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8.46 Compound **3** below, called mycoepoxydiene, was isolated from twig litter collected from an alluvial forest in Brazil. It contains an unusual oxygen-bridged cylooctadiene skeleton, and it has been shown to possess anti-cancer and anti-inflammatory properties. Using the general approach shown below, both enantiomers of **3** were made in the laboratory. Show reagents that can be used to convert compound **1** into compound **2**.

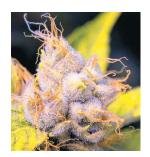
An ordinary-looking forest floor might contain extraordinary medicines.

need more PRACTICE? Try Problems 8.53, 8.76c,d, 8.84

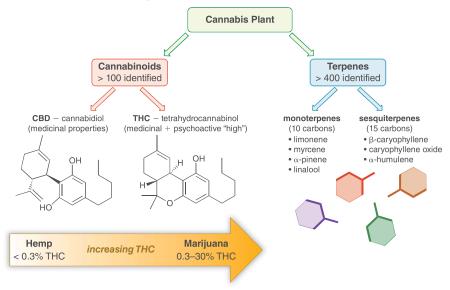
MM BioLinks Terpenes and the Chemistry of Cannabis

Have you ever felt energized and clear-headed after a walk through a pine forest? Or perhaps you have enjoyed a good night's sleep after having a relaxing bath with lavender bath salts? If so, you have had some first-hand experience interacting with terpenes. Earlier in the chapter we saw a few examples of terpenes that are found in essential oils, and in this BioLink we will learn about their role in cannabis and their potential for medicinal use. Why do plants make terpenes? Because they play many roles to help the plant survive. Terpenes can attract pollinators, combat the growth of microbes like fungus and bacteria, or fend off hungry insects and herbivores that are looking for a feast. Many terpenes have antimicrobial, anti-inflammatory, or pain-relieving properties, so it is not surprising that many plants with interesting terpene profiles have been used in folk medicines throughout history.

Terpenes can be found in cannabis plants (i.e., the species *Cannabis sativa* L.), along with another class of compounds called cannabinoids. The highest concentrations of both terpenes and cannabinoids are in the flowering "buds" of female cannabis plants. Over 100 cannabinoids have been identified, but the two that predominate—both in the plant and with respect to human interest—are cannabidiol (CBD) and tetrahydrocannabinol (THC):



Cannabis flowers are covered with tiny hairs (called trichomes) that secrete a sticky resin, rich in organic compounds.

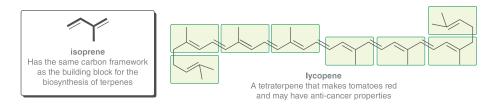


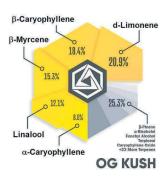
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THC is the component responsible for the "high" that is associated with smoking, vaping, or ingesting marijuana. THC fits into the two types of cannabinoid receptors in the human body (called CB1 and CB2). These receptors play a role in the body's immune system as well as a variety of central nervous system processes including pain, memory, mood, appetite, and stress. CBD is a non-intoxicating component that has proven anti-inflammatory, anti-anxiety, and pain relieving properties. CBD supports cognitive functions, and it can protect against memory loss caused by THC. Cannabis plants have been cultivated and selectively bred for decades to produce varieties (called *cultivars*) with desired characteristics. A 2022 analysis of over 40,000 cannabis samples from cultivators across six states revealed that 96.5% of them were THC-dominant. Only 1.4% of the samples were classified as CBD-dominant, and 2.2% were balanced, with significant amounts of both THC and CBD. Cannabis plants that contain less than 0.3% THC are categorized as hemp, and plants with more than 0.3% THC are described as marijuana.

Cannabis labels and terminology used by industry and consumers are not standardized and are therefore unreliable. Cultivars that are labeled as "indica" are often expected to have sedating effects, while "sativa" varieties are supposedly energizing (with "hybrids" having a blend of these features), but there is no consistency among these "strain" labels and their chemical profiles.^a The lack of standardization is due in part to cannabis being classified by the US Drug Enforcement Agency (DEA) as a Schedule 1 controlled substance—a drug "with no proven medical use and high potential for abuse" since 1970. As a result, scientific research has been severely restricted, and growing operations have been secretive and, until recently, wholly unregulated. Over the past 30 years, however, laws and public opinion have been steadily evolving. In 1996, California became the first state to legalize marijuana for medical use, a policy that has since been adopted by 36 additional states. In 2012, Colorado and Washington were the first states to legalize the recreational use of marijuana for adults, and by 2024 such laws existed in 24 states. The 2018 Farm Bill reclassified hemp, thus severing it from the Schedule 1 status of marijuana. This law legalized hemp-derived CBD at the federal level, as long as the plant's dry weight had less than 0.3% THC content. Marijuana remains illegal at the federal level, but in 2022 the Medical Marijuana and Cannabidiol Research Expansion Act cleared the way for future research on its medicinal use.

Terpenes are largely responsible for the flavors and fragrances of plants, but their impact extends well beyond our senses. Before we explore some of their medicinal uses, let's see how they are named. Terpenes are alkenes, but if other functional groups are present, then they are more precisely described as terpenoids. In Section 26.8, we will learn that terpenes are all derived from the same five-carbon building block. The molecule isoprene (2-methyl-1,3-butadiene) has the same branched skeleton as the building block, so the relationship of all terpene structures to the common building block is called the *isoprene rule*. When two building blocks are assembled, the resulting 10-carbon compound is described as a monoterpene. If three building blocks are used, then the compound will have 15 carbon atoms. These are called sesquiterpenes. Shown below is lycopene, the compound responsible for the red color in tomatoes. With 40 carbon atoms, lycopene is classified as a tetraterpene, and it is composed of eight isoprene units (highlighted):





Hundreds of terpenes are produced by cannabis plants, and the profile of each cultivar is unique. While the effects of marijuana are certainly related to the amounts of THC and CBD in a given cultivar, it is the presence and quantities of various terpenes that drives the overall experience. Marijuana can make you energetic, giggly, or chatty, but with a different variety you might become focused, quiet, or sleepy. As described by TJ Martin (former organic chemistry student and current Vice President of R&D at Abstrax Tech): if THC is the gas pedal, then the terpenes are the steering wheel.

In addition to the individual effects of a given terpene, it is the combination of components that determine the actual results. The synergistic nature of the various elements, known as the "entourage effect," can enhance benefits and physiological responses. One such example can be found in the CBD-based drug Epidiolex that was approved in 2018 to treat certain epileptic seizures. Because the purified CBD (aka CBD "isolate") is missing the terpenes and any other cannabinoids that would be present in the natural flower (aka "full-spectrum" CBD), the entourage effect is lost.

As a result, researchers in Brazil demonstrated that the therapeutic dose of Epidiolex is nearly *five times higher* than the amount needed if a full spectrum CBD product was used instead. Essential oils and natural product extracts might contain many dozens of organic compounds. This explains why there is such a significant difference in flavor between real vanilla extract (a complex mixture with vanillin as the major component) and artificial vanilla flavor (pure vanillin). The presence

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of even trace amounts of terpenes and other cannabinoids can make the CBD from a whole-plant extract more effective, but only purified components have been able to achieve FDA approval. In addition to the cannabis-derived drug Epidiolex, the THC-based medication dronabinol has been used by chemotherapy patients since 1985 to combat nausea and reduce vomiting.

TERPENE/TERPENOID	FUN FACTS	MEDICINAL/PHYSIOLOGICAL PROPERTIES
myrcene	 Found in hops, cloves, mangoes One of the most common terpenes in cannabis Can cause a deep state of relaxation described as "couch-lock" 	SedatingPain-relievingAnti-inflammatory
β-caryophyllene	 Found in black pepper, oregano "BCP" is the most common sesquiterpene in cannabis Can counteract effects of THC (e.g., by chewing on peppercorns) 	 Anti-inflammatory Binds to CB2 receptors Treats malaria, ulcers, itching Antibacterial Neuroprotective
α -pinene	 Found in conifers and isolated from pine resin Used as a paint thinner (turpentine) Most common terpene in nature 	 Anti-inflammatory Bronchodilator Neuroprotective Aids memory, concentration
limonene	 A major constituent of lemon and orange essential oils; can be isolated by steam distillation of their peels Second-most common terpene in nature 	Anti-anxietyAntibacterialImmunostimulant
HO	 (S) enantiomer is found in lavender (R) enantiomer in found in cilantro 	SedatingAnti-anxietyPain relieverAnti-parasitic
caryophyllene oxide	 Found in the lemon balm plant Used to train drug-sniffing dogs 	Antifungal Insecticidal
humulene	Found in hops, ginseng	Anti-inflammatory Antibacterial

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Despite the challenges associated with conducting cannabis research, there is a significant amount of literature documenting the medicinal properties of THC, CBD, and various terpenes. In 2017, the National Academy of Sciences issued a report that summarized such therapeutic effects.^c According to that report, there is evidence that cannabis or cannabinoids are effective for treating chronic pain, treating nausea from chemotherapy, reducing spasms from multiple sclerosis, treating certain sleep disorders, increasing appetite and decreasing weight loss associated with HIV/AIDS, improving symptoms of Tourette syndrome, treating posttraumatic stress disorder (PTSD), and reducing anxiety.

- a Smith CJ, Vergara D, Keegan B, Jikomes N (2022) The phytochemical diversity of commercial Cannabis in the United States. PLoS ONE 17(5): e0267498. https://doi.org/10.1371/ journal.pone.0267498
- b Pamplona FA, da Silva LR and Coan AC (2018) Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis. Front. Neurol. 9:759
- c National Academies of Sciences, Engineering, and Medicine. 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625 doi: 10.3389/fneur.2018.00759

DOM:

REVIEW OF REACTIONS



- 1. Hydrohalogenation (Markovnikov)
- 2. Hydrohalogenation (anti-Markovnikov) 5. Hydrogenation
- 3. Acid-catalyzed hydration and oxymercuration-demercuration
- 4. Hydroboration-oxidation

- 6. Bromination
- 7. Halohydrin formation
- 8. Anti dihydroxylation
- 9. Syn dihydroxylation
- 10. Ozonolysis

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