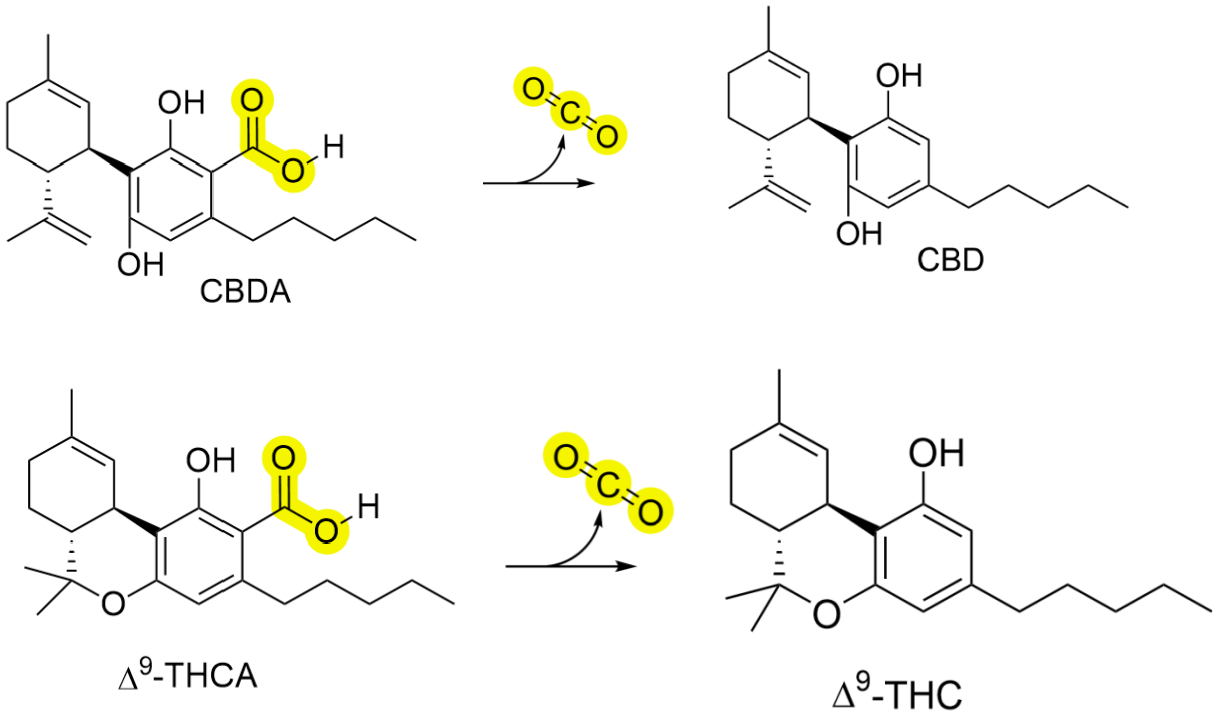
Cannabinoids exert their primary effect via binding receptors of the human endocannabinoid system – to a first order approximation, this can be considered like a lock & key, where the 'key' can still unlock the 'lock' even if it's not the exact ideal fit [1]. The category of cannabinoids is then generally split into phytocannabinoids (i.e. derived from plants), endocannabinoids (neurotransmitters of our internal cannabinoid system), and synthetic cannabinoids (self-explanatory), seen below.

I know, I hate vocab too.

Phytocannabinoids	Endocannabinoids	Synthetic Cannabinoids
Found from plants	**Neurotransmitters** of our internal (endogenous) **cannabinoid system**	**Synthetic designer molecules**
Bind cannabinoid receptors	**Bind cannabinoid receptors**	**Bind cannabinoid receptors**
 **Δ⁹-THC:** Main psychoactive compound of cannabis	 **Anandamide**: endogenous cannabinoid receptor ligand	 **HU-210** [Hebrew University]
 **Δ⁸-THC :** Structural isomer of THC	 **2-Arachidonoylglycerol** (2-AG): CB_1 agonist, CB_2 ligand	 **AM-2201** [Alexandros Makriyannis]
 **CBD:** Precursor to THC; non-psychotropic		 **JWH-249** [John F. Huffman]
 **CBN:** Oxidation/breakdown product of THC		 **CP-47,497** [Charles Pfizer]

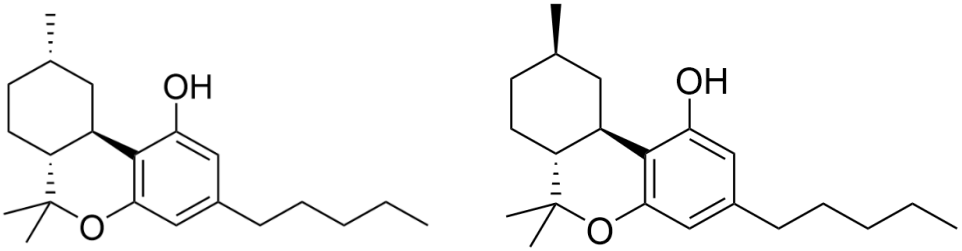
A brief library of synthetic cannabinoids, or SCs or Spice, can be seen above, in the same chart on the right-hand side. These compounds are frequently named for the scientist that discovered them, and most differ significantly from natural cannabinoids in their structure; these cannabinoids are known to be *extremely* potent, many more than 50x as potent as THC. They are specific agonists (i.e. binders or activators) of the cannabinoid receptors, hence their potency, but they also may have off-target effects; a number of hospitalizations and deaths have been reported due to these compounds all around the world. Seizures, strokes, acute kidney and cardiac injury, and hypokalemia [low Ca^{2+} levels, wherein Ca^{2+} is a vitally important secondary-messenger in humans] are well known potential adverse effects of these compounds.

Compounds such as THCA and CBDA, which can also be found in smoke shops around the country, are two major natural products of cannabis, and are the precursors to THC and CBD respectively [2]: the only structural difference between the forms is an acetyl group (highlighted below), which is easily removed as needed. Both acid forms break down with heat and make up about 95% of the THC and CBD content in fresh plant matter.



The flowering tips of the are rich in two compounds also worth mentioning, Δ^8-THC and CBN. Δ^8-THC is the more stable isomer of Δ^9-THC, the only difference being the position of the double bond and was among the first semi-synthetics commercialized. CBN is beyond the scope of this discussion, though suffices to say that it is an end product of cannabinoid metabolism [specifically Δ^9-THC oxidation] and is an interesting cannabinoid in its own right.

Semi-synthetics are compounds derived from chemical reactions on natural, non-psychoactive phytocannabinoids, making them different in a variety of ways from the SCs, which are better characterized now for lack of better terminology. Hexahydrocannabinols (HHCs) specifically are derivatives of CBD, of which two epimers exist. For the purposes of this, please just consider epimers as a specific type of stereoisomers, or molecules which only differ in their spatial orientation and not connectivity. They result from a hydrogenation reaction which occurs either on the front face, to form the α-epimer, or on the backside, to form the β-epimer [3]. The structures are below.



9α-HHC 9β-HHC

Given the high degree of similarity between HHC and THC, it would surprise no one that the hexahydrobenzochromene scaffold also appears in various SCs, such as HU-210 above, and moreover (and more interestingly to professionals) is common in a variety of natural products [4].

The Chemistry: Making HHC from Hemp

There are two main approaches to making HHC: one processes CBD, and the other, of course, is full small molecule synthesis, which gives more stereochemical control. For the sake of simplicity and relevance, we will only consider one fully synthetic reaction and otherwise focus on what chemical transformations can be performed with the precursors.

A note on interpreting mechanisms: in all organic mechanisms, the arrows represent the flow of electrons. The "backbone" sticks are carbons with hydrogens attached, whether or not the hydrogens are shown. The hydrogens are expanded out and shown whenever relevant. Key reaction areas are highlighted, with shades of blue used to signify high electron density, and red for higher proton density, as protons are positively charged – hence why our protons are red, bases blue, and nucleophiles a lighter blue. All of the animations below are meant to serve as visual aids, do not necessarily represent exact reaction intermediates, reaction steps, nor imply sequentiality; some of the 'steps' may occur simultaneously.

Part 1: CBD → THC (Cyclization)

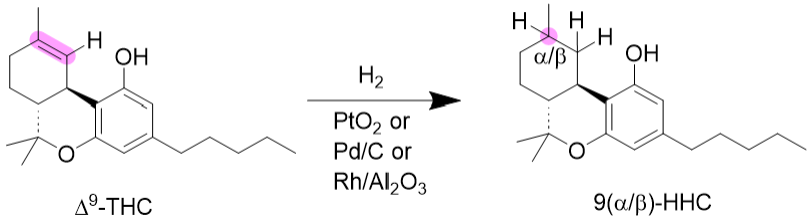
CBD readily cyclizes into THC even under mildly acidic conditions. In this cyclization reaction both isomers of THC are formed (remember that they only differ in their placements of 1 double bond), along with a number of byproducts; the greater thermodynamic stability of Δ^8-THC slightly favors its formation, since all matter tends toward its energetic minima, but various reaction conditions can favor the Δ^9-THC isomer, including the use of only a mild acid [5]. Note that these conditions imply that CBD could hypothetically convert to THC inside the human body, particularly in the stomach with its exceedingly low pH, which is a transformation that has been observed in the lab but not in any clinical setting. To that end, we can temporarily conclude that this conversion is unlikely to take place under normal conditions inside the body.

Cartridge designs featuring solid catalysts for the cyclization of CBD to THC have recently been patented, posing interesting design and legal issues, but any further discussion is beyond the scope of this project.

Cyclization_Animation

Part 2: THC → HHC (Hydrogenation)

Pd/C, PtO_2, and Rh/Al_2O_3 catalysts have all been regularly used to reduce the double bond to a single bond via hydrogenation, or hydrogen addition, in a variety of common solvents. This produces a mixture of isomers since both sides of the ring are relatively accessible, and irrespective of whether the Δ^8-THC or Δ^9-THC isomer is reduced. The exact ratio of product isomers favored depends highly on the exact reaction conditions and starting materials. For instance, platinum hydrogenation [PtO_2] of Δ^9-THC results in a 1:2 ratio of the α/ β-epimers, while using Δ^8-THC results in a 3:1-2 ratio of α/β epimers. More reaction conditions can be found in the main reference.



Δ^9-THC 9(α/β)-HHC

Part 3: Other routes: leveraging intramolecular DA for enantiomer specificity

This reaction is catalyzed by a Lewis Acid and is the most elegant enantiomer-specific synthetic route to date [6]. Both isomers have been synthesized at high purities and yields

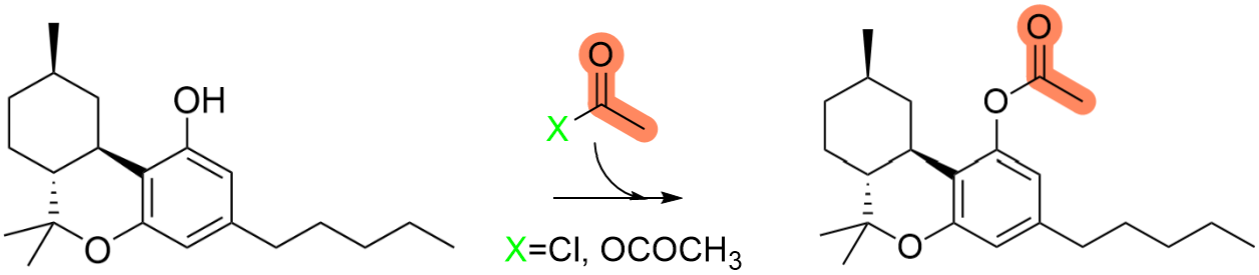
via this method, and the isomer identity only depends on the stereochemistry (or exact spatial orientation) of the starting materials.

Synthesis_Animation

Close-Up_Animation

Part 4: HCC-O

HHC-O is the acetate of HCC, which can be formed by acyl-addition with acetic anhydride or acetyl chloride. Although no pharmacological data on its action exists yet, reasoning from what we know about the acetate forms of Δ^8-THC and Δ^9-THC suggests that the potency of HHC-O would be less than that of HHC, and less than that of either form of THC; additionally, the acetate forms appear to have a later onset and longer duration, suggesting that the body may have to metabolize it a bit before the drug can take effect on the receptors.



9β-HHC 9β-HHC-O

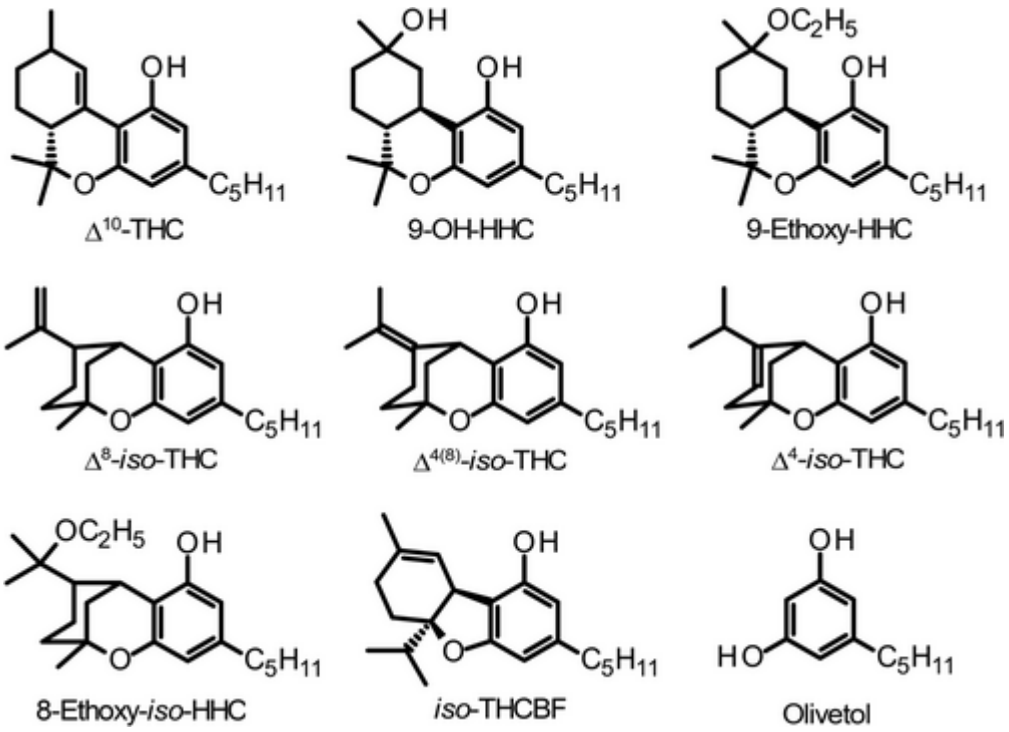
Known acetates of THC:

Δ^9-THC-O Δ^8-THC-O

The relative potency could be estimated to be Δ^9-THC > Δ^8-THC > Δ^9-THC-O ≈ Δ^8-THC-O > 9β-HHC > 9α-HHC > 9β-HHC-O > 9α-HHC-O, listed in order of decreasing potency.

Byproducts/Impurities:

Byproducts and impurities are a given in any chemical transformation, and semi-synthetic cannabinoids are no exception. Below is a figure of common byproducts of the CBD → THC transformation, as was given in the paper that inspired this work. Contamination by remaining solvents, catalysts, and unreacted starting materials are also common issues of any chemical synthesis.



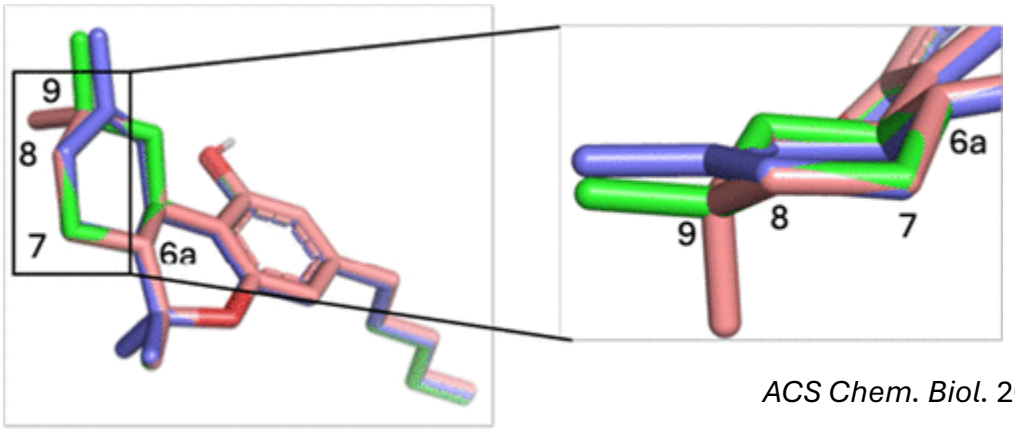
The lack of regulation only intensifies the issue of product purity. For instance, a recent chemical analysis of an "HHC" product in the US indicated no HHC and was instead comprised of a mixture of Δ^8 -THC, Δ^9 -THC, $\Delta^{6a,10a}$-THC, and CBN; another chemical analysis of an "HHC" product showed the presence of a restricted synthetic cannabinoid MDMB-4en-PINACA as the main ingredient. Currently, there's no way to tell whether these mislabelings are intentional or accidental, but they can easily become dangerous for consumers.

Structure Determines Everything

Pharmacology:

The pharmacological discussion will be kept brief, with additional information available in the references and further information. Of the two forms of HHC, the β-epimer shows significantly more activity than the α-epimer, though it is still about an order of magnitude less potent than Δ^9 -THC, acting on a variety of receptors. The relatively high activity of the β-epimer is due to its stereochemistry: the C-11 methyl group is equatorial in the β-epimer, and axial in the α-epimer, making the β-epimer more stable and better aligned with the flat

(sp^2 hybridized) C-11 methyl of Δ^9-THC. The close alignment of the 9β-HHC and of Δ^9-THC rationalizes the comparable, though weaker, effects of 9β-HHC observed in animal studies.



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Toxicology, a word for consumers:

As has already been stated numerous times, the present lack of regulation makes it near-impossible to know what is actually in any of these products without undergoing the arduous task of laboratory analysis. The pharmacological and toxicological data also unable keep pace with the rate at which new compounds are developed, so caution is strongly recommended to all consumers. As some may recall, in 2019 there was an outbreak of e-cigarette/vaping associated acute lung injury, which was specifically linked to the consumption of vaping products containing vitamin E acetate (VEA), which is commonly used to dilute gray and black market vaping liquids; as far as I am aware, all hospitalizations were linked to gray market vaping liquids. By February 2020, 2,807 people were hospitalized and there'd been a total of 68 deaths in the US. Although we still do not fully understand what caused this serious lung injuries, ketene gas has been suggested as a potential culprit. This points to another potential issue: cannabinoid acetates may be inherently prone to causing this type of lung injury, as they could also release the reactive ketene upon heating, which has been observed in experiments conducted on vape pen cartridges in the lab setting. Although more testing is necessary to elucidate the exact mechanisms, metabolic, toxicological, and pharmacological profiles, it is my recommendation that the prudent consumer avoids these (semi-)synthetic products altogether.

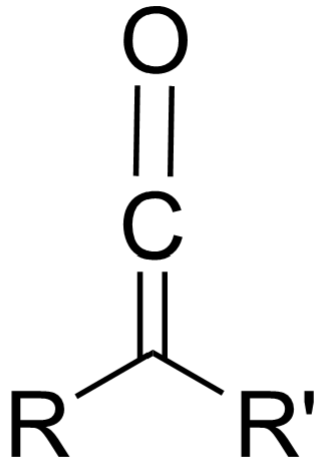


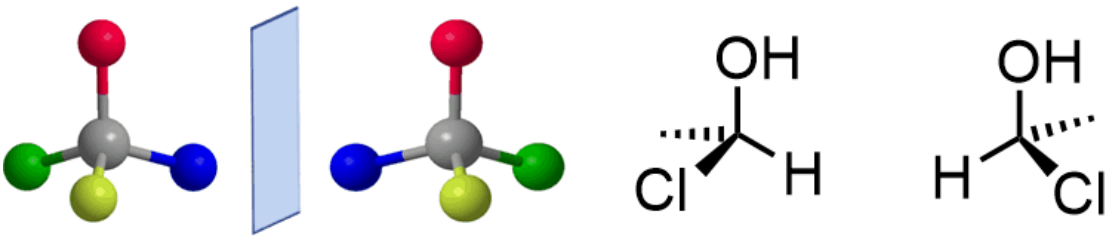
Figure 4. ketene structure

Ironically enough, the semi-synthetic loophole that this article covered is closing fast: an amendment to the 2018 Farm Bill was included in the funding appropriations bill signed into law by president Trump on November 12 of this year which restricts the acceptable levels of THC to 0.4%, and this time that number includes THCA. However, it is unlikely that semi-synthetic cannabinoids will completely disappear off the market, since once a door is opened, it can never truly be closed; most likely, we will see new semi-synthetics emerge by next year.

Vocabulary Quick Reference (Floating button/link)

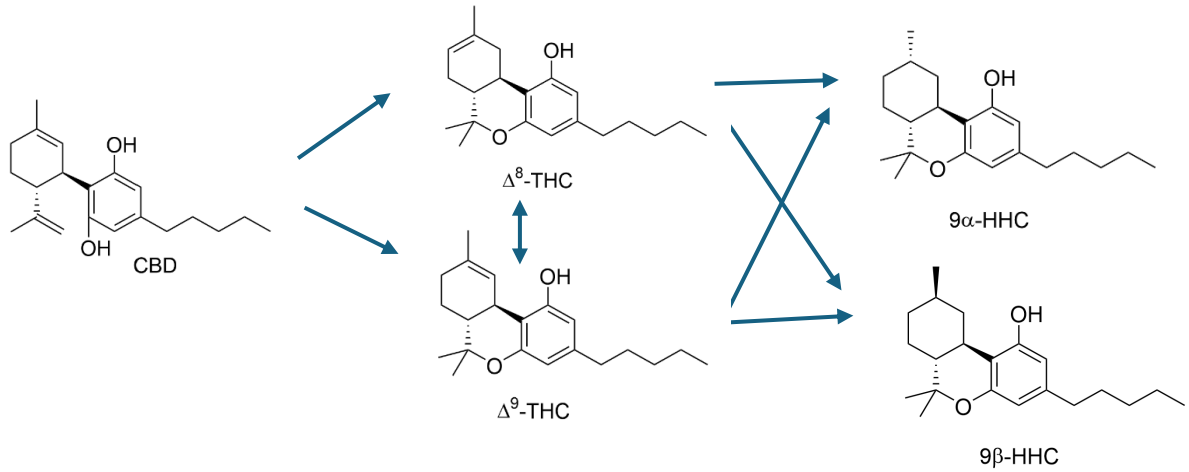
Isomer: molecules which have the same atom identities and counts, but differ in their arrangement in space

Stereoisomers: a subclass of isomers which only differ in their spatial arrangement, and not connectivity. The most classic example can be seen below, of two enantiomers [stereoisomers which are exact mirror images of one another]



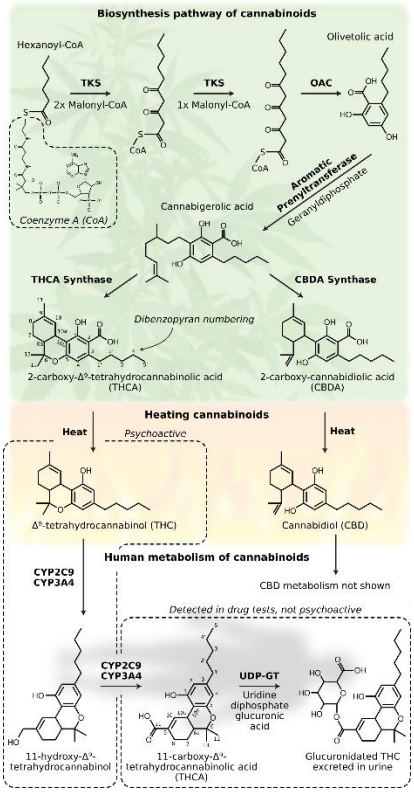
Enantiomers - mirror images

Structure Quick Reference (Floating button/link)



Further Reading

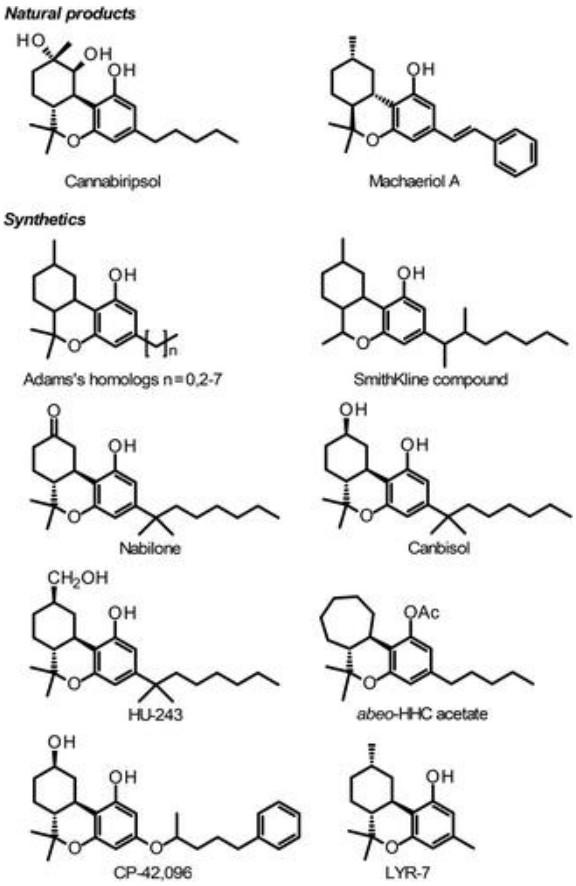
[1] CB_1 and CB_2 are two known subtypes of human cannabinoid receptors, which are G-protein coupled receptors. The CB1 receptor is expressed primarily in the CNS, while the CB_2 receptor is expressed in the immune system and other parts of the brain. They have relatively low sequence similarity.



[2] Biosynthesis pathway of cannabinoids

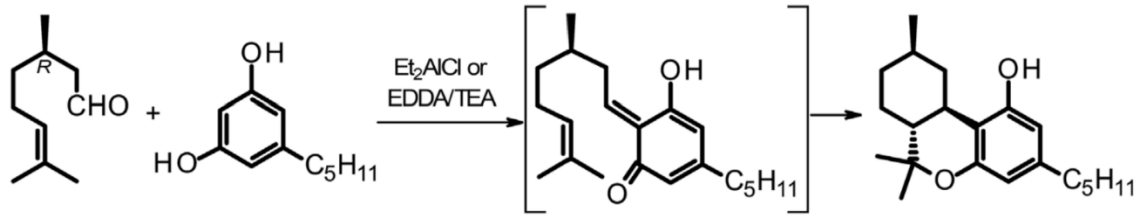
[3] Epimers can be separated by a variety of analytical techniques, including HPLC, TLC, and GC-MS

[4] Below are some of the natural products discussed in the primary reference, which have structural motifs that are very similar to the phytocannabinoids and semi-synthetic cannabinoids discussed. They are the motivation behind the synthetic analysis, since the synthesis of cannabinoids teaches lessons that are highly transferable to the synthesis of all drugs, or drug-like compounds – not just the illicit ones!



[5] Other reaction conditions: p-toluene sulfonic acid and boron trifluoride catalysts, under specifically optimized reaction conditions, result in high yields of Δ^8 -THC or Δ^9 -THC, respectively. A variety of protic and Lewis acids in different solvents have been investigated. Excess of either camphorsulfonic acid or TosA in toluene at room temperature was optimal for Δ^9 -THC, while camphorsulfonic acid in toluene at higher temperature or TosA in methylene chloride (@RT) resulted in a high yield of Δ^8 -THC.

[6] LA intramolecular DA reaction scheme, and solvents. All of the reaction conditions featured below result in ~77-98% enantiomer specificity.



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