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Cannabichromene Racemization and Absolute Stereochemistry Based on a Cannabicyclol Analog

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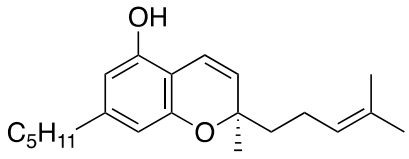
ABSTRACT: Cannabichromene (CBC) is unusual among cannabinoids in having been described as both a racemic and a scalemic compound from natural *Cannabis* sources. Several explanations are available for this circumstance, including facile racemization. Cannabichromene was resolved chromatographically, and the enantiomer matching CBC from local *Cannabis* was identified. To preclude racemization, CBC was converted to cannabicyclol for further stereochemical analysis. This permitted the (*R*) absolute stereochemistry to be assigned to natural CBC based on chiroptical data for related natural products and the absolute configuration of a cannabicyclol analog determined by x-ray crystallography. The racemization of CBC was found to be rather slow in the laboratory, but handling practices for natural cannabis products can be inferred to promote the process.

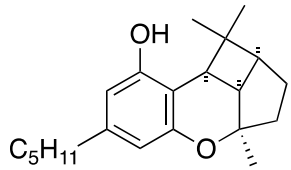
INTRODUCTION

There is a long history of study of the chemical constituents of *Cannabis* species, and a vast dataset is available.[1] As expected, most cannabinoid natural products are isolated in optically active form, typically as one dominant enantiomer (Chart 1). Exceptions to that observation include cannabichromene (CBC, **1**), and its derived [2+2] cycloaddition product, cannabicyclol (CBL, **2**), both of which have been reported to be found in

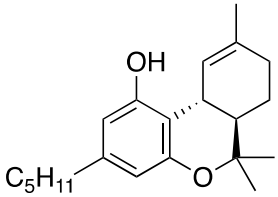
racemic form from *Cannabis* plants.[2] However, there are several inconsistencies in the record. A recent study reports that CBC in a *Cannabis* cultivar popular in Europe, Bedrocan, is scalemic.[3] One explanation for that observation is that it is originally generated in optically active form and then (partially) racemized. Understanding the basis of these observations motivated the following study.



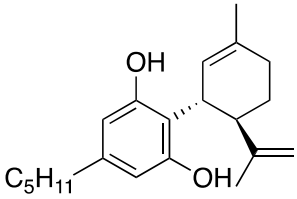
(-)-cannabichromene (CBC)
1



cannabicyclol (CBL)
2



(-)-Δ^9-trans-tetrahydrocannabinol (THC)

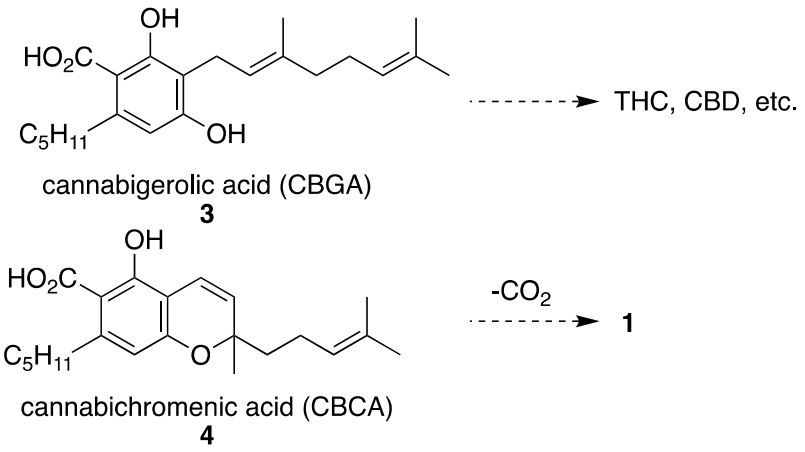


(-)-cannabidiol (CBD)

Chart 1

Cannabinoids are biosynthesized (Scheme 1) from monoterpene and polyketide portions via a key intermediate that unites the two, cannabigerolic acid (CBGA, **3**). Various cyclization pathways lead from it to the well-known natural cannabinoid structures, which are initially formed as their salicylic acid versions. Relatively facile decarboxylation of these species leads to the more recognized cannabinoid structures. An oxidative cyclization of **3** can generate **4**, and it then leads to **1**. While it is conceivable that the natural production of **4** gives a racemic compound, in the original isolation of CBCA from *Cannabis*, it *was* reported to have a positive optical rotation.[4] However, the biosynthesis of CBCA performed in vitro by Morimoto with an enzyme preparation

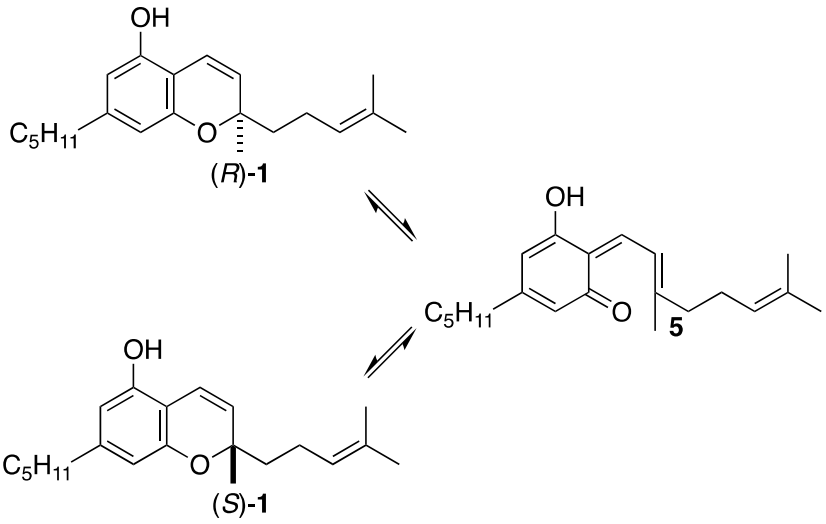
partially purified from *Cannabis* leaves produced a sample with negligible optical rotation.[5] These two accounts are at odds with one another. Further, the in vitro-produced CBCA is apparently scalemic based on its exhibiting a CD signal. Morimoto converted his CBCA to CBC (120 °C, 5 min) and concluded that decarboxylation does not cause racemization. The CBCA enantiomers could not be separated by chiral HPLC, but the CBC enantiomers could be separated using a Chiralcel OD-R column. If the lack of racemization in decarboxylation of CBCA seen by Morimoto also reflects the outcome in a plant, the reported isolation of natural, racemic CBC must be the result of racemization of **1** with age or handling after biosynthesis. We therefore wished to study CBC racemization to understand how easily it occurs. We also took this opportunity to determine the absolute configuration of natural CBC and CBL, since this has been unknown and cannot be inferred from the configuration of other cannabinoids.



Scheme 1

We considered one mechanism for the racemization of CBC or related compounds from *Cannabis* plants involving electrocyclic ring opening to an achiral quinone methide **5** (Scheme 2). Such species are well-known and often invoked in reaction pathways to

chromene structures based on condensation of α,β-unsaturated aldehydes (like citral, in racemic syntheses of CBC[6]) with resorcinol derivatives. Mechanisms of racemization involving ether protonation and tertiary allylic cation formation are also reasonable.



Scheme 2

RESULTS

CBC Enantiomers

Literature procedures for the preparation of racemic CBC from citral and olivetol were used to obtain material that was supplied to Regis Technologies, which resolved it by preparative chiral HPLC. Analytical chiral HPLC (Lux® 5 μm Amylose-1 LC Column, 250 × 4.6 mm) shows clean separation of the enantiomers. CBC was obtained from several US-based, commercial, naturally derived cannabis products and analyzed using this HPLC method. The *er*s found were: cannabicitran tincture – 44:56; *Cannabis* extract 1 – 29:71; *Cannabis* extract 2 ($scCO_2$) – 21:79; with the enantiomers listed in elution order. Since in all samples the slower eluting enantiomer was the greater component, an obvious conclusion is that this is the natural enantiomer, which was initially dominant in

Cannabis plants upon its biosynthesis, and partial racemization has occurred. Taken together, these data identify the enantiomer naturally produced in native plants as the slower eluting component in this chromatographic method. They also show that CBC is not intrinsically produced in racemic form. It is reasonable to believe that the biocatalytic production of CBCA gives a single enantiomer, and that its stereochemistry is compromised subsequent to conversion to CBC. Measurement of the CBC enantiomeric ratio could also be performed by analytical chiral supercritical fluid chromatography (SFC) (Lux Cellulose-5), providing baseline separation.

Chiroptical Properties of CBC

Chiral SFC of the CBC enantiomers showed the natural isomer is the faster eluting and has a negative optical rotation, while the slower eluting isomer has a positive optical rotation. CD spectra of both are shown in Figure 1, reflecting their expected mirror-image relationship. In the earlier Morimoto study,[5] CD spectra of CBC were also reported. There is some agreement of the data for our samples and that past work, in that the appearances of the spectra are similar. However, Morimoto identified the isomer with the positive CD signal at ca. 280 nm as the *natural*, *enzymatically produced* enantiomer. Though his publication appeared over two decades ago, we were able to correspond with Morimoto on the inconsistency. He shared unpublished information, that CD spectra were similar for natural CBC (presumably, from *Cannabis*) and the *minor* of the enzymatically-derived enantiomers of CBC, which he had attributed to experimental error and had not disclosed publicly. Therefore, his conclusions about the sign of the CD signal of the natural CBC enantiomer are truly ambiguous. We believe that it has a

negative rotation and a negative CD signal at 280 nm. In an earlier study of CBC by chiral chromatography (using a Whelk 01 column),[3] the major enantiomer of a sample of *er* 63:37 was that with a positive CD signal at 280 nm. This work contradicts our belief, which we cannot readily explain.

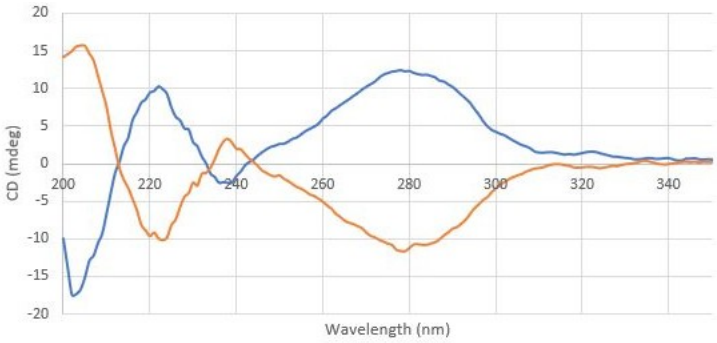


Figure 1. CD spectra of CBC enantiomers (0.2 mg/mL) in methanol. The gold line is the natural enantiomer and the blue line is the unnatural enantiomer.

Absolute configuration of CBL (and CBC by inference)

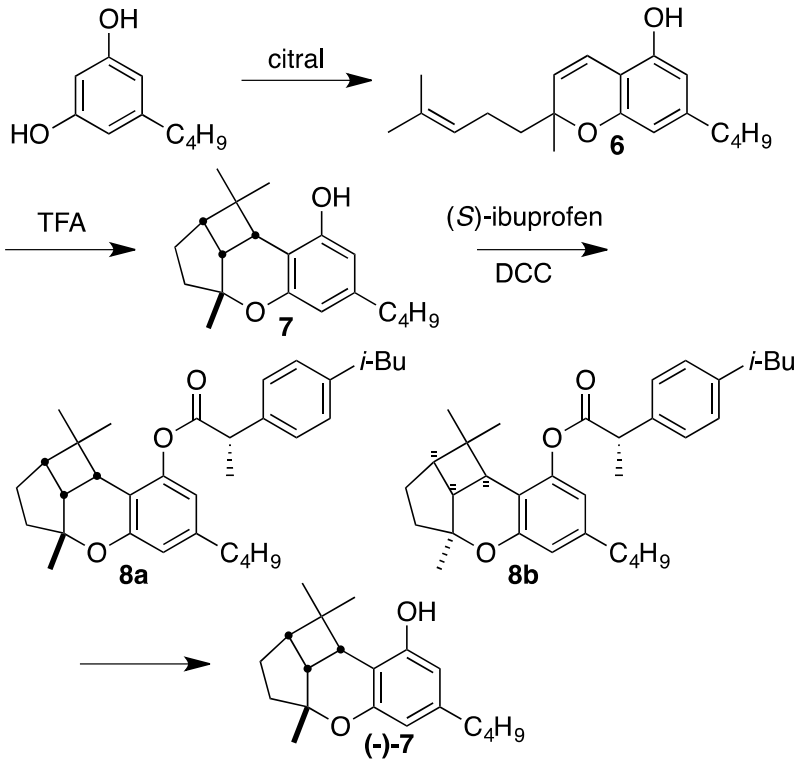
We aimed to further address the natural stereochemistry of CBC by determining its absolute configuration by reference to a known stereocenter. This might be accomplished by resolving CBC classically via a derivative prepared from a chiral compound. Several attempts failed to identify an ester resolving agent for CBC using acids of known absolute configuration. We became concerned that the manipulations involved in a classical resolution could racemize CBC, since the ease of racemization was unknown, so we developed a strategy to lock in its stereochemistry. This could be accomplished by converting CBC to CBL, which does not have an obvious pathway of racemization such as is shown in Scheme 2. We then chose to synthesize a CBL derivative of known

absolute configuration that could be used to provide a comparison to CBL prepared from natural CBC.

Cannabinoids currently have ambiguous regulatory status in the United States, with many conflicts between Federal rules (Drug Enforcement Administration, DEA) and the rules of various States. Details are covered in a recent publication.[7] Some plant-derived compounds are subject to DEA Schedule 1, depending on their source, with hemp-derived cannabinoids being free of that regulation. In one instance, the DEA has de-scheduled *synthetic* cannabinoids other than those prominent in drugs, such as THC and CBD. To remove any ambiguity concerning the source of the materials we prepared, and therefore establish the propriety of their synthesis and use, we chose to make a minor structural modification, replacing the pentyl group of the olivetol portion of our cannabinoids with a butyl group, creating *nor* analogs. Since olivetol/olivetolic acid is derived from a polyketide-based biosynthesis, a butyl cannabinoid should not have arisen from grown *Cannabis*. We believed this structural change would cause only a subtle change in any biological activities that might be studied for compounds we would prepare. We likewise thought that the chiroptical properties of these analogs could be validly compared to those of natural CBC-derived materials.

The synthesis of *nor*-CBL was performed as shown in Scheme 3. 5-Butyl resorcinol was condensed with citral using the procedure of Lee.[6] That reaction generates *nor*-CBC **6** in modest yield. Application of the Hsung procedure[8] converted it to *nor*-CBL **7**. That compound was esterified with (+)-ibuprofen to give the diastereomers **8a** and **8b**. These were separable by chromatography and the former was crystalline. Compound **8a** was

analyzed by x-ray crystallography to establish the stereochemistry depicted (Figure S1), which is the (*R*) absolute configuration at the methyl-bearing stereocenter of the pyran. The ibuprofen esters could be removed from **8a** and **8b** by trans-esterification in alcohol with mild base. For **8a**, that delivers the levorotatory **7**. CD spectra were obtained for both enantiomers of **7**, and as expected they show a mirror-image relationship.



Scheme 3

Using the procedure of Hsung, the unnatural enantiomer (+)-CBC was converted to the unnatural enantiomer of CBL (**2**) in 89% yield. It proved to have a positive optical rotation. This matches with the *nor*-cannabicyclol that has the *S* absolute configuration at the tertiary ether. The CD spectrum of CBL was compared with each enantiomer of synthetic **7** (Figure S3), which have their major CD signals at ca. 215 nm. Its CD signal at this wavelength is positive. Therefore, the absolute configuration of natural cannabicyclol

is *R*, and since it was derived from cannabichromene **1**, its absolute configuration at the tertiary ether is also *R* (as depicted at the beginning of this article).

Racemization of CBC

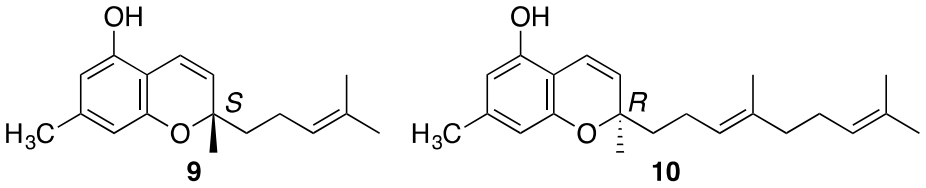
Our observation that CBC samples of different provenance show different *er*s suggests that handling practices for plant material once CBC has been produced in the plant may promote racemization. We wished to examine that process under controlled laboratory conditions as a guide to minimizing CBC racemization. Thermal racemization of the unnatural enantiomer of CBC was examined at 80, 90, and 100 °C in toluene (1 mg/mL). At time points, aliquots were removed and immediately cooled in ice-water. Samples were then analyzed by SFC. After 24 h at 80 °C, only 3.0% racemization had occurred. After 6 h at 90 and 100 °C, 3.0% and 11.3%, respectively, racemization had occurred. Acid-catalyzed CBC racemization was examined at ambient temperature in acetonitrile. *p*-TsOH (10 mol%) was used as the catalyst, and aliquots were removed at time points and quenched with 10 mol% triethylamine. No detectable racemization occurred up to 24 h. These findings suggest that racemization of CBC is not very easy, which is somewhat at odds with the suggestion from diverse natural CBC sources having variant *er*s that it is facile. Unknown factors may be at work in the storage and handling of plants or the production of extracts (now appearing for commercial sale in many jurisdictions) that are more effective in promoting racemization.

DISCUSSION

The thermal or acid-catalyzed racemization of CBC were surprisingly difficult to achieve. The results suggest that rough handling of the plant or the isolated material

could indeed be responsible for the lack of detectable optical activity in samples that have been analyzed in past published reports. However, the lack of an optical rotation is a poor criterion to assert that a compound is racemic. Other information is required to make that pronouncement definitive, such as CD or the chiral chromatographic methods used here.

The assignment of CBC absolute configuration made above is further supported by other experimental data. Two classes of natural products closely related in structure to CBC have been reported (Chart 2), cannabiorcichromene (**9**)[9] and confluentin (**10**).[10] Both come from *Rhododendron* sp., but they lie in different enantiomeric series. Interestingly, congeners of **9**, all *S* isomers, all have positive rotations. Congeners of **10** all have negative rotations, and their CD spectra show the same negative signal at 280 nm as does natural CBC.



9 **10**

Chart 2

The chiral properties of these different chromene natural products are summarized in Table 1. Absolute configuration assignments for **9** and **10** made by Kitanaka, who isolated them, were based on analysis of their CD spectra.

Table 1. Stereochemical measures of chromene natural products

Compound	Name	Source	CD @ 280 nm	$[\alpha]_D$	assigned absolute configuration	Reference
1	CBC	*Cannabis*	negative	negative	R	this work
9	cannabiorcichromen	*Rhododendron*	positive	NR	S	Kitanaka[10]

	e					
10	confluentin	*Rhododendron*	negative	negative	R	Kitanaka[11]

Our results have shown that CBC is not easily racemized under fairly stringent laboratory conditions, but that practices in the cultivation, harvesting, and preparation for sale of *Cannabis*-derived products may erode its optical purity.

We have considered the possibility that different *Cannabis* cultivars from diverse geographies might produce different enantiomers of CBC, to explain the inconsistency of the absolute configurations assigned to different samples of CBC in different labs. This is not such a foreign concept, especially considering that enzymes in different *Rhododendron* species are capable of producing similar natural products in different enantiomeric series. Systematic surveys of CBC chirality would be necessary to assess this idea, though. CBC racemization could complicate the analysis of such studies. It might be preferable to use the *er* of CBL derived from CBC as a better representation of the dominant stereoisomer in a particular plant.

EXPERIMENTAL SECTION

General. TLC was performed using Merck 60 F254 aluminum-backed plates and visualized using UV and $KMnO_4$ stain. Flash column chromatography was performed using Silicycle silica gel (230-400 mesh). Melting points were determined using an automated Buchi B-545 melting point apparatus, which provides a specific melting point, not a range, and are corrected. ^{1}H NMR spectra were obtained on a Bruker Avance (500 MHz) spectrometer. $^{13}C\{^{1}H\}$ NMR spectra were obtained on Bruker Avance NEO (100 MHz) and Bruker Avance (150 MHz) spectrometers. Chemical shifts are referenced to

the residual solvent signal ($CDCl_3$: δ_H 7.26, δ_C 77.16). Infrared spectra were recorded on a Bruker Alpha spectrometer. High-resolution mass spectra were obtained using an Agilent 6545 LC/SFC Hybrid Q-TOF spectrometer. Optical rotations were taken on a Rudolph AutoPol IV polarimeter. Circular dichroism experiments were performed on a Jasco J-815 CD spectrometer.

(+)-Cannabichromene (1). This sample was obtained as described. $[\alpha]_D^{22}$ (*c* 1.1, $CHCl_3$) + 96°. The CD spectrum is provided in Figure 1, blue. SFC (Lux Cellulose-5; 35 °C; CO_2:MeOH 98:2; 2.75 mL/min) R_t 5.13 min.

(-)-Cannabichromene (1). This sample was obtained as described. It shows a HPLC retention time identical to the major peak in naturally-derived CBC samples. $[\alpha]_D^{22}$ (*c* 1.1, $CHCl_3$) - 96°. The CD spectrum is provided in Figure 1, gold. SFC (Lux Cellulose-5; 35 °C; CO_2:MeOH 98:2; 2.75 mL/min) R_t 3.23 min.

(+)-Cannabicyclol (2). A sample of (+)-cannabichromene described above (35 mg, 0.11 mmol) was converted to cannabicyclol by the Hsung procedure. The crude residue was purified by flash chromatography (1% ethyl acetate in hexanes) to afford a white solid (31 mg, 89%). $[\alpha]_D^{23}$ +4° (*c* 0.7, $CHCl_3$). mp 87.7 °C (pentane). Its spectroscopic properties matched those earlier reported.[11] The CD spectrum is provided in Figure S2.

5-Butylresorcinol. The spectroscopic data for this compound were consistent with the structure and information available from the literature.[12]

***nor*-Cannabichromene (6)**. Using the procedure of Lee,[11] this compound was prepared from 5-butylresorcinol and citral in 32% yield (35 mg) as an orange oil. R_f (10% ethyl acetate in hexanes) 0.28. ^{1}H NMR (500 MHz, CDCl3): δ 6.61 (d, *J* = 10 Hz, 1H), 6.25 (s,

1H), 6.12 (s, 1H), 5.49 (d, *J* = 10 Hz, 1H), 5.09 (t, *J* = 7.1 Hz, 1H), 4.77 (s, 1H), 2.45 (t, *J* = 7.7 Hz, 2H), 2.10 (m, 2H), 1.75 – 1.67 (m, 2H) 1.66 (s, 3H), 1.57 (s, 3H), 1.54 (m, 2H), 1.38 (s, 3H), 1.32 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 154.2, 151.1, 144.8, 131.8, 127.4, 124.3, 116.9, 109.3, 107.8, 107.1, 78.3, 41.2, 35.7, 33.2, 26.4, 25.8, 22.8, 22.4, 17.7, 14.1. IR (neat) 3397, 3045, 2960, 2926, 2857, 1622, 1575 cm^{-1}. HRMS (ESI) *m/z* $[M-H]^-$ Calcd for $C_{20}H_{27}O_2$: 299.2011; Found: 299.2023. SFC (Lux Cellulose-1; 35 °C; CO_2:MeOH 98:2; 2.75 mL/min) R_t 8.21 min and 9.11 min.

(±)-*nor*-Cannabicyclol (7). Using the procedure of Hsung,[9] this compound was prepared from *nor*-cannabichromene and purified by flash column chromatography (2% ethyl acetate in hexanes) in 77% yield (27 mg). R_f (10% ethyl acetate in hexanes) 0.45. mp 138.6 °C (petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.18 (s, 1H), 4.53 (s, 1H), 3.07 (d, *J* = 9.6 Hz, 1H), 2.58 (m, 1H), 2.46 (m, 2H), 2.40 (t, *J* = 7.2 Hz, 1H), 1.98 (s, 1H), 1.72 – 1.65 (m, 1H), 1.65 – 1.50 (m, 4H), 1.38 (s, 3H), 1.38 (s, 3H), 1.32 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.80 (s, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 154.2, 154.1, 142.7, 110.5, 108.7, 107.4, 83.3, 46.4, 39.1, 37.9, 37.8, 36.2, 35.5, 34.1, 33.3, 27.8, 25.8, 22.5, 18.1, 14.1. IR (neat) 3353, 2950, 2929, 2861, 1620, 1582 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ Calcd for $C_{20}H_{29}O_2$: 301.2168; Found: 301.2175.

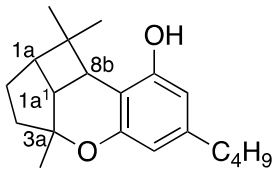
***nor*-Cannabicyclyl ibuprofenate (8)**. To a solution of (±)-*nor*-cannabicyclol (87 mg, 0.29 mmol) in methylene chloride (5 mL) was added *N,N'*-dicyclohexylcarbodiimide (90 mg, 0.43 mmol) and 4-dimethylaminopyridine (21 mg, 0.17 mmol). (*S*)-(+)-Ibuprofen (90 mg, 0.43 mmol) was added and the solution was stirred at room temperature under nitrogen for 24 h. The precipitate was filtered off and the filtrate was evaporated *in vacuo*.

The residue was dissolved in ethyl acetate and washed with water. The organic phase was dried with Na_2SO_4 and concentrated via rotary evaporation to give an oily solid. The oily solid was purified by flash column chromatography (20% methylene chloride in hexanes) to afford the two diastereomeric products separately: one as an oil (62 mg, 44%) and the other as a solid (62 mg, 44%).

(1aS,1a^{1}R,3aR,8bR,2'S)-(8a). White solid. mp 69.2 °C (ethanol/water). R_f (40% methylene chloride in hexanes) 0.30. ^{1}H NMR (500 MHz, CDCl3): δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.58 (s, 1H), 6.27 (s, 1H), 3.91 (q, *J* = 7.1 Hz, 1H), 2.94 (d, *J* = 9.6 Hz, 1H), 2.55 – 2.45 (m, 5H), 2.36 (m, 1H), 2.00 – 1.80 (m, 2H), 1.74 – 1.65 (m, 1H), 1.60 (d, *J* = 7.1 Hz, 3H), 1.53 (m, 4H), 1.34 (s, 3H), 1.30 (m, 2H), 1.22 (s, 3H), 0.93 – 0.87 (m, 9H), 0.66 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 173.0, 154.3, 149.6, 142.4, 140.9, 137.3, 129.6, 127.5, 115.7, 114.7, 113.9, 83.7, 46.5, 45.6, 45.2, 39.6, 38.7, 38.4, 36.3, 35.3, 34.2, 33.1, 30.4, 29.9, 27.1, 25.6, 22.5, 18.8, 18.3, 14.1. IR (neat) 2952, 2925, 2855, 1754, 1624, 1568. HRMS (ESI) *m/z* [M+H]$^+$ Calcd for $C_{33}H_{45}O_3$: 489.3369; Found: 489.3352. $[\alpha]_D^{23}$ +60° (*c* 0.2, $CHCl_3$). The stereostructure was established by x-ray crystallography.

(1aR,1a^{1}S,3aS,8bS,2'S)-(8b). Pale yellow oil. R_f (40% methylene chloride in hexanes) 0.23. ^{1}H NMR (500 MHz, CDCl3): δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.58 (s, 1H), 6.42 (s, 1H), 3.90 (q, *J* = 7.1 Hz, 1H), 2.86 (d, *J* = 9.6 Hz, 1H), 2.46 (m, 5H), 2.31 (m, 1H), 1.97 (m, 1H), 1.86 (m, 1H), 1.68 (m, 1H), 1.61 (d, *J* = 7.2 Hz, 3H), 1.55 (m, 4H), 1.35 – 1.27 (m, 5H), 1.03 (s, 3H), 0.94 – 0.85 (m, 9H), 0.63 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3): δ 173.2, 154.4, 149.4, 142.3, 140.9, 137.4, 129.6,

127.5, 115.6, 115.0, 114.2, 83.9, 46.5, 45.6, 45.2, 39.6, 39.4, 38.8, 35.8, 35.4, 33.9, 33.2, 30.4, 29.9, 26.6, 25.5, 22.5, 19.5, 18.6, 14.1. IR (neat) 2952, 2926, 2857, 1755, 1624, 1573. HRMS (ESI) *m/z* [M+H]$^+$ Calcd for $C_{33}H_{45}O_3$: 489.3369; Found: 489.3358. $[\alpha]_D^{23}$ +13° (*c* 0.2, $CHCl_3$).



(+)-(1aR,1a^{1}S,3aS,8bS)-*nor*-Cannabicyclol (7). To a solution of the non-crystalline diastereomer **8b** (1a*R*,1a^1*S*,3a*S*,8b*S*,2′*S*)-*nor*-cannabicyclyl ibuprofenate (62 mg, 0.13 mmol) in methanol (2 mL) was added potassium carbonate (27 mg, 0.19 mmol), and the solution was stirred at room temperature for 48 h. The solvent was removed under reduced pressure to afford a yellow oily solid. It was purified by flash column chromatography (1% ethyl acetate in hexanes) to give a white solid (31 mg, 81%). mp 107.4 °C (petroleum ether). $[\alpha]_D^{21}$ +6° (*c* = 0.8, $CHCl_3$). The CD spectrum is provided in Figure S3.

(-)-(1aS,1a^{1}R,3aR,8bR)-*nor*-Cannabicyclol (7). The crystalline diastereomer **8a** was dissolved in ethanol (2 mL) at 50 °C. The solution remained homogenous upon cooling to room temperature. To the solution was added potassium carbonate (12 mg, 0.09 mmol) and the mixture was stirred at room temperature for 24 h. The mixture was passed through a silica plug and eluted with ethyl acetate. The collected pale yellow solution was concentrated under reduced pressure into a yellow oily solid. The solid was purified by

flash column chromatography (1% ethyl acetate in hexanes) to afford a white solid (21 mg, 81%). Mp 107.7 °C (petroleum ether). $[\alpha]_D^{21}$ = -6° (*c* 0.6, $CHCl_3$).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at {URL}

^1H and $^{13}C\{^1H\}$ NMR spectra of **6**-**8**, CD spectra of **7** and CBL, solution of the x-ray structure of **8a**, and x-ray data tables (PDF)

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Notes

CBC is a commercial product of BayMedica. The authors declare no other competing financial interests.

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