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Article

Easy and Accessible Synthesis of Cannabinoids from CBD

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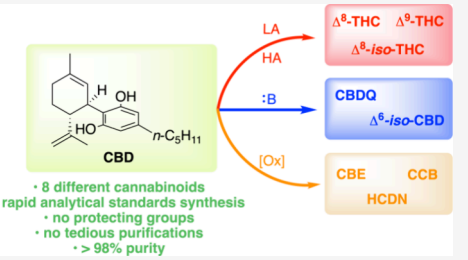
ABSTRACT: Cannabidiol (CBD), a prominent phytocannabinoid found in various *Cannabis* chemotypes, is under extensive investigation for its therapeutic potential. Moreover, because it is nonpsychoactive, it can also be utilized as a functional ingredient in foods and supplements in certain countries, depending on its legal status. From a chemical reactivity point of view, CBD can undergo conversion into different structurally related compounds both during storage and after the consumption of CBD-based products. The analytical determination of these compounds is of paramount concern due to potential toxicity and the risk of losing the active ingredient (CBD) title. Consequently, the complete stereoselective total synthesis of representative CBD-derived compounds has become a matter of great interest. The synthesis of pure CBD-derived compounds, achievable in a few synthetic steps, is essential for preparing analytical standards and facilitating biological studies. This paper details the transformation of the readily available CBD into Δ^8-THC, Δ^9-THC, Δ^8-*iso*-THC, CBE, HCDN, CBDQ, Δ^6-*iso*-CBD, and 1,8-cineol cannabinoid (CCB). The described protocols were executed without the extensive use of protecting groups, avoiding tedious purifications, and ensuring complete control over the structural features.



Cannabidiol (CBD, **1**) is a prominent phytocannabinoid found in significant quantities across various *Cannabis* chemotypes. CBD is nonpsychoactive, and its therapeutic potential has garnered increasing interest within the scientific community.[1] The global market for CBD, spanning cosmetic products, food, beverages, supplements, and pharmaceuticals, is estimated to reach approximately 4.6 billion dollars in the next few years.[2] While a rigorous scientific foundation is still under development, the perception of CBD as a "natural" panacea has steadily grown in recent years. Given the widespread use of pharmaceutical formulations containing CBD and concerns regarding its degradation products, there is a pressing need for CBD derivatives with a high level of purity to serve as analytical standards. Additionally, a streamlined method for their preparation in milligram-scale quantities for biological activity evaluation is imperative. These aspects constitute the novel contributions of this research.

As the biological properties of a bioactive compound are directly influenced by its stereochemical features, this paper outlines the regioselective synthesis of tetrahydrocannabinols Δ^9-THC (**2**), Δ^8-THC (**3**), and Δ^8-*iso*-THC (**4**),[3] as well as derivatives such as cannabielsoin (CBE, **5**) and cineocannabinol (CCB, **7**). Additionally, the synthesis of CBD *p*-benzoquinone (HU-331, CBDQ, (1′R,6′R)-6-hydroxy-3′-methyl-4-pentyl-6′-(prop-1-en-2-yl)-[1,1′-bi(cyclohexane)]-2′,3,6-triene-2,5-dione, **8**)[4] and a bisaryl derivative (HCDN, **6**) is detailed (see Figure 1). These compounds represent the most significant structures closely associated with CBD that may emerge during the storage and/or use of CBD-based formulations.[5]

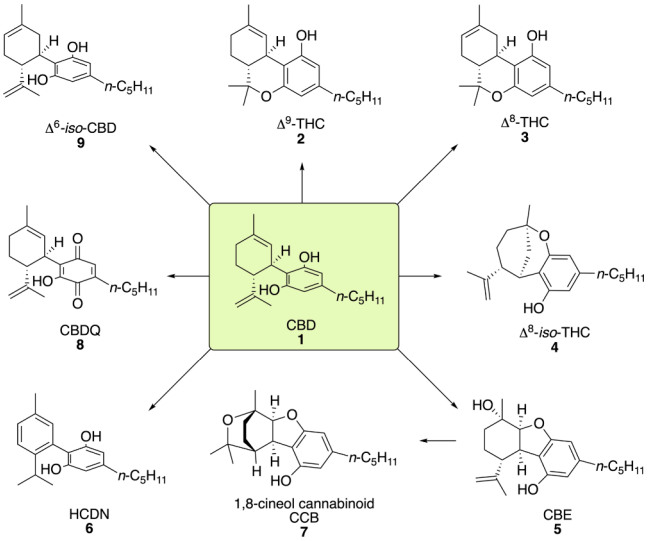


Figure 1. Representative transformation from CBD (**1**) to the desired compounds.

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In this study, the optimization of various procedures was conducted to obtain the desired products from CBD through simple protocols, minimizing the use of protecting groups. For rapid and reproducible analysis of reaction outcomes, GC-(EI)MS was employed to monitor the reactions.[6,7]

The starting material for all procedures described, CBD, is characterized by a prenylic-based methyl cyclohexene derived from a mevalonic pathway (see Figure 2, green highlight) and a 2,3,6-trisubstituted bis-phenolic originating from the acetate pathway (see Figure 2, red highlight).[8]

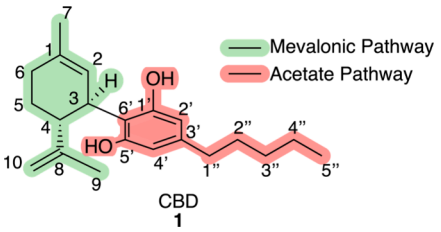


Figure 2. Structure of CBD (**1**) with the numeration of carbon skeleton, colored according to the biosynthetic pathway.

To elucidate the novelty of the synthetic approach, the results are presented based on the structural motifs in the synthesized compounds. The reactions on CBD are categorized into two groups: (a) manipulating hexatomic rings to alter the oxidative state of carbon atoms on terpene or phenolic rings, resulting in CBD-related compounds, and (b) generating new heterocyclic rings with complete stereo- and regioselectivity for THC-related structures. These regioselectivities include 8−1′/5′ interactions yielding THCs (Δ^9-THC **2** and Δ^8-THC **3**), 1−1′/5′ providing Δ^8-*iso*-THC (**4**), and, finally, cannabielsoin-related compounds CBE (**5**) and 1,8-cineol cannabinoid (**7**) via regioselective reaction at the 2-position followed by intramolecular cyclization with the phenolic −OH moiety at either the 1′- or 5′-position. The abbreviations in this paper follow the conventions outlined by Appendino and co-workers.[9] The abbreviations are also reported in the Supporting Information.

RESULTS AND DISCUSSION

The regioselectivity achieved through the optimized protocols outlined in this section, coupled with the "protecting group free" approach, constitutes the primary novelty in this research. Furthermore, the comprehensive regiocontrol detailed in the procedures presented in this paper yields the desired compounds with a high level of purity (>95%).

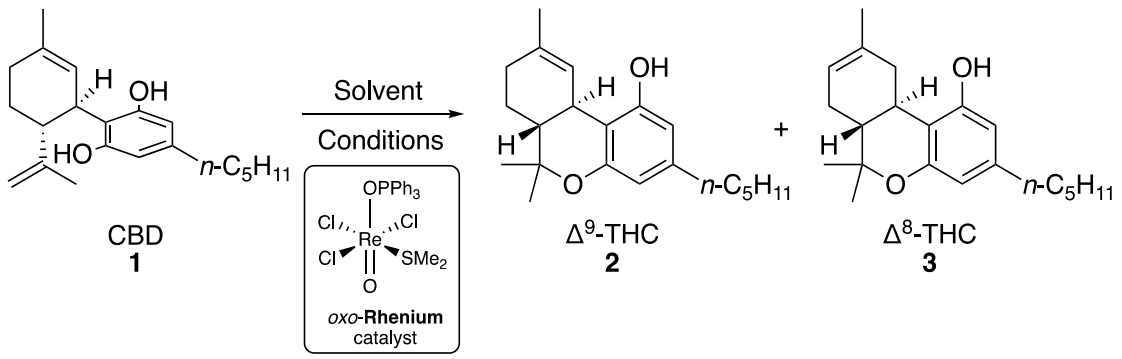
The investigation started with the conversion of CBD (**1**) into Δ^9-THC (**2**) and Δ^8-THC (**3**).

In accordance with the literature,[10,11] the cyclization of the phenolic group by attaching one of the two olefins present in CBD (**1**) is responsible for the formation of at least two regioisomeric series of THC substructures. If the Δ^1 double bond of CBD is activated, an *iso*-THC substructure can be formed, whereas activation of the Δ^8 double bond of CBD yields Δ^9-THC and Δ^8-THC (**2** and **3**, respectively). Achieving the regioselective total synthesis of pure Δ^9-THC poses a considerable synthetic challenge due to its rapid acid-catalyzed isomerization to the thermodynamically more stable Δ^8-THC.[12] Despite the abundance of literature on this subject, only a few examples exist that provide a single isomer with catalytic amounts of acid without traces of starting material and/or regioisomers. In 2020, Passarella and co-workers described various experimental conditions involving different solvents, acid types (Bronsted or Lewis acids), and temperature to obtain THC isomers as single products from the readily available enantiopure CBD (**1**).[3] However, these procedures commonly result in a difficult to separate mixture of compounds. As a result, attention was directed toward optimizing selective regioisomeric protocols. Recently, Kappe and co-workers published a continuous-flow methodology for the preparation of Δ^9-THC and the thermodynamically more stable Δ^8-THC, along with an exhaustive study of Lewis acid-promoted cyclization−isomerization of these compounds.[13] This novel methodology results in pure Δ^9-THC or Δ^8-THC through a catalytic process using a flow-chemistry approach. In the current study, the preparation of Δ^9-THC and Δ^8-THC was approached using an oxorhenium(V) Lewis acid, (i.e., oxotrichlorobis(triphenylphosphine)rhenium(V), *oxo*-rhenium).[13,14]

Leveraging the highly sensitive and versatile modulation of *oxo*-rhenium properties, the experimental conditions were fine-tuned by adjusting solvent, temperature, and the presence of a cocatalyst. This optimization aimed to produce either pure Δ^9-THC or Δ^8-THC on a milligram scale, ensuring high levels of purity for their application as analytical standards. A representation of the described catalyst flexibility is summarized in Scheme 1.

The experimental conditions were initially assessed by varying the amount of the *oxo*-rhenium(V) Lewis acid, in accordance with literature guidelines.[15] Initial attempts involved the use of 5 mol % of the catalyst, with 3 mol % of copper(II) triflate as a cocatalyst in dichloromethane as the solvent, at room temperature for 72 h. Under these conditions,

Scheme 1. General Reaction for the Preparation of Two Different THC's Regioisomers



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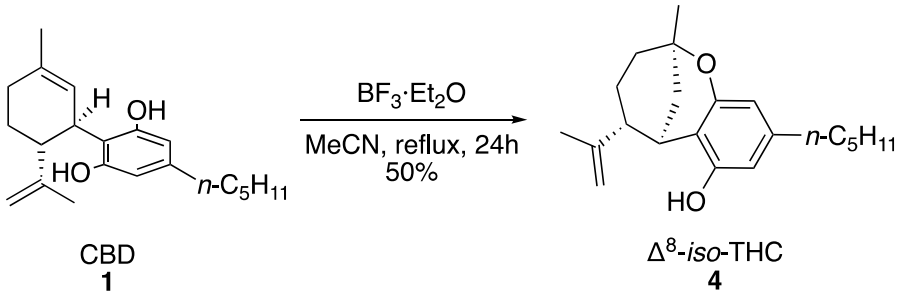
Scheme 2. Synthesis of Compound 4 from CBD (1)



pure Δ^8-THC (**3**) was obtained as a single diastereoisomer with an isolated yield of 92%.[7]

As previously mentioned, the synthetic challenge involved the preparation of pure, less stable Δ^9-THC (**2**). This was successfully achieved using a toluene−dichloromethane mixture in a 7:3 ratio, employing 3 mol % of oxotrichlorobis-(triphenylphosphine)rhenium(V) for 44 h at room temperature. Under these optimized conditions, almost pure Δ^9-THC (>97:3 Δ^9/Δ^8) was isolated with 89% yield.[7] Additional experiments were conducted to assess the impact of other variables, and a detailed summary can be found in the Supporting Information.[7] For instance, the utilization of ethers such as THF as a solvent yielded inferior results,[14] and when CBD was reacted at room temperature for 46 h, **2** was obtained with a 75% isolated yield and 18% of Δ^6-*iso*-CBD (**9**) was formed.[5]

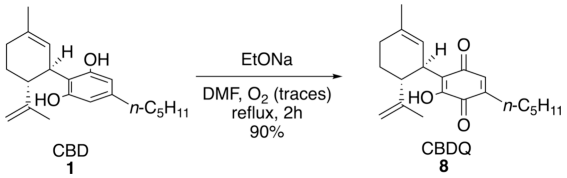
The study moved forward toward the synthesis of Δ^8-*iso*-THC (**4**). Selective protocols to synthesize **4** with the aim of directly activating the double bonds of the CBD (**1**) scaffold have been reported. However, no procedures for the high-yielding and selective synthesis of these isomers were found in the literature.[10,11] Thus, building upon Passarella and co-workers' procedure,[3] an extensive adjustment of reaction conditions was undertaken.[7] The synthesis involves activating the Δ^8 double bond by using $BF_3{\cdot}Et_2O$ in acetonitrile as a polar aprotic solvent. The optimized protocol, outlined in the Scheme 2, represents the most favorable conditions for this reaction, resulting in an isolated yield of 50% with a good level of purity (i.e., >95%) for compound **4** (see Supporting Information for details).[7]

The purification of the crude reaction is a crucial step in this procedure, given the instability of Δ^8-*iso*-THC (**4**), which decomposes when exposed to silica. The usage of Florisil (60−100 mesh) proved to be a valuable choice for the purification step. The results of NMR analysis validate the structure proposed.[16]

An effective synthesis of HU-331 (CBDQ, **8**) has not been reported. To this end, a solution of CBD (**1**) in DMF was refluxed under ambient conditions for 2 h in the presence of 3 equiv of sodium ethoxide. The synthesis of CBDQ, starting from CBD, was then optimized, resulting in an overall yield of approximately 90% (refer to the Supporting Information for details on the optimization). The quantity of DMF used is crucial for the quinone formation; indeed, the necessary amount of oxygen for the reaction is present in a suitable concentration in commercially available nonanhydrous, non-degassed DMF. It is noteworthy that this protocol yielded only one benzoquinone-type cannabinoid, CBDQ (**8**), as confirmed by NMR analysis.

Conducting the reaction in a pure oxygen atmosphere or with DMF saturated with oxygen resulted in a mixture of inseparable compounds, while the use of degassed DMF did not yield the desired compound.[17,18] The general procedure can be summarized in Scheme 3.

Scheme 3. Conversion of CBD (1) to CBDQ (8)

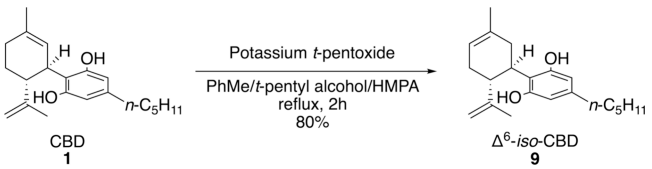


The Δ^6-*iso*-CBD represents the noncyclized analogue of Δ^8-THC and is thermodynamically more stable than CBD. The availability of this isomer as an analytical standard is crucial because it could be an overlooked byproduct of CBD degradation, and its biological properties remain unexplored. Following the Mechoulam protocol,[18] the only synthetic procedure described in the literature for compound **9**, which involves the treatment of CBD (**1**) with neat alkoxide (potassium *t*-pentylate) in toluene-hexamethylphosphoramide (HMPA), resulted in an inseparable mixture of compounds. This mixture included small amounts of the desired Δ^6-CBD isomer, CBDQ (**8**), and unreacted CBD. To obtain Δ^6-*iso*-CBD (**9**) as a single regioisomer through base-catalyzed double bond isomerization, we extensively explored the reaction conditions.

In detail, it was discovered that treating CBD (**1**) with the alkoxide in the presence of an excess of the corresponding alcohol (*t*-pentyl alcohol) led to the desired compound, reaching complete conversion after a 2 h reaction with an isolated yield of 80% for Δ^6-*iso*-CBD (**9**) (Scheme 4). The only observed byproduct was olivetol, with approximately 20% isolated yield.

Due to the fact that Δ^6-*iso*-CBD (**9**) is prone to oxidation, a rapid purification procedure was necessary. A successful approach involved filtration on a silica column using degassed hexane:acetate (95:5) as the eluent.

Scheme 4. Conversion of CBD (1) to Δ^6-*iso*-CBD (9)



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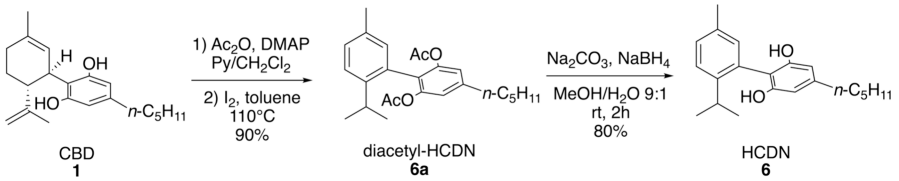
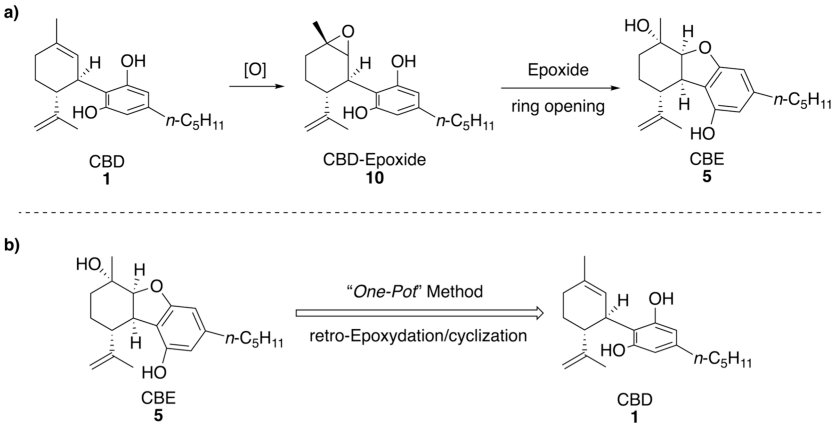
Scheme 5. Conversion of CBD (1) to HCDN (6)



Scheme 6. (a) General Reaction Sequences for the Synthesis of CBE (5); (b) New Retrosynthetic Approach for CBE (5) from CBD (1) without Using Protecting Groups



Another compound of interest was the dihydrocannabinodiol (HCDN, **6**), whose bis-aryl structure was prepared according with the two-step procedure illustrated in Scheme 5.

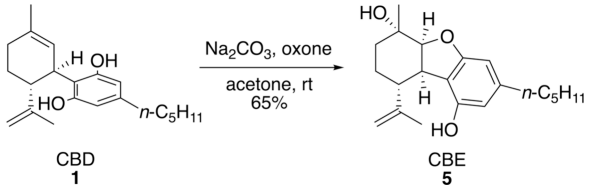
Applying a modified procedure outlined by Pollastro and co-workers[19] for the direct synthesis of cannabinol (CBN) from **1**, the diacetyl-HCDN (**6a**) was successfully isolated with a satisfying yield of 90%. Subsequent reductive deprotection of this intermediate resulted in the production of the desired compound (HCDN, **6**) in 80% yield. It is noteworthy that attempts to prepare HCDN without the acetylation of phenolic functions proved ineffective. For instance, using palladium on activated charcoal in various solvents such as ethyl acetate, toluene, and THF under a nitrogen flow at reflux resulted in unreacted CBD. Other oxidative protocols, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in DCM or MeCN, yielded a complex mixture of degradation products, including CBDQ (**8**) and other oxidized compounds.

The exploration extended to structural-related cannabielsoin derivatives, which share connections with THCs but differ significantly from both retrosynthetic and biogenetic viewpoints. The characteristic structural motif of cannabielsoin (CBE, **5**) involves a benzo-condensate dihydrofuran derived from the cyclization of one of the two phenolic −OH groups at positions 1′/5′ to carbon 2, and an intra-annular double bond Δ-1,2 of the terpenic substructure which occurs via an epoxide-opening reaction (see Figure 2 for standard CBD positions numbering system).

Due to the reactivity of CBD (**1**) under acidic conditions,[3] where 1′(OH)/1 or 5′(OH)/8 cyclization can occur, the strategy involved the utilization of a stereodefined epoxide, as illustrated in Scheme 6a (CBD epoxide, **10**). This approach enabled the directed nucleophilic attack at position 2, leading to the formation of CBE (**5**) through a ring-opening reaction.

The goal was to achieve the preparation of CBE (**5**) through a stereoselective and protecting-groups free approach, optimally in a *one-pot* fashion (Scheme 6b). All syntheses outlined in the literature necessitate the protection of the phenolic group before epoxidation.[20] The only one-step procedure reported by Ali and co-workers is characterized by a notably low yield (approximately 24%).[21] In following the procedure, the protocol described by Dethe and co-workers was adapted and optimized.[22] The synthesis of the stereodefined epoxide framework can be accomplished by utilizing *in situ* prepared DMDO (dimethyldioxirane) from acetone-oxone,[23] while the stereospecific epoxide-opening is induced by the addition of a suitable base. To do so, different bases were employed, including NaOH, *t*BuOK, K_2CO_3, LiOMe, and Na_2CO_3.[7] CBE (**5**) was exclusively obtained with a 65% isolated yield and as a single diastereoisomer when Na_2CO_3 was used as the base, and oxone in acetone served as the epoxidizing agent (Scheme 7). The spectroscopic data aligns with literature findings.[24]

Scheme 7. Optimized Conversion of CBD (1) to CBE (5)



Following the optimization of a robust, stereoselective, and scalable synthesis of CBE, various manipulations of this compound were explored to obtain other related cannabielsoin derivatives. The reaction of CBE with a strong Lewis acid, such as $BF_3{\cdot}Et_2O$ at 0 °C for 40 min, resulted in the formation of the tricyclic compound 1,8-cineol cannabinoid, (CCB, **7**)[25] with an excellent isolated yield of 92% (Scheme 8).

The experimental conversion of **5** into **7** is noteworthy as it confirms the relative 1,4-*cis* stereochemistry between the −OH

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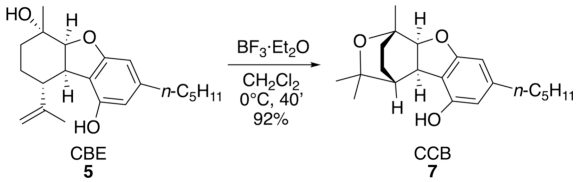
Scheme 8. Conversion of CBE (5) to CCB (7)



moiety and the isopropenyl side chain of the terpene-derived ring (Figure 3).

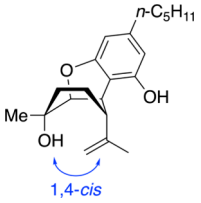


Figure 3. Conformation and absolute configuration of CBE (**5**).

Furthermore, all attempts to induce the dehydration of CBE (**5**) to the corresponding olefin proved to be unsuccessful. This observation aligns with results obtained for analogous structures by Dethe and co-workers.[22] Conventional protocols for eliminating the *tert*-alcohol of CBE (**5**) using classical reagents such as potassium bisulfate, anhydrous zinc chloride, anhydrous copper sulfate, phosphorus pentoxide, or Martin's sulfurane resulted in a complex mixture of undesired byproducts. Unfortunately, even PTSA in toluene at 115 °C was incapable of promoting the dehydration of **5**, yielding only a complex mixture of undefined byproducts.

EXPERIMENTAL SECTION

General Experimental Procedures. All of the reagents were purchased from Sigma-Aldrich and used without any further purification.

CBD (API grade, >99) was purchased from Libella, (FI). Silica gel F254 was used in analytical thin-layer chromatography (TLC, particle size 40−63, Merck), and visualizations were accomplished with UV lamp at 254 nm. Purifications were performed using silica gel cartridges (particle size 40−63 μm, Biotage SNAP column) for flash chromatography MPLC system (utilizing Biotage IsoleraOne instrument) equipped with UV detectors at 212 and 230 nm both.

GC-MS were performed on a Thermo DSQ-II MS spectrometer, EI 70 eV single quadrupole, equipped with Thermo Focus GC. Column type: Restek Rtx5-MS 30 m, ID 0.25 mm. Typical GC rate settings for analysis were: 80 °C (1′ min) → 12 °C/min → 300 °C (5 min), injector temperature 260 °C, MS transfer line temperature 280 °C, and MS ion source temperature 250 °C. Detector and energy: EI (70 eV).

NMR spectra were recorded on Bruker Avance 300 MHz and Bruker Neo 400 MHz. Infrared spectra were collected with a Cary 630 Agilent FTIR spectrometer.

Polarimetric analysis were carried out using PerkinElmer Polarimeter model 241 with a 1 mL glass polarimetric cell.

General Procedure for THCs Synthesis. Cannabidiol **1** (31.4 mg, 0.1 mmol) was dissolved in a dry solvent or mixture of solvents (4 mL): Re-catalyst (2.9 mg, 5 mol %) and, if required (see below), cocatalyst $Cu(OTf)_2$ (1.0 mg, 3 mol %), were added to this solution. The resulting clear reaction mixture was stirred under argon at the selected temperature, and consumption of CBD **1** was checked by GC-MS. When the reaction was completed, it was quenched by filtration over a short pad of silica and eluted with MTBE (15 mL) to obtain a solution of crude product. Volatiles were removed under vacuum and residue purified with silica gel column (5 g, 95:5 *n*Hex-AcOEt), see Supporting Information for more details.

Method A: Regioselective Synthesis of Δ^8-THC (3). Cannabidiol **1** (31.4 mg, 0.1 mmol) was dissolved in dry DCM (4 mL), Re catalyst 2.9 mg (5 mol %) and cocatalyst copper(II) triflate $Cu(OTf)_2$ (1.0 mg, 3 mol %) were added to this solution. The resulting clear reaction mixture was stirred at room temperature under an argon atmosphere for 72 h, and it was checked with GC-MS.

When the starting material was consumed, the reaction was quenched by filtration over a short pad of silica and eluted with MTBE (15 mL) to obtain a solution of crude product. Volatiles were removed under vacuum and residue purified with silica gel column (5 g, 95:5 *n*Hex-AcOEt) to give Δ^8-THC (**3**) (28.9 mg, 92% yield).

$[\alpha]^{20}_D$ −231.0 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, *J* = 1.6 Hz, 1H), 6.13 (d, *J* = 1.7 Hz, 1H), 5.45 (ddt, *J* = 5.6, 2.9, 1.5 Hz, 1H), 4.78 (s, 1H), 3.32−3.12 (m, 1H), 2.72 (td, *J* = 10.8, 4.5 Hz, 1H), 2.59−2.34 (m, 2H), 2.26−2.08 (m, 1H), 1.97−1.77 (m, 3H), 1.73 (d, *J* = 1.8 Hz, 3H), 1.67−1.51 (m, 2H), 1.46−1.25 (m, 7H), 1.13 (s, 3H), 1.00−0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 154.6, 142.6, 134.6, 119.2, 110.4, 110.0, 107.5, 44.8, 35.9, 35.3, 31.5, 30.5, 27.8, 27.4, 23.4, 22.4, 18.4, 13.9; FT-IR (film, cm^{-1}) 3481, l623, 1569, 1417, l361, l263, 1197, 1163, 1049, 963, 911, 803; HRMS (ESI) *m*/*z* 315.2318 [M + H]$^+$ (calcd for $C_{21}H_{31}O_2$, 315.2319).

Method B: Regioselective Synthesis of Δ^9-THC (2). Using the same procedure described in method A without cocatalyst and toluene−DCM (7:3) as a solvent, stirring under an argon atmosphere for 44 h at room temperature, pure Δ^9-THC (**2**) with 89% isolated yield was obtained.

$[\alpha]^{20}_D$ −155.0 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 6.31 (d, *J* = 1.5 Hz, 1H), 6.14 (d, *J* = 1.5 Hz, 1H), 5.08−4.86 (m, 2H), 3.49 (q, *J* = 3.0 Hz, 1H), 2.47 (dd, *J* = 8.9, 6.7 Hz, 2H), 2.36 (d, *J* = 4.5 Hz, 1H), 1.89 (d, *J* = 9.1 Hz, 4H), 1.82−1.45 (m, 7H), 1.34 (d, *J* = 6.0 Hz, 8H), 0.98−0.83 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 157.2, 156.1, 143.2, 133.4, 126.2, 110.2, 110.1, 108.5, 77.6, 47.3, 36.5, 35.1, 32.6, 32.2, 32.0, 28.3, 26.2, 23.9, 23.6, 19.9, 14.7; FT-IR (film, cm^{-1}) 3475, 1625, 1571, l429, l366, l262, 1193, 1164, 1043, 967, 912, 802; HRMS (ESI) *m*/*z* 315.2317 [M + H]$^+$ (calcd for $C_{21}H_{31}O_2$, 315.2319).

Synthesis of Δ^8-*iso*-THC (4). Under an Ar atmosphere to a magnetically stirred solution of CBD **1** (300 mg, 0.95 mmol) in nitrogen-degassed dry CH_3CN (30 mL), $BF_3{\cdot}Et_2O$ (600 μL, 4.86 mmol, 5.1 equiv) was added dropwise. The resulting clear reaction mixture was stirred at reflux for 24 h and then quenched with saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (10 mL) and then dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on 20 g of Florisil (60−100 U.S. mesh). Elution with *n*Hex-Et_2O (95:5) gave Δ^8-*iso*-THC (**4**) (150 mg, 50%) as a colorless oil.

$[\alpha]^{20}_D$ −247.0 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (d, *J* = 1.5 Hz, 1H), 6.14 (d, *J* = 1.5 Hz, 1H), 5.08−4.86 (m, 2H), 3.49 (q, *J* = 3.0 Hz, 1H), 2.47 (dd, *J* = 8.9, 6.7 Hz, 2H), 2.36 (d, *J* = 4.5 Hz, 1H), 1.89 (d, *J* = 9.1 Hz, 4H), 1.82−1.45 (m, 7H), 1.34 (d, *J* = 6.0 Hz, 8H), 0.98−0.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 152.1, 146.0, 142.5, 110.9, 110.7, 107.8, 105.9, 74.6, 42.9, 35.6, 35.3, 31.5, 30.7, 30.4, 29.3, 27.8, 22.6, 22.4, 21.0, 13.9; FT-IR (film, cm^{-1}) 3477, 1631, 1574, l433, l368, l261, 1195, 1161, 1042, 916, 808; HRMS (ESI) *m*/*z* 315.2318 [M + H]$^+$ (calcd for $C_{21}H_{31}O_2$, 315.2319).

Synthesis of CBE (5). To a magnetically stirred solution of CBD **1** (300 mg, 0.95 mmol) in nitrogen-degassed, HPLC grade acetone under static nitrogen atmosphere (20 mL), Na_2CO_3 (260 mg, 2.45 mmol, 2.6 equiv), and 20 mg tetrasodium EDTA (0.05 mmol, 0.05 equiv) were added. The reaction mixture was then cooled to 0 °C and stirred for 10 min. Then, a solution of oxone (1.76 g, 5.73 mmol, 6 equiv in 10 mL of water) was added dropwise in 10 min. After 1 h, the reaction mixture was removed from the ice bath and left at room temperature for an additional 2 h. After completion of the reaction (3

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h), the resulting reaction mixture was quenched with H_2O (5 mL) and was extracted with ethyl acetate (3 × 10 mL). Organic layers were collected, washed with brine (10 mL), and dried over Na_2SO_4. After filtration, the solvent was evaporated and the residue was purified by silica gel column chromatography (5g) and *n*Hex-AcOEt (8:2) to give 186 mg of CBE (**5**) in 60% of isolated yield.

$[\alpha]^{20}_D$ +12.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) 7.47 (s, 1H), 6.18 (s, 2H), 4.70−4.50 (m, 2H), 4.05 (dd, *J* = 5.4, 1.4 Hz, 1H), 3.79 (s, 1H), 3.32 (dd, *J* = 10.7, 5.4 Hz, 1H), 2.94 (s, 1H), 2.53−2.40 (m, 2H), 1.95 (qd, *J* = 12.5, 3.6 Hz, 1H), 1.88−1.77 (m, 4H), 1.75−1.64 (m, 2H), 1.56 (dq, *J* = 9.0, 7.5 Hz, 2H), 1.39 (s, 3H), 1.36−1.23 (m, 4H), 0.92−0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) *δ* 161.0, 154.7, 150.5, 144.8, 118.6, 111.8, 109.8, 103.2, 91.3, 69.2, 51.1, 41.9, 37.0, 36.1, 32.6, 32.2, 28.7, 26.9, 23.5, 20.1, 14.7; FT-IR (film, cm^{-1}) 3492, l624, 1570, l358, l261, 1199, 1166, 1042, 965, 913, 805; HRMS (ESI) *m*/*z* 331.2267 $[M + H]^+$ (calcd for $C_{21}H_{31}O_3$, 331.2268).

Synthesis of Diacetyl-HCDN (6a). CBD (**1**) (200 mg, 0.64 mmol) was dissolved in 2 mL of DCM in the presence of pyridine (2 mL) and of acetic anhydride (2 mL, 20.6 mmol, 33 equiv). A catalytic amount of DMAP was added, and resulting reaction mixture was stirred overnight under nitrogen atmosphere at room temperature. The reaction was quenched with 10 mL of saturated sodium bicarbonate in water. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The organic phase was washed two times with 2 mL of 1 M HCl and 2 mL of brine. The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The so obtained CBD diacetate was used for the further steps without any purification.[24]

A solution of CBD diacetate (95.5 mg, 0.24 mmol, 1.0 equiv) was dissolved in 12 mL of dry toluene under an argon atmosphere, iodine (122 mg, 0.48 mmol, 2.0 equiv) was then added, and the resulting deep-purple solution was heated to reflux for 2 h, until the TLC analysis, using *n*Hex-AcOEt (9:1) as the eluent, showed the complete consumption of the starting material. The reaction mixture was cooled to room temperature, diluted with MTBE (12 mL), and quenched with 5% aqueous solution of $Na_2S_2O_3$ (10 mL). The organic phase was collected, and the aqueous phase was extracted with MTBE (3 × 5 mL). Combined organic layers were washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure (without heating). The pale-yellow oil was purified by silica gel column (12g) using *n*Hex-AcOEt (8:2) as the eluent. The overall yield of diacetyl-HCDN (**6a**) is 90%.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.21 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.88 (s, 2H), 6.81 (d, *J* = 1.9 Hz, 1H), 2.72−2.57 (m, 3H), 2.27 (s, 3H), 1.88 (s, 6H), 1.77−1.62 (m, 2H), 1.37 (dq, *J* = 6.9, 3.6 Hz, 4H), 1.10 (d, *J* = 6.8 Hz, 6H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 169.1, 149.3, 145, 144, 134.4, 131, 130.3, 129.2, 125.8, 125, 120.2, 35.6, 31.7, 30.5, 30.1, 24.2, 22.6, 20.9, 20.6, 14.1; HRMS (ESI) *m*/*z* 397.2372 $[M + H]^+$ (calcd for $C_{25}H_{33}O_4$, 397.2373).

Synthesis of HCDN (6). Pure diacetyl-HCDN (**6a**) (42.9 mg, 0.11 mmol, 1.0 equiv) was dissolved in 1 mL of nitrogen-degassed methanol, this solution was slowly added to another solution (3 mL) prepared with degassed 9:1 methanol:water, containing Na_2CO_3 (35 mg, 0.33 mmol, 3.0 equiv) and $NaBH_4$ (12.5 mg, 0.33 mmol, 3.0 equiv). The resulting clear solution was stirred for 2 h under nitrogen atmosphere and after check with TLC using *n*Hex-AcOEt (9:1) as the eluent, was quenched with 2 mL of 1 M HCl. Methanol was removed under reduced pressure (P_{max} >40 Torr) and aqueous media was extracted with DCM (3 × 3 mL), organic layers were collected, washed with brine (3 mL), and dried over Na_2SO_4. After filtration, volatiles were removed under reduced pressure, and the crude was purified using a silica gel column (12 g, gradient elution from 95:5 to 90:10 *n*Hex-AcOEt). Pure HCDN (**6**) was obtained in 27.4 mg yield with an isolated yield of 80%.

Sodium borohydride was necessary to maintain a reducing environment, preventing oxidation of the phenolic moiety.

^{1}H NMR (400 MHz, CD_3CN) *δ* 7.31 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.30 (s, 2H), 6.13 (s, 2H), 2.67 (p, *J* = 6.9 Hz, 1H), 2.57−2.45 (m, 2H), 2.31 (s, 3H), 2.21 (s, 1H), 1.73−1.54 (m, 2H), 1.46−1.27 (m, 4H), 1.09 (d, *J* = 6.9 Hz, 6H), 0.97−0.89 (m, 2H); ^{13}C NMR (101 MHz, CD_3CN) *δ* 155.7, 146.9, 145.0, 136.3, 132.8, 132.6, 130.0, 126.5, 114.0, 107.9, 36.3, 32.3, 31.7, 30.8, 24.1, 23.2, 20.9, 14.4; HRMS (ESI) *m*/*z* 313.2163 $[M + H]^+$ (calcd for $C_{21}H_{29}O_2$, 313.2162).

Synthesis of CCB (7). Under an Ar atmosphere, cannabielsoin (**5**) (33 mg, 0.1 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (5 mL), the resulting solution was cooled at 0 °C with an ice bath, and then $BF_3{\cdot}Et_2O$ (0.8 mL, 1.6 mmol, 2.0 M in CH_2Cl_2, 1.6 equiv) was added dropwise. The resulting clear reaction mixture was stirred at the same temperature for 40 min and then quenched with saturated aqueous solution of $NaHCO_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on a silica gel. Elution with *n*Hex-AcOEt (92:8) gave CCB (**7**) as colorless oil (30.4 mg, 92%).

$[\alpha]^{20}_D$ +74.2 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3CN) *δ* 6.77 (s, 1H), 6.22−6.12 (m, 2H), 4.54 (dd, *J* = 10.4, 1.8 Hz, 1H), 4.04 (ddd, *J* = 10.4, 3.6, 1.9 Hz, 1H), 2.56−2.43 (m, 2H), 2.07−1.90 (m, 1H), 1.75 (ddtd, *J* = 13.7, 11.8, 3.7, 2.0 Hz, 1H), 1.67−1.40 (m, 4H), 1.39−1.06 (m, 14H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, CD_3CN) *δ* 162.8, 154.9, 146.0, 112.8, 108.6, 102.2, 86.1, 74.3, 71.4, 40.2, 36.5, 35.9, 32.2, 31.9, 29.4, 29.0, 25.7, 25.3, 23.2, 17.8, 14.3; FT-IR (film, cm^{-1}) 3473, 1631, 1569, l432, l363, l265, 1194, 1161, 1045, 963, 917, 809; HRMS (ESI) *m*/*z* 331.2266 $[M + H]^+$ (calcd for $C_{21}H_{31}O_3$, 331.2268).

Synthesis of CBDQ (8). A solution of CBD (**1**) (200 mg, 0.64 mmol) in air equilibrated DMF (30 mL), obtained with 15′ of air bubbling directly in the solvent (see Supporting Information for optimization details), was heated at reflux in an oil bath for 2 h in a 50 mL sealed pressure tube in the presence of NaOEt (65 mg, 0.95 mmol, 1.5 equiv). The resulting reaction mixture was quenched with 1 M HCl (5 mL) and diluted with CH_2Cl_2 (15 mL), the two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL).

The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by filtration on a short pad of silica (3 g) by using degassed *n*Hex-AcOEt (95:5) as the eluent. The overall isolated yield of CBDQ (**8**) is 90%.[18]

$[\alpha]^{20}_D$ −80.0 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.92 (s, 1H), 6.33 (t, *J* = 1.5 Hz, 1H), 5.16−5.00 (m, 1H), 4.48 (dq, *J* = 3.9, 2.4, 1.8 Hz, 2H), 3.66 (ddq, *J* = 10.9, 4.5, 2.3 Hz, 1H), 2.69 (ddd, *J* = 12.1, 10.8, 3.0 Hz, 1H), 2.33 (tt, *J* = 7.1, 1.3 Hz, 2H), 2.22−2.06 (m, 1H), 2.00−1.88 (m, 1H), 1.77−1.50 (m, 8H), 1.50−1.36 (m, 2H), 1.33−1.20 (m, 4H), 0.92−0.73 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 187.2, 184.1, 151.3, 148.4, 144.5, 134.7, 134.0, 122.8, 122.4, 110.7, 44.7, 35.8, 31.4, 30.5, 28.9, 28.1, 27.2, 23.4, 22.4, 18.7, 13.9; FT-IR (neat, cm^{-1}) 3281, 2958, 1348, 1189; HRMS (ESI) *m*/*z* 329.2119 $[M + H]^+$ (calcd for $C_{21}H_{29}O_3$, 329.2119).

Synthesis Δ^6-*iso*-CBD (9). CBD (**1**) (150 mg, 0.48 mmol) was dissolved in dry toluene (12 mL) in the presence of potassium *t*-pentylate (1.7 M solution in toluene, 1 mL) and of *t*-pentyl alcohol (3 mL). HMPA (3 mL) was added to the reaction mixture and refluxed under static nitrogen atmosphere. After 2 h, the solution was washed with 1 M HCl (5 mL) and aqueous phases were extracted with diethyl ether (2 × 10 mL). The extract was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by filtration on a silica column (3 g) using degassed *n*Hex-AcOEt (95:5) as the eluent. The overall isolated yield of Δ^6-*iso*-CBD (**9**) is 70%.

$[\alpha]^{20}_D$ +12.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.40 (s, 2H), 6.18 (s, 2H), 5.33 (d, *J* = 2.5 Hz, 1H), 4.65−4.38 (m, 2H), 4.17−3.95 (m, 1H), 2.92 (td, *J* = 10.3, 5.4 Hz, 1H), 2.39 (dd, *J* = 8.8, 6.6 Hz, 2H), 2.06 (dq, *J* = 5.2, 2.5 Hz, 1H), 1.98 (s, 1H), 1.83−1.62 (m, 7H), 1.61−1.46 (m, 2H), 1.43−1.16 (m, 5H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 157.5, 150.1, 142.7, 134.9, 127.1,

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115.6, 110.9, 108.6, 46.4, 37.2, 36.5, 32.6, 31.9, 31.6, 30.9, 30.6, 29.4, 24.0, 23.6, 19.9, 14.7; HRMS (ESI) m/z 315.2316 $[M + H]^+$ (calcd for $C_{21}H_{31}O_2$, 315.2319).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.3c01117.

Optimization tables and collection of all the NMR spectra and chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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