Synthetic Access to Cannabidiol and Analogs As Active Pharmaceutical Ingredients

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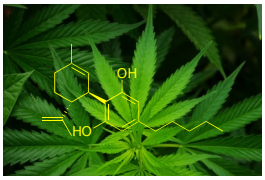
ABSTRACT: Cannabinoids have surely been one of the most widely self-administered drugs, other than caffeine. The US FDA recently approved one cannabinoid-based drug whose active pharmaceutical ingredient (API) is cannabidiol (CBD). The long history of individual use of cannabis for a wide range of conditions has sparked great interest in other uses of CBD, in ethical drugs and botanical supplements as well as in foods and non-prescription wellness products. CBD may be sourced from cannabis plants, but can also be prepared synthetically, the topic of this review.

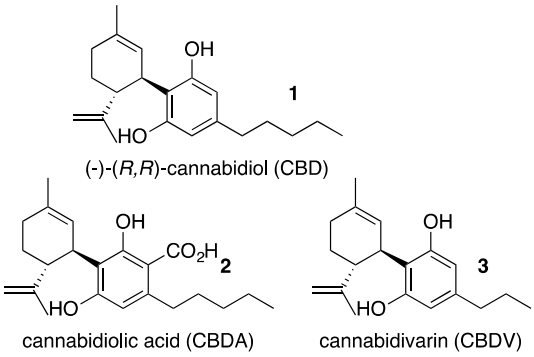


INTRODUCTION

Seeking solace for human infirmities in the plants that surround us is an ancient practice. The medicinal uses of *Cannabis sp*., like hemp and marijuana, date to several millennia B.C.E.[1] Finding novel pharmaceuticals in plants like cannabis also follows a well-worn path. Cannabis-derived drugs have been marketed since 1985, such as dronabinol (Δ^9-tetrahydrocannabinol (THC)) for chemotherapy-induced nausea.[2] THC is also the psychoactive cannabinoid in recreational marijuana.

There are over 60 known cannabinoids in *Cannabis sp*., which are natural products derived from polyketide and monoterpene fragments.[3] The compound of interest here, cannabidiol (Chart 1), arises from the corresponding acid CBDA (**2**), which has readily identified hexaketide and terpene segments. Such cannabinoid acids can decarboxylate spontaneously to generate familiar structures that include the resorcinol olivetol.[3] In some cases, variants of the well-known cannabinoids, such as cannabidivarin (**3**), arise from a pentaketide acid.

Chart 1. Select cannabinoids, including cannabidiol (CBD, **1**)



At this point in time, late Spring of 2020, there is political contradiction in that recreational use of marijuana has been decriminalized in many US states despite the plant being prohibited under US Federal regulations. Such restrictions extend to any substances isolated from marijuana, providing a significant impediment to research on or clinical use of cannabinoids, including CBD. Synthetic cannabinoids may provide one means to address this dilemma, however, providing one motivation for this review.

The latest cannabinoid to reach market is Epidiolex®, a product of GW Pharmaceuticals approved in the US in 2018 for treatment of Lennox-Gastaut and Dravet syndromes, which are rare childhood seizure disorders. Over 100 clinical studies of CBD are underway for other conditions including pain, Parkinson disease, Crohn disease, traumatic brain injury, Prader-Willi syndrome, Rett syndrome, and several mental health conditions, including addiction disorders.

Plant sources for APIs are certainly well-precedented. Projections are for significantly

increased production of cannabis plants in North America, owing to its decriminalization in many jurisdictions, which could supply CBD. However, some of the need for CBD production will be fulfilled by chemical synthesis, the main topic of this review. It is interesting to compare this situation with that for therapeutic peptides. While many are manufactured by biological (recombinant DNA) techniques, chemical synthesis is still widely used.[4] Surprisingly, this even applies to relatively large peptides, such as exenatide, with 39 amino acids. The long-standing experience using chemical synthesis to make molecularly pure materials on significant scale must counterbalance the convenience of the production of peptides biologically. The latter may necessitate more onerous purification protocols. Likewise, chemical synthesis can provide ready access to pristine cannabinoids using proven API purification methods. Problematic contaminants in plant-derived CBD (heavy metals, pesticides) are widely discussed.

Another attraction of chemical synthesis of APIs is that it can access stereoisomers not found in Nature. The preparation and study of antipodal cannabinoids including CBD has been reported. Interestingly, (*S,S*)-CBD is not strictly inactive, and for some properties, such as anticonvulsant activity, the two enantiomers are essentially equipotent.[5] (*S,S*)-CBD has a somewhat different profile of receptor activities than the natural isomer.[6]

CANNABIDIOL AS AN ACTIVE PHARMACEUTICAL INGREDIENT

The API in the approved drug is a highly purified CBD from marijuana plants, which has raised some interesting regulatory considerations as discussed above. The matter is complicated by the multiple US cabinet departments involved (Justice, Health and Human Services, Agriculture). Marijuana is classified by the US Drug Enforcement Administration (DEA) as a controlled substance on Schedule 1, and any compound derived from it is also Schedule 1. CBD is typically the second most abundant cannabinoid found in marijuana, after THC. CBDA is also prevalent, and the relative amounts of CBD and CBDA can depend on handling of the plant source. CBD is the most abundant cannabinoid in hemp, and based on a statute (US 2018 Farm Bill), cultivation of hemp that contains less than 0.3% THC and obtaining cannabinoids from it is permitted. A major distinction between marijuana and hemp is that the latter typically lacks THC, providing the rationale for this statute. The approved drug in its finished dosage forms is specifically classified on Schedule V, and requires a physician's prescription. Late in 2019, the DEA informed Purisys, recently spun-off from Noramco, that it had removed its *synthetic* CBD from Schedule 1, along with 30 other cannabinoids. This is more liberal than the approach in Europe, where the European Commission has found that CBD and all products containing it are novel and require pre-market authorization for human consumption.

It is common that the solid form of an API is important, and this is equally true with CBD. The best known crystalline form is a low-melting solid with a melting point of 66-67 °C. However, a second form has recently been generated by crystallization from MTBE/heptane with the assistance of seed crystals of cannabadivarin, with a melting point of 43-47 °C.[7]

Since the approval of the drug, several commercial entities have announced their intentions to offer fully synthetic CBD. These include AMRI, BioVectra, Insys Therapeutics, Johnson Matthey, Noramco, and THC Pharm. Rarely has the process used in manufacturing been specified publicly. Those who have provided drug master files on CBD to the US FDA are, in chronological order: NIDA, STI Pharmaceuticals, Insys Therapeutics, AMRI, National Center for Natural Products Research, THC Pharm, Johnson Matthey, Noramco, and Farmabios. Some modification of the syntheses reported below will presumably be used in their work, our motivation for this analysis. There is no documentation of the method used by Johnson Matthey, which is claimed in press reports to have been performed on the metric ton scale. Noramco lists in its commercial materials a large capacity for CBD manufacturing under cGMP of 180 metric tons per year.

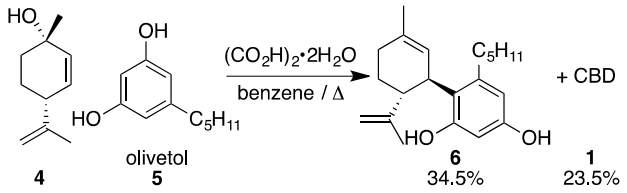
SYNTHESES OF CANNABIDIOL

a. Chiral pool

1. Olivetol-based syntheses

A common terpene component used in CBD syntheses is (+)-*p*-mentha-2,8-dien-1-ol (**4**). This compound can be prepared in several ways from natural precursors like citrus-derived (+)-limonene,[8] but the interest in cannabinoids overall has led to an active and competitive supply market, and it can be purchased in kilogram quantities.

Scheme 1. Petrzilka et al. Preparation of CBD



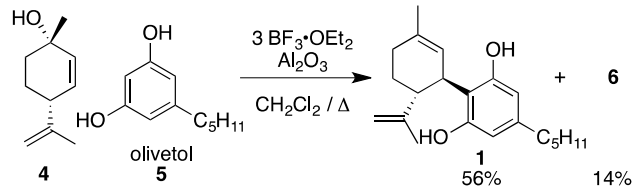
4 **5** **6** 34.5% **1** 23.5%

An early use of this chiral pool starting material highlights some difficulties that must be faced in any CBD synthesis (Scheme 1).[9] Mild acid is used to generate the terpene cation for electrophilic aromatic substitution on olivetol. Stereoselectivity is excellent in this transformation, with attack by olivetol occurring exclusively trans to the

isopropenyl group. However, both aromatic sites (between the pentyl group and a phenol, and between the phenols) of olivetol react and CBD is obtained in only 23.5% isolated yield, with the undesired product **6** (34.5%) and recovered olivetol (36.5%) dominating the product mixture. Compound **6** has been called "abnormal cannabidiol". Stronger acids cause further reaction of CBD by addition of its phenol to its isopropenyl group, forming the THC skeleton. The CBD preparation in Scheme 1 could be enhanced by performing it at high pressure.[10] While the CBD yield increases to 41%, it seems unlikely this method could be applied on scale.

A significant early contribution came from a long-time investigator of cannabis chemistry, Mechoulam. When the acid used for activation of **4** is BF_3•OEt_2 (3 equiv) on alumina (Scheme 2), with olivetol in 25% excess, CBD is obtained in 55% isolated yield, and **6** is only 14% of the product mixture.[11] Even three decades ago, very early in the history of cannabinoid research, this reaction was performed on a 100 mmol scale to obtain CBD in 46% isolated yield.

Scheme 2. Baek et al. Preparation of CBD

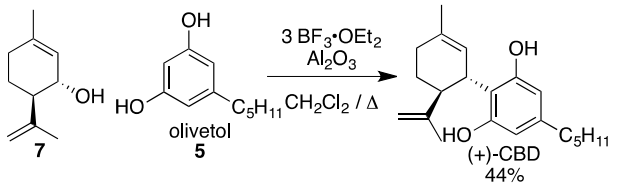


$ZnCl_2$ in water/dichloromethane has also been used to promote this transformation.[12] Crucial details about the selectivity for formation of CBD vs. **6** are unavailable from this report, however. When the reaction is conducted with 10% *p*-TsOH and 1.3 equiv of olivetol, CBD is obtained in 24% yield after chromatography.[13]

The reaction of **4** with **5** (in excess) can also be catalyzed by $Zn(OTf)_2$, with stringent heating to 150 °C in a conventional hydrocarbon solvent or a reaction that begins neat and then is diluted with solvent and cooled (reaction not shown).[14] This method has been conducted on multimole scales, but again, the selectivity of the formation of CBD vs. **6** is not mentioned. This issue may be of less concern in this work because the crude CBD was purified by forming a solid complex with the amine DABCO. Complexation was reversed by acid treatment and the CBD was directly crystallized. The yield for this process overall is 72%. With such high efficiency, there must have been minimal loss of reaction product to **6** in the electrophilic aromatic substitution.

The synthesis of the unnatural enantiomer of CBD (Scheme 3) required a new monoterpene accessible in the opposite enantiomeric series. Isopiperitenone was used in this work.[6a] It was reduced to alcohol **7** for reaction with olivetol, analogous to the condensation reported by Mechoulam.

Scheme 3. Mechoulam Preparation of (+)-CBD

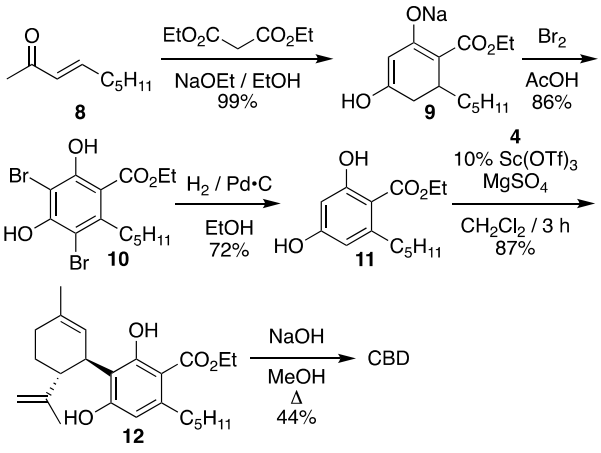


Control of regioselectivity in the electrophilic aromatic substitution reaction on olivetol is an ongoing concern. Gu reported that a complex could be pre-formed between the hydrophobic receptor β-cyclodextrin and olivetol that blocks the undesired positions of reactivity.[15] Greater details on this method are needed to evaluate its utility.

2. Olivetol derivative-based syntheses

Essentially mimicking the biosynthesis of CBD is one way to control the site of reaction on the olivetol fragment. The AMRI team uses ethyl olivetolate (**11**) in place of olivetol (Scheme 4).[16] This ester was prepared via a classical Michael-Claisen condensation that generates **9**. Oxidation by bromine and hydrogenolysis by catalytic reduction produce **11**. It is the limiting reagent in a reaction with 1.6 equiv of **4** and catalytic Lewis acid. This generates an ester of CBDA (**12**), which is saponified and decarboxylated. The overall yield of this process (23%) is competitive with simply using olivetol. It was conducted on a 200 mmol scale by these workers, and on a 2 mole scale by others.[17] This method was used with minor modifications in the production of a novel crystalline form of CBD.[7]

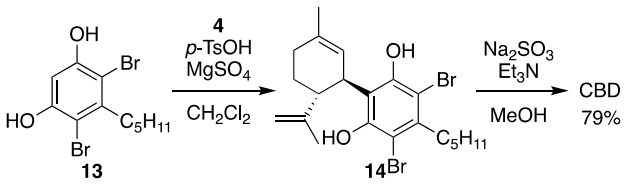
Scheme 4. Burdick et al. Preparation of CBD



Another strategy to block undesired reaction sites on olivetol was reported by a Noramco team (Scheme 5).[18] Using a fairly stringent procedure (CH_2Cl_2, -50 °C, 2 Br_2), dibromination of olivetol gives **13** in 82% yield. Its coupling with 1.3 equiv

of terpene **4** was performed at -50 °C for a few hours, used 0.5 equiv of acid, and produced **14**. Its reductive debromination used sodium sulfite and catalytic ascorbic acid, delivering CBD after 18 h at reflux. For this two-step process, an impressive 79% yield was obtained. The product was directly crystallized from a concentrated solution in *n*-heptane. Reduction of **14** could also be accomplished using hydrogen and a Pd catalyst, though the risk of doing so in a molecule that includes two reducible alkenes makes the chemical reduction more appealing.

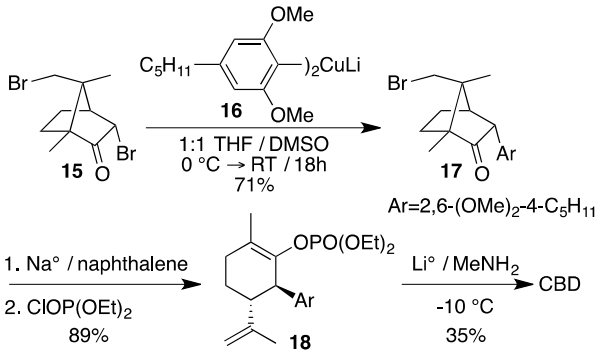
Scheme 5. Dialer et al. Preparation of CBD



3. Other terpene-based syntheses

Albizati used camphor to provide the terpenoid chirality in his 3-step CBD synthesis (Scheme 6).[19] Reagent **16** comes from olivetol via a straightforward route. The 3,9-dibromocamphor **15** is readily available by bromination of camphor, and undergoes an aryl cuprate coupling with product equilibration to the more stable endo stereochemistry. Fragmentation triggered by reduction of the bromide in **17** leads to an enolate that was trapped as the vinyl phosphate. Reduction of **18** gives CBD (35%) as well as its monomethyl ether (43%). The deprotection of a methyl ether under reductive conditions observed here is unexpected.

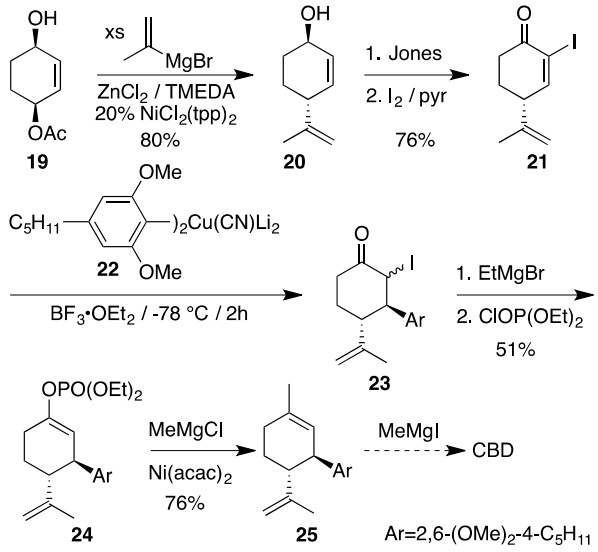
Scheme 6. Albizati Preparation of CBD



b. Asymmetric synthesis

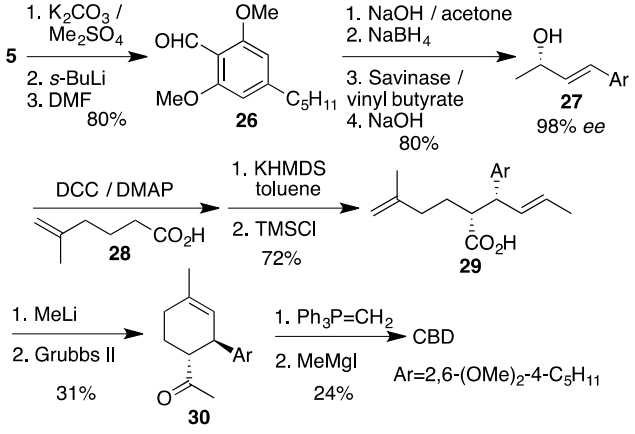
Kobayashi used a synthon **19** readily available by enzymatic desymmetrization in his CBD synthesis (Scheme 7).[20] Nickel-catalyzed substitution introduced the isopropenyl group, and an enone was created for conjugate addition. The higher-order cuprate reagent **22** was used for this step. The product was converted to the enolate that was trapped as the vinyl phosphate **24**. Kumada coupling gave the known **25**. The cleavage of its methyl ethers to give CBD relies on a literature procedure of Mechoulam,[21] but is a demanding, high temperature transformation.

Scheme 7. Kobayashi Asymmetric Synthesis of CBD



Leahy recently achieved a CBD total synthesis (Scheme 8).[22] Olivetol is converted to aldehyde **26** by methylation, metalation, and formylation. Aldol condensation, reduction, and kinetic resolution (or asymmetric reduction) deliver alcohol **27**. It is esterified with acid **28**, and the ester is subjected to the Ireland-Claisen rearrangement. The product **29** is obtained as the sole stereoisomer. Conversion of the acid to the methyl ketone and ring-closing metathesis generate **30**. A Wittig methylenation of the ketone gives the same intermediate as above.

Scheme 8. Leahy Asymmetric Synthesis of CBD

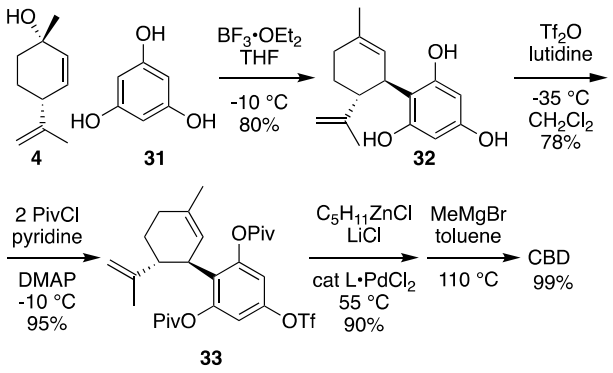


While excellent demonstrations of the power of modern organic synthesis, neither of these works provides a solution to a large and sustainable supply of CBD as an API.

Recently, a scalable CBD synthesis that also facilitates late-stage diversification of the aromatic ring was developed.[23] It relies on the condensation of terpene **4** with a 10× excess of

phloroglucinol (**31**) to give a known compound **32**. Using **31** instead of a resorcinol removes regiochemical issues in the electrophilic aromatic substitution. Very controlled conditions enable the selective triflation of the less hindered phenol. The other phenols required protection for a Negishi coupling to introduce a pentyl group. Finally, removal of the protecting esters required a 5× excess of methyl Grignard reagent. This synthesis was reported to proceed in 52% overall yield and was conducted on scale to prepare as much as 10 g in the final reaction.

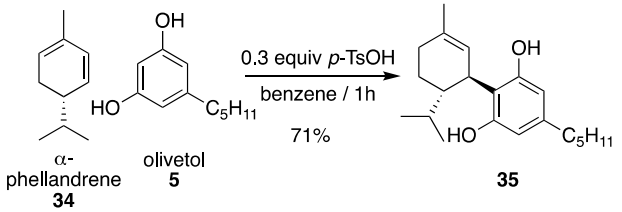
Scheme 9. Shen and Aisa Synthesis of CBD



c. Relevant analog syntheses

Mascal targeted a reduced version of CBD (Scheme 10), freeing him from **4** as the chiral pool starting material.[24] In this and in past work, the pharmacological properties of dihydro-CBD (**35**) proved quite similar to CBD. The starting material for Mascal's synthesis, the common fragrance/flavor compound α-phellandrene, is available in bulk from eucalyptus oil. The (*R*)-(-) enantiomer **34** has the appropriate absolute configuration for a dihydro-CBD synthesis based on acid-catalyzed addition to the diene. This process was performed on a 10 mmol scale in 71% yield. An update of the procedure to a greener solvent would be essential for preparative application of this synthesis. A large appeal of this route is that it gives a product that cannot be knowingly diverted to the THC skeleton, reducing the temptation for abuse. CBD has also been hydrogenated using PtO_2 at low pressure to produce **35** predominantly.[25] A selective hydrogenation catalyst such as Wilkinson's catalyst would presumably enable exclusive reduction at the less substituted alkene. There is yet another access to dihydro-CBD: it is a minor over-reduction product in the Albizati CBD synthesis discussed earlier, and its production might be increased by experimentation.

Scheme 10. Mascal Preparation of dihydro-CBD



BIOSYNTHESES OF CANNABIDIOL

It is no surprise that the possibility would be pursued of producing CBD biologically, but in the laboratory, not the greenhouse.[26] Since the instant biosynthetic product is CBDA, it is that compound whose production could be bio-engineered. Its decarboxylation would need to be achieved in a separate step. An initial investigation into this concept used plant cell culture. Adventitious root cultures of *C. sativa* produce cannabinoids, but the level of CBDA was only 1.7 μg g^{-1} dry weight.[27] The researchers developing this method concluded it would be difficult to scale up and is not competitive with chemical synthesis.

A more modern approach is genetic engineering of prolific producer cells like yeast.[28] In a yeast strain having all appropriate genes introduced for the biosynthetic production of CBDA, its production was 4.3 μg L^{-1}. This level is orders of magnitude below any reasonable preparative process, so this work represents a technological feat that does not yet apply to addressing supply needs for the API.

SUMMARY AND FUTURE PROSPECTS

As a target with many decades of history, CBD *should* be a compound whose synthesis has been nearly perfected. Many resources can be identified in its past literature, including scalable purification methods that are well suited to the manufacturing setting. Use of terpene feedstocks has effectively addressed any questions of stereochemistry. Albizati's relatively underappreciated CBD synthesis has significant potential. If the incomplete deprotection in the ultimate step could be addressed, this route would offer an overall yield of ca. 50% and as few unit operations as competing routes. It might also be tweaked to provide alternative access to dihydro-CBD. This compound offers many attractions provided it proves interchangeable with CBD in its medicinal applications. The popularity of this topic is also shown by a related recent publication.[29]

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ABBREVIATIONS USED

API, active pharmaceutical ingredient. CBD, cannabidiol. CBDA, cannabidiol acid. THC, Δ^9-tetrahydrocannabinol.

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Notes

The author declares no competing financial interest.

Biography

Michael C. Pirrung was trained as a synthetic chemist via studies at UT-Austin, UC-Berkeley, and Columbia University. He has held faculty positions in chemistry at Stanford University and Duke University, and been a visiting professor at UC-Berkeley, Baylor College of Medicine, Oxford, UC-San Diego, UC-Irvine and Caltech. He received Hertz, Sloan, and Guggenheim fellowships and a NSF Presidential Young Investigator Award. In 2004 he joined the UC-Riverside Chemistry department as UC Presidential Chair and in 2012 was named Distinguished Professor. He added a joint appointment in Pharmaceutical Sciences at UC-Irvine in 2013. His current research emphasizes organic and peptide synthesis, medicinal chemistry, and bioluminescence. He has >180 peer-reviewed publications and >40 patents, and has authored six books.

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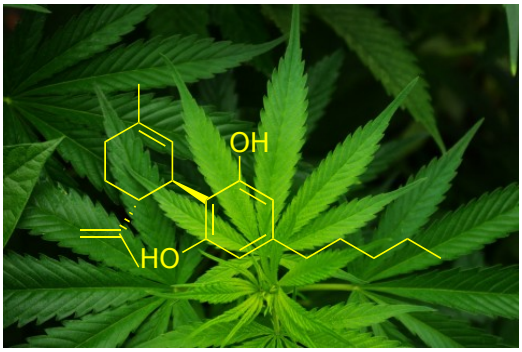

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