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## Cannabinoid Ester Constituents from High-Potency *Cannabis sativa*

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Eleven new cannabinoid esters, together with three known cannabinoid acids and  $\Delta^9$ -tetrahydrocannabinol ( **$\Delta^9$ -THC**), were isolated from a high-potency variety of *Cannabis sativa*. The structures were determined by extensive spectroscopic analyses to be  $\beta$ -fenchyl  $\Delta^9$ -tetrahydrocannabinolate (**1**), *epi*-bornyl  $\Delta^9$ -tetrahydrocannabinolate (**2**),  $\alpha$ -terpenyl  $\Delta^9$ -tetrahydrocannabinolate (**3**), 4-terpenyl  $\Delta^9$ -tetrahydrocannabinolate (**4**),  $\alpha$ -cadinyl  $\Delta^9$ -tetrahydrocannabinolate (**5**),  $\gamma$ -eudesmyl  $\Delta^9$ -tetrahydrocannabinolate (**6**),  $\gamma$ -eudesmyl cannabigerolate (**7**), 4-terpenyl cannabinolate (**8**), bornyl  $\Delta^9$ -tetrahydrocannabinolate (**9**),  $\alpha$ -fenchyl  $\Delta^9$ -tetrahydrocannabinolate (**10**),  $\alpha$ -cadinyl cannabigerolate (**11**),  $\Delta^9$ -tetrahydrocannabinol ( **$\Delta^9$ -THC**),  $\Delta^9$ -tetrahydrocannabinolic acid A ( **$\Delta^9$ -THCA**), cannabinolic acid A (**CBNA**), and cannabigerolic acid (**CBGA**). Compound **8** showed moderate antimicrobial activity against *Candida albicans* ATCC 90028 with an  $IC_{50}$  value of 8.5  $\mu$ g/mL. CB-1 receptor assay indicated that the esters, as well as the parent acids, are not active.

The family Cannabaceae is currently recognized as containing only one genus, namely, *Cannabis*, which includes only one highly variable species: *Cannabis sativa* L. Other previously reported species include *Cannabis indica* Lam. and *Cannabis ruderalis* Janisch. Plants considered to have belonged to these species are now recognized as varieties of *C. sativa* L. (var. *indica* and var. *ruderalis*, respectively). *C. sativa* L. has been used by humans for thousands of years, providing fiber for spinning and making paper, seed for human and animal consumption, and aromatic resin for medicinal use. The chemotypes of *C. sativa* L. can be divided into drug type (marijuana), intermediate type, and fiber type (hemp), with the tetrahydrocannabinol ( $\Delta^9$ -THC) content ranging from 1 to 20%, 0.3–1.0%, and <0.3%, respectively.<sup>1–3</sup>

*Cannabis* is very complex in its chemistry due to the vast number of its constituents and their possible interaction with one another. The compounds reported include many natural product classes, e.g., mono- and sesquiterpenes, sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds, and amino acids.<sup>4–10</sup> The best-known and the most specific group of compounds found in *cannabis* is the C<sub>21</sub> terpenophenolics, the cannabinoids, with (–)- $\Delta^9$ -*trans*-(6aR,10aR)-tetrahydrocannabinol ( **$\Delta^9$ -THC**) being the most psychoactive constituent.<sup>11</sup> The development of synthetic cannabinoids and the discovery of chemically different endogenous cannabinoid receptor ligands (endocannabinoids) have prompted the use of the term “phytocannabinoids” to describe these compounds.<sup>12</sup> The class cannabinoids can be divided into 11 groups: cannabigerol type (7 known), cannabichromene type (5 known), cannabidiol type (7 known), (–)- $\Delta^9$ -*trans*-tetrahydrocannabinol type (9 known), (–)- $\Delta^8$ -*trans*-tetrahydrocannabinol type (2 known), cannabicyclol type (3 known), cannabielsoin type (5 known), cannabinol type (7 known), cannabinodiol type (2 known), cannabitriol type (9 known), and miscellaneous type (14 known).<sup>7</sup>

The medicinal properties of *Cannabis* have been much debated from scientific and political points of view, and the subject has lost and gained interest over the years. After the discovery of the primary active constituent in marijuana,  **$\Delta^9$ -THC**, in 1964,<sup>13</sup> various clinical trials were undertaken to determine its efficacy as an analgesic,<sup>14</sup> antiemetic,<sup>15</sup> antidepressant,<sup>16</sup> and appetite suppres-

sant<sup>17</sup> and for the treatment of glaucoma<sup>18</sup> and chemotherapy-induced nausea and vomiting.<sup>19</sup> The onset of HIV as a worldwide problem refocused marijuana as a possible symptom management drug and led to the discovery of the endocannabinoid (endogenous cannabinoid) system.<sup>20</sup>

Features of this system include that cannabinoids act through receptors, that there are at least two types of receptors (CB1<sup>21</sup> and CB2<sup>22</sup>), and that there are endogenous cannabinoid receptor agonists and antagonists (ligands). The CB1 receptor, uniquely recognized by cannabinoids, is found in brain and peripheral tissue of the central nervous system (CNS),<sup>23</sup> while the CB2 receptor is primarily found outside the CNS in tissues associated with immune function.<sup>24</sup>

The availability of high-potency marijuana on the illicit market with unprecedented  **$\Delta^9$ -THC** concentrations (>20% by dry weight)<sup>25</sup> has renewed our interest in the discovery of new constituents from *C. sativa* L. We herein report the isolation and structure elucidation of 11 new esters from a high-potency variety of *cannabis*. These esters are  $\beta$ -fenchyl  $\Delta^9$ -tetrahydrocannabinolate (**1**), *epi*-bornyl  $\Delta^9$ -tetrahydrocannabinolate (**2**),  $\alpha$ -terpenyl  $\Delta^9$ -tetrahydrocannabinolate (**3**), 4-terpenyl  $\Delta^9$ -tetrahydrocannabinolate (**4**),  $\alpha$ -cadinyl  $\Delta^9$ -tetrahydrocannabinolate (**5**),  $\gamma$ -eudesmyl  $\Delta^9$ -tetrahydrocannabinolate (**6**),  $\gamma$ -eudesmyl cannabigerolate (**7**), 4-terpenyl cannabinolate (**8**), bornyl  $\Delta^9$ -tetrahydrocannabinolate (**9**),  $\alpha$ -fenchyl  $\Delta^9$ -tetrahydrocannabinolate (**10**), and  $\alpha$ -cadinyl cannabigerolate (**11**). In addition, four known cannabinoids were isolated,  $\Delta^9$ -tetrahydrocannabinol ( **$\Delta^9$ -THC**),  $\Delta^9$ -tetrahydrocannabinolic acid A ( **$\Delta^9$ -THCA**), cannabinolic acid A (**CBNA**), and cannabigerolic acid (**CBGA**). All isolated compounds were evaluated for antimicrobial and antimalarial activity, as well as CB-1 receptor binding.

## Results and Discussion

*Cannabis* plant material was sequentially extracted with hexanes, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc, EtOH, EtOH/H<sub>2</sub>O, and H<sub>2</sub>O. The hexanes extract was subjected to vacuum liquid chromatography (VLC) on flash silica gel. Fractions were combined according to their TLC profiles and chromatographed using flash silica gel eluting with hexanes. Fractions with *R<sub>f</sub>* higher than  **$\Delta^9$ -THC** were combined and purified by flash silica gel and Sephadex LH-20 chromatography, followed by final purification by semipreparative reversed-phase (RP) and chiral HPLC. This yielded 11 new esters (**1–11**).

The spectroscopic data of **1–6**, **9**, and **10** were similar to that of  **$\Delta^9$ -THCA**, with the characteristic four methyls resonating at  $\delta$  1.67 (3H, s, H-11), 1.43 (3H, s, H-13), 1.09 (3H, s, H-12), and 0.88

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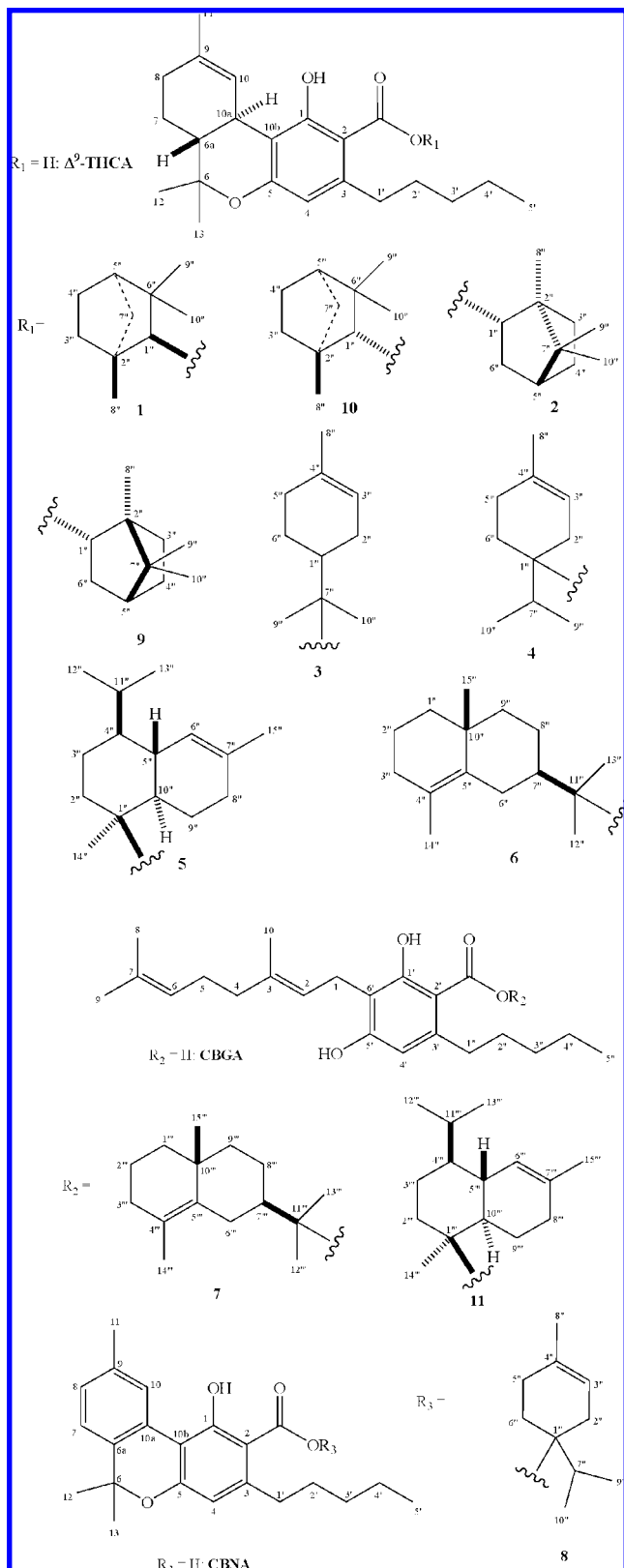
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Table 1. <sup>1</sup>H NMR Data (δ) for Δ<sup>9</sup>-THCA Esters **1**, **2**, **4**, **5**, **6**, **9**, and **10** in CDCl<sub>3</sub> (*J* in Hz)

no.	Δ <sup>9</sup> -THCA <sup>a</sup>	<b>1</b> <sup>a</sup>	<b>2</b> <sup>a</sup>	<b>4</b> <sup>a</sup>	<b>5</b> <sup>a</sup>	<b>6</b> <sup>b</sup>	<b>9</b> <sup>a</sup>	<b>10</b> <sup>a</sup>
4	6.25 s	6.23 s	6.23 s	6.20 s	6.20 s	6.22 s	6.23 s	6.23 s
6a	1.71 m	1.71 m	1.71 m	1.63 m	1.63 m	1.71 m	1.71 m	1.71 m
7	1.40, 1.90 m	1.40, 1.90 m	1.40, 1.90 m	1.40, 1.86 m	1.40, 1.86 m	1.43, 1.92 m	1.40, 1.90 m	1.40, 1.90 m
8	2.14 m	2.17 m	2.15 m	2.20 m	2.20 m	2.11 m	2.15 m	2.17 m
10	6.38 s	6.41 s	6.41 s	6.41 s	6.41 s	6.32 s	6.41 s	6.40 s
10a	3.20 (d, <i>J</i> = 10.4)	3.20 (d, <i>J</i> = 10.8)	3.20 (d, <i>J</i> = 10.8)	3.20 (d, <i>J</i> = 9.4)	3.20 (d, <i>J</i> = 10.8)	3.20 (d, <i>J</i> = 11.0)	3.20 (d, <i>J</i> = 10.8)	3.20 (d, <i>J</i> = 10.8)
11	1.67 s	1.67 s	1.67 s	1.67 s	1.67 s	1.68 s	1.67 s	1.67 s
12	1.09 s	1.09 s	1.09 s	1.08 s	1.11 s	1.06 s	1.09 s	1.09 s
13	1.43 s	1.43 s	1.43 s	1.43 s	1.43 s	1.43 s	1.43 s	1.43 s
1'	2.80, 2.93 m	2.90, 3.08 m	2.80, 2.92 m	2.70, 2.80 m	2.70, 2.80 m	2.80, 3.10 m	2.80, 2.92 m	2.90, 3.08 m
2'	1.57 m	1.57 m	1.57 m	1.57 m	1.57 m	1.57 m	1.57 m	1.57 m
3'	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m
4'	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m	1.33 m
5'	0.88 (t, <i>J</i> = 6.4)	0.88 (t, <i>J</i> = 6.4)	0.88 (t, <i>J</i> = 6.4)	0.88 (t, <i>J</i> = 6.4)	0.88 (t, <i>J</i> = 6.4)	0.88 (t, <i>J</i> = 7.0)	0.88 (t, <i>J</i> = 6.4)	0.88 (t, <i>J</i> = 6.4)
1''	4.70 s	4.70 s	5.19 m	1.93 m	1.57 m	1.63, 1.42 m	5.19 m	4.65 s
2''			1.80 m	5.30 (t, <i>J</i> = 11.8)	1.90 m	1.69 m	1.80 m	1.85 m
3''			1.26 m		1.99 m	1.98, 1.95 m	1.26 m	1.72 m
4''			1.75 m	1.93 m	1.26 m		1.75 m	1.77 (t, <i>J</i> = 4.2)
6''			1.17 (t, <i>J</i> = 3.2)	1.25 m	5.51 (d, <i>J</i> = 11.8)	1.98, 1.82 m	1.17 (t, <i>J</i> = 3.2)	
7''		1.20, 1.60 (d, <i>J</i> = 8.0)		3.02 sep		1.58 m		1.20, 1.60 (d, <i>J</i> = 7.8)
8''	1.12 s	1.12 s	0.93 s	1.67 s	1.99 m		0.93 s	1.12 s
9''	0.82 s	0.82 s	0.97 s	0.95 (d, <i>J</i> = 6.4)	1.31 m	1.27, 1.48 m	0.97 s	0.82 s
10''	1.12 s	1.12 s	0.91 s	0.95 (d, <i>J</i> = 6.4)	2.16 m	1.38, 1.14	0.91 s	1.12 s
11''					1.90 m			
12''					0.90 (d, <i>J</i> = 6.0)	1.28 s		
13''					0.81 (d, <i>J</i> = 7.0)	1.28 s		
14''					1.26 s	1.63 s		
15''					1.68 s	1.06 s		
OH	12.18 s	12.72 s	12.54 s	12.84 s	12.52 s	12.52 s	12.54 s	12.74 s

<sup>a</sup> 400 MHz. <sup>b</sup> 500 MHz.

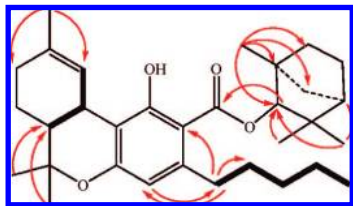
**Table 2.**  $^{13}\text{C}$  NMR Data ( $\delta$ ) for  $\Delta^9$ -THCA Esters **1**, **2**, **4**, **5**, **9**, and **10** in  $\text{CDCl}_3$ 

no.	$\Delta^9$ -THCA <sup>a</sup>	1 <sup>a</sup>	2 <sup>a</sup>	4 <sup>a</sup>	5 <sup>a</sup>	9 <sup>a</sup>	10 <sup>a</sup>
1	165.1	164.1	163.8	164.2	166.3	163.8	164.1
2	102.6	104.3	104.5	104.9	105.8	104.5	104.3
3	147.3	145.2	145.1	145.9	147.0	145.1	145.2
4	113.0	111.4	111.7	111.9	112.0	111.7	111.7
5	160.1	158.7	158.6	158.7	159.7	158.6	158.7
6	79.2	78.7	78.7	78.6	79.0	78.8	78.7
6a	46.0	46.0	45.9	46.0	45.8	45.9	46.0
7	25.3	25.3	25.3	25.2	25.2	25.3	25.3
8	31.6	31.5	31.4	31.6	31.3	31.4	31.4
9	134.2	133.9	133.8	133.9	134.6	133.9	133.8
10	124.0	124.1	124.1	124.2	124.8	124.1	124.1
10a	33.8	33.8	33.8	33.8	33.6	33.8	33.8
10b	110.2	110.0	110.0	109.9	110.0	110.0	110.0
11	23.7	23.6	23.6	23.6	23.8	23.6	23.6
12	19.9	19.9	19.6	19.7	19.7	19.6	19.9
13	27.7	27.6	27.6	27.6	27.6	27.6	27.6
1'	36.9	36.3	36.5	36.4	36.7	36.5	36.3
2'	31.6	31.2	31.5	31.5	31.5	31.5	31.2
3'	32.4	32.0	32.1	32.3	32.3	32.0	32.0
4'	22.9	23.0	23.0	22.9	22.7	23.0	23.0
5'	14.4	14.3	14.3	14.4	14.3	14.3	14.3
1''		89.6	82.8	89.9	85.7	82.8	90.1
2''		48.5	49.0	34.8	35.4	48.6	48.5
3''		27.6	28.4	117.7	18.7	28.5	27.6
4''		26.1	31.4	134.2	37.0	31.4	26.1
5''		48.6	44.9	27.7	44.3	44.9	48.6
6''		39.9	37.2	31.8	126.0	37.2	39.58
7''		41.8	48.1	36.9	134.6	48.1	40.0
8''		19.7	14.0	23.4	37.0	14.0	19.7
9''		20.7	19.2	17.2	21.7	19.2	20.7
10''		29.7	20.0	18.4	53.6	20.0	29.7
11''					26.6		
12''					21.9		
13''					15.5		
14''					28.1		
15''					23.59		
COOH	176.4	173.6	172.2	173.3	171.3	173.3	173.6

<sup>a</sup> 100 MHz.

Compound **1** was obtained as a colorless oil, and its molecular formula was determined to be  $\text{C}_{32}\text{H}_{46}\text{O}_4$  by HRESIMS ( $m/z$  495.3532 [ $\text{M} + \text{H}$ ] $^+$ ), representing 10 degrees of unsaturation. The  $^{13}\text{C}$  NMR spectrum of **1** revealed 32 carbon resonances, of which 22 corresponded to the  $\Delta^9$ -THCA moiety (assigned through  $^2J$  and  $^3J$  HMBC correlations). A comparison between the  $^{13}\text{C}$  NMR spectra of **1** and  $\Delta^9$ -THCA revealed that the carbon resonances were almost identical, except for an upfield chemical shift of the carbonyl signal from  $\delta$  176.4 to  $\delta$  173.6. The 10 additional signals were assigned to an oxymethine carbon of the ester moiety at  $\delta$  89.6 (C-1'') and three methyl, three methylene, one methine, and two quaternary carbons. The HMBC spectrum of **1** displayed correlation between H-1'' ( $\delta_{\text{H}}$  4.70, s) and the carbonyl carbon ( $\delta_{\text{C}}$  173.6), indicating that **1** was a monoterpenol  $\Delta^9$ -THCA ester. HMQC and HMBC data suggested that the monoterpenol moiety was fenchol, in which the position of the oxygenated methine ( $\delta_{\text{C}}$  89.6,  $\delta_{\text{H}}$  4.70, s) was confirmed by HMBC correlations between  $\text{H}_3$ -8''/C-1'' ( $^3J_{\text{CH}}$ ),  $\text{H}_3$ -9''/C-1'' ( $^3J_{\text{CH}}$ ), and  $\text{H}_3$ -10''/C-1'' ( $^3J_{\text{CH}}$ ). The structure was confirmed by GC-MS: compound **1** spontaneously hydrolyzed and decarboxylated on injection to give  $\Delta^9$ -THC and a monoterpenol. The monoterpenol was identified as  $\beta$ -fenchol by library search (NIST), by retention time comparison with an authentic sample, and by comparison with published mass spectra.<sup>27</sup> The trimethylsilyl derivative of **1** showed a molecular ion at  $m/z$  566 in the GC-MS, confirming the HRESIMS result and the presence of one phenolic group. Full assignments of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR resonances were completed via analysis of the COSY,

(3H, t,  $J = 6.4$  Hz, H-5'), an aromatic proton signal at  $\delta$  6.23 (1H, s, H-4), and a broad olefinic resonance at  $\delta$  6.41 (1H, s, H-10) for **1** (Table 1).<sup>26</sup> Significant differences between these compounds and  $\Delta^9$ -THCA were observed in the NMR spectra, in which the carbonyl resonance was shifted upfield from  $\delta$  176.4 to  $\delta$  173.6 and the OH resonance shifted downfield from  $\delta$  12.18 to  $\delta$  12.72. These findings, together with an IR absorption band at  $1718\text{ cm}^{-1}$  (ester C=O), indicated that compounds **1**–**6**, **9**, and **10** are  $\Delta^9$ -THCA esters.



**Figure 1.** Important HMBC (arrows) and COSY (bold) correlations of **1**.

HMQC, HMBC, and ROESY spectra (Tables 1 and 2, Figure 1), confirming **1** as  $\beta$ -fenchyl  $\Delta^9$ -tetrahydrocannabinolate.

Compounds **2–6**, **9**, and **10** were isolated as oily compounds, with  $^1\text{H}$  NMR (Table 1),  $^{13}\text{C}$  NMR (Table 2), and GC-MS data similar to the data for **1**, indicating that they also were  $\Delta^9$ -THCA esters. Analyses of the spectroscopic data in the manner described above for **1** led to the structure elucidation of these compounds as *epi*-bornyl  $\Delta^9$ -tetrahydrocannabinolate (**2**),  $\alpha$ -terpenyl  $\Delta^9$ -tetrahydrocannabinolate (**3**), 4-terpenyl  $\Delta^9$ -tetrahydrocannabinolate (**4**),  $\alpha$ -cadinyl  $\Delta^9$ -tetrahydrocannabinolate (**5**),  $\gamma$ -eudesmyl  $\Delta^9$ -tetrahydrocannabinolate (**6**), bornyl  $\Delta^9$ -tetrahydrocannabinolate (**9**), and  $\alpha$ -fenchyl  $\Delta^9$ -tetrahydrocannabinolate (**10**).

The spectroscopic data of **7** and **11** were in accordance with that of **CBGA**.<sup>28</sup> The  $^1\text{H}$  NMR spectrum for **11** displayed three methyl resonances at  $\delta$  1.58 (3H, s, H-8), 1.68 (3H, s, H-9), and 1.83 (3H, s, H-10), three methylenes at  $\delta$  2.11 (2H, m, H-5), 2.21 (2H, m, H-4), and 3.44 (2H, d,  $J$  = 7.0 Hz, H-1), and two olefinic proton resonances at  $\delta$  5.07 (1H, t,  $J$  = 6.4 Hz, H-6) and 5.28 (1H, t,  $J$  = 7.0 Hz, H-2), attributed to a geranyl substituent. It also displayed an aromatic proton signal at  $\delta$  6.23 (1H, s, H-4'). Detailed analyses of the spectroscopic data indicated that **7** and **11** were **CBGA** esters.

Compound **11** was obtained as a colorless oil, and its molecular formula was determined to be  $\text{C}_{37}\text{H}_{56}\text{O}_4$  by HRESIMS ( $m/z$  563.4122 [ $\text{M} - \text{H}]^-$ ), representing 10 degrees of unsaturation. The  $^{13}\text{C}$  NMR spectrum of **11** revealed 22 carbon resonances almost identical to those of **CBGA**, except for an upfield chemical shift of the carbonyl carbon from  $\delta$  176.2 to  $\delta$  171.3. The spectrum showed 15 additional carbon resonances attributed to an oxygenated quaternary carbon at  $\delta$  85.0 (C-1'') and four methyl, four methylene, five methine, and one quaternary carbon, indicating that **11** is a sesquiterpenol **CBGA** ester. GC-MS analysis spontaneously hydrolyzed and decarboxylated **11** to give **CBG** and a sesquiterpenol. The sesquiterpenol was initially identified as a cadinol isomer via a library search (NIST) and was subsequently found to be  $\alpha$ -cadinol through retention time comparison with an authentic sample and by comparison with published mass spectra.<sup>27</sup> GC-MS analysis of the trimethylsilyl derivative of **11** yielded a molecular ion at  $m/z$  636, confirming the presence of one phenolic group in **11**. Therefore, the structure of **11** was assigned as  $\alpha$ -cadinyl cannabigerolate.

The structure of **7** was similarly elucidated as  $\gamma$ -eudesmyl cannabigerolate based on  $^1\text{H}$  NMR,<sup>29</sup> HRESIMS, GC-MS, trimethylsilyl derivatization, and IR data.

The spectroscopic data of **8** were in accordance with that of **CBNA**, displaying characteristic aromatic protons at  $\delta$  8.46 (1H, s, H-10), 7.14 (1H, d,  $J$  = 7.8, H-7), and 7.09 (1H, d,  $J$  = 7.8, H-8)<sup>30</sup> and carbons at  $\delta$  127.3 (C-10), 122.5 (C-7), and 128.2 (C-8), indicating, in conjunction with HRESIMS, GC-MS, trimethylsilyl derivatization, and IR data, that **8** was a **CBNA** ester. Compound **8** was obtained as a yellow oil, and its molecular formula was determined to be  $\text{C}_{32}\text{H}_{42}\text{O}_4$  by HRESIMS ( $m/z$  513.2133 [ $\text{M} + \text{Na}]^+$ ), representing 12 degrees of unsaturation. The  $^{13}\text{C}$  NMR spectrum revealed 22 carbon resonances corresponding to the **CBNA** moiety, with only an upfield shift of the carbonyl group from  $\delta$  176.2 to  $\delta$  171.9. Compound **8** showed 10 additional carbon resonances due to an oxygenated  $\text{sp}^3$  quaternary carbon at  $\delta$  89.0

(C-1'') and three methyl, three methylene, two methine, and one  $\text{sp}^2$  quaternary carbon, indicating that **8** was a monoterpeneol **CBNA** ester. GC-MS analysis gave CBN and the liberated monoterpeneol. The alcohol was identified as a terpineol isomer via a library search (NIST) and was subsequently found to be 4-terpineol through retention time comparison with an authentic sample and by comparison with published mass spectra.<sup>27</sup> GC-MS analysis of the trimethylsilyl derivative of **8** yielded a molecular ion at  $m/z$  562, confirming the HRESIMS result. On the basis of these observations, **8** was assigned as 4-terpenyl cannabinate.

In identifying the mono- and sesquiterpene moieties of these esters, an extensive search was undertaken to determine whether these terpenols have previously been found in *Cannabis*. This was problematic, since in most cases only a general identification was made. For example, fenchol is reported in eight publications as a volatile oil constituent of cannabis, without any indication of stereochemistry, with  $\beta$ -fenchol being reported in two publications<sup>31,32</sup> and  $\alpha$ -fenchol not being reported. All reports for borneol are for ( $\pm$ )-*endo*-borneol,<sup>32</sup> as in **9**; however **2**, which is a C-1'' epimer of borneol, has not been reported before. ( $\pm$ )- $\alpha$ -Terpineol has been reported in numerous publications,<sup>32</sup> with only two publications giving the absolute configuration as ( $-$ )-(*S*), although identification was achieved only via GC-MS analysis. ( $\pm$ )-4-Terpeneol has also been reported in a number of publications, without any indication of stereochemistry.<sup>32</sup> Cadinol has been reported as the *epi*- $\alpha$ -isomer ( $\tau$ -cadinol);<sup>33</sup> however based on GC-MS library data,<sup>27</sup> **5** and **11** were identified as  $\alpha$ -cadinol esters.  $\gamma$ -Eudesmol has been reported before.<sup>32,34</sup>

Although the cannabis plant has been studied extensively over the past four decades, this is, to the best of our knowledge, the first phytochemical analysis of a high-potency material,<sup>25</sup> and the first newly isolated cannabinoids since 1995,<sup>7</sup> indicating that the high-potency nature of the plant material could open the field to the isolation of other new metabolites.

## Biological Activity

The isolated compounds were evaluated for antimicrobial activity<sup>35</sup> (*Candida albicans* ATCC 90028, *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium intracellulare* ATCC 23068, and *Aspergillus fumigatus* ATCC 90906), as well as antimalarial activity [*Plasmodium falciparum* (D6 clone) and *Plasmodium falciparum* (W2 clone)].<sup>35</sup> The isolated esters and the parent acids were tested for their binding affinity to CB-1 receptor.<sup>36</sup>

Compound **8** showed moderate antimicrobial activity against *C. albicans* ATCC 90028, with an  $\text{IC}_{50}$  value of 8.5  $\mu\text{g/mL}$ , and mild antimalarial activity against *P. falciparum* (D6 clone) and *P. falciparum* (W2 clone), with  $\text{IC}_{50}$  values of 2.7 and 2.4  $\mu\text{g/mL}$ , respectively. CB-1 receptor binding assay indicated that the esters, as well as the parent acids, are not active.

## Experimental Section

**General Experimental Procedures.** 1D and 2D NMR spectra were recorded in  $\text{CDCl}_3$  on a Bruker Avance DPX-500 spectrometer and on a Varian AS 400 spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrophotometer. UV spectra were obtained on a Varian Cary 50 Bio UV-visible spectrophotometer. Optical rotations were measured at ambient temperature using a Rudolph Research Analytical Autopol IV automatic polarimeter. HRESIMS was obtained using a Bruker Bioapex FTMS in ESI mode.

TLC was carried out on aluminum-backed plates precoated with silica gel F<sub>254</sub> (20  $\times$  20 cm, 200  $\mu\text{m}$ , 60  $\text{\AA}$ , Merck) and on glass-backed plates precoated with C18 silica gel F<sub>254</sub> (10  $\times$  10 cm, 200  $\mu\text{m}$ , 60  $\text{\AA}$ , 11% carbon loading, Silicycle). Visualization was accomplished by spraying with Fast Blue B salt (0.5% w/w in  $\text{H}_2\text{O}$ ) or *p*-anisaldehyde [0.5 mL in glacial acetic acid (50 mL) and  $\text{H}_2\text{SO}_4$  (97%, 1 mL)] spray reagent followed by heating. Flash silica gel (40–63  $\mu\text{m}$ , 60  $\text{\AA}$ , Silicycle) and SiliaBond C18 silica gel (40–63  $\mu\text{m}$ , 60  $\text{\AA}$ , 17% carbon loading, Silicycle) were used for column chromatography. Analytical HPLC was



**Table 3.** <sup>1</sup>H and <sup>13</sup>C NMR Data (δ) for CBGA Esters **7** and **11** and CBNA Ester **8** in CDCl<sub>3</sub> (*J* in Hz)

no.	δ <sub>H</sub> of CBGA <sup>a</sup>	δ <sub>C</sub> of CBGA <sup>b</sup>	δ <sub>H</sub> of 7 <sup>a</sup>	δ <sub>H</sub> of 11 <sup>a</sup>	δ <sub>C</sub> of 11 <sup>b</sup>	no.	δ <sub>H</sub> of CBNA <sup>a</sup>	δ <sub>C</sub> of CBNA <sup>b</sup>	δ <sub>H</sub> of 8 <sup>a</sup>	δ <sub>C</sub> of 8 <sup>b</sup>
1	3.44 (d, <i>J</i> = 7.0)	22.7	3.44 (d, <i>J</i> = 7.0)	3.44 (d, <i>J</i> = 7.0)	22.7	1		163.7		163.9
2	5.28 (t, <i>J</i> = 7.0)	121.5	5.28 (t, <i>J</i> = 7.0)	5.28 (t, <i>J</i> = 7.0)	121.6	2		104.2		104.9
3		139.3			139.5	3		149.2		149.5
4	2.21 m	40.0	2.19 m	2.21 m	40.0	4	6.44 s	113.2	6.44 s	113.2
5	2.11 m	26.6	2.11 m	2.11 m	26.6	5		159.5		159.2
6	5.06 (t, <i>J</i> = 6.4)	124.0	5.07 (t, <i>J</i> = 7.0)	5.07 (t, <i>J</i> = 6.4)	124.0	6		78.8		78.7
7		130.2			130.2	6a		136.0		136.0
8	1.58 s	17.9	1.58 s	1.58 s	17.9	7	7.14 (d, <i>J</i> = 7.8)	122.5	7.14 (d, <i>J</i> = 7.8)	122.5
9	1.68 s	25.9	1.69 s	1.68 s	25.9	8	7.11 (d, <i>J</i> = 7.8)	128.2	7.09 (d, <i>J</i> = 7.8)	128.2
10	1.83 s	16.4	1.82 s	1.83 s	16.4	9		137.2		137.2
1'		163.0			163.0	10	8.46 s	127.3	8.46 s	127.3
2'		104.0			104.0	10a		127.3		127.3
3'		147.0			147.0	10b		109.2		109.2
4'	6.23 s	111.4	6.22 s	6.23 s	111.4	11	2.38 s	21.8	2.40 s	21.8
5'		162.3			162.3	12	1.62 s	27.6	1.63 s	27.6
6'		110.0			110.0	13	1.62 s	27.6	1.63 s	27.6
1''	2.71 (t, <i>J</i> = 7.2)	36.8	2.72 (t, <i>J</i> = 7.2)	2.71 (t, <i>J</i> = 7.2)	37.0	1'	2.94 m	37.0	2.97 m	37.1
2''	1.60 m	31.7	1.60 m	1.60 m	31.7	2'	1.66 m	31.4	1.66 m	31.4
3''	1.36 m	32.2	1.36 m	1.36 m	32.2	3'	1.26 m	32.2	1.26 m	32.2
4''	1.36 m	22.7	1.36 m	1.36 m	22.7	4'	1.26 m	22.8	1.26 m	22.8
5''	0.88 (t, <i>J</i> = 7.2)	14.3	0.88 (t, <i>J</i> = 7.2)	0.88 (t, <i>J</i> = 7.2)	14.3	5'	0.91 (t, <i>J</i> = 6.9)	14.3	0.91 (t, <i>J</i> = 6.9)	14.3
1'''			1.61, 1.42 m		85.0	1''				89.0
2'''			1.69 m	1.58 m	35.4	2''			1.93 m	34.7
3'''			1.99, 1.95 m	1.91 m	18.7	3''			5.31 (t, <i>J</i> = 11.8)	118.5
4'''				2.01 m	37.0	4''				134.2
5'''				1.28 m	44.3	5''			1.93 m	27.3
6'''			1.98, 1.82 m	5.55 (d, <i>J</i> = 11.8)	125.0	6''			1.26 m	31.0
7'''			1.59		134.6	7''			3.02 sep	37.2
8'''			1.27, 1.48 m	2.01 m	31.3	8''			1.69 s	23.5
9'''			1.38, 1.14	1.32 m	21.7	9''			0.95 (d, <i>J</i> = 6.4)	17.1
10'''				2.16 m	54.3	10''			0.95 (d, <i>J</i> = 6.4)	18.1
11'''				1.90 m	26.6	11''				
12'''			1.28 s	0.94 (d, <i>J</i> = 6.0)	21.9	12''				
13'''			1.28 s	0.81 (d, <i>J</i> = 7.0)	15.5	13''				
14'''			1.63 s	1.28 s	28.1	14''				
15'''			1.06 s	1.69 s	23.8	15''				
OH	11.60 s		12.52 s	12.25 s		OH	12.78 s		12.85 s	
COOH		176.2			171.3	COOH		176.2		171.9

<sup>a</sup> 400 MHz. <sup>b</sup> 100 MHz.

performed on a Waters 2695 separations module [Empower Pro 2 software (Build 2154)] connected to a Waters 2996 photodiode array (PDA) detector (190–500 nm) and a Sedere Sedex 75 evaporative light scattering (ELS) detector (3.5 psi N<sub>2</sub>, 50 °C) using a Phenomenex Luna C18(2) column (150 × 4.6 mm, 5 μm, 100 Å) [MeCN (100%), 1.0 mL/min], a Phenomenex Luna Silica (2) column (150 × 4.6 mm, 5 μm, 100 Å) [*n*-hexane/EtOH (99:1), 1.0 mL/min], and a Regis (*R,R*)-DACH DNB 10/100 chiral column (250 × 4.6 mm, 10 μm, 100 Å) [*n*-hexane/EtOH (99:1), 1.0 mL/min]. Semipreparative HPLC was performed on a Waters Delta Prep 4000 preparative chromatography system [Empower Pro Software (Build 1154)] connected to a Waters 486 tunable absorbance detector (206 nm) using a Phenomenex Luna C18(2) column (250 × 21.2 mm, 5 μm, 100 Å) [MeCN (100%), 35.4 mL/min], a Phenomenex Luna Silica (2) column (250 × 21.2 mm, 5 μm, 100 Å) [*n*-hexane/EtOH (99:1), 35.4 mL/min], and a Regis (*R,R*)-DACH DNB 10/100 chiral column (250 × 10 mm, 10 μm, 100 Å) [*n*-hexane/EtOH (99:1), 35.4 mL/min].

GC-MS analyses were carried out on a ThermoQuest Trace 2000 GC, equipped with a single split/splitless capillary injector, a ThermoQuest AS2000 autosampler, and a Phenomenex ZB-5 column (30 m × 0.25 mm × 0.25 μm), interfaced to a ThermoQuest-Finnigan Trace MS quadrupole detector. The injector temperature was 250 °C, and 1 μL injections were performed in splitless mode, with the splitless time set at 60 s, the split flow set at 50 mL/min, and the septum purge valve set to close 60 s after the injection occurred. The oven temperature was raised from 70 to 270 °C (hold 20 min) at a rate of 5 °C/min, for a total run time of 60 min; the transfer line temperature was 250 °C. Helium was used as the carrier gas at a constant pressure of 20 psi. The mass spectrometer was operated in the electron impact mode (EI<sup>+</sup>) and scanned from 40 to 800 amu at 1 scan/s, with an ionizing voltage of 70 eV and an emission current of 350 μA. Data were recorded using an IBM Netfinity 3000 workstation with Microsoft Windows NT 4.0 operating system (Build 1381, Service pack 6) and Xcalibur data acquisition and analysis software (Version 1.2). The NIST Mass Spectral Search Program (Version 1.7, Build 11/05/1999) for the NIST/EPA/NIH Mass Spectral Library was employed to assist in the identification of the mono- and sesquiterpenols.

Mono- and sesquiterpene reference standards, including DL-isoborneol, (–)-borneol, (+)-fenchol, β-terpineol, α-terpineol, (–)-4-terpineol, (+)-4-terpineol, and cadinol, were purchased from Acros Organics (Morris Plains, NJ), Alfa Aesar (Ward Hill, MA), Chem-SampCo (Trenton, NJ), Sigma (St. Louis, MO), Aldrich (Milwaukee, WI), Fluka (St. Louis, MO), and MicroSource Discovery Systems (Gaylordsville, CT). Solutions (1 mg/mL) were prepared in CH<sub>2</sub>Cl<sub>2</sub> for GC-MS analysis.

**Plant Material.** Plants were grown from high-potency Mexican *C. sativa* seeds (variety code CHPF-01). Whole buds of mature female plants were harvested, air-dried, manicured, packed in barrels (# 1196), and stored at low temperature (–24 °C).

**Extraction and Isolation.** The plant material (9.0 kg) was sequentially extracted with hexanes (2 × 60 L), CH<sub>2</sub>Cl<sub>2</sub> (48 L), EtOAc (40 L), EtOH (37.5 L), EtOH/H<sub>2</sub>O (36 L, 1:1), and H<sub>2</sub>O (40 L) at room temperature. The extracts were evaporated under reduced pressure at 40 °C to afford hexanes (1.48 kg), CH<sub>2</sub>Cl<sub>2</sub> (0.15 kg), EtOAc (0.13 kg), EtOH (0.09 kg), EtOH/H<sub>2</sub>O (0.77 kg), and H<sub>2</sub>O (0.54 kg) extracts for a total extract of 3.16 kg (35.1%, w/w).

The hexanes extract (0.96 kg) was subjected to VLC on flash silica gel eluting with a hexanes, EtOAc, and MeOH gradient. Reversed-phase column chromatography of VLC fraction 4 (hexanes gradient) (7 g) using MeOH as eluent, followed by pooling of fractions with *R<sub>f</sub>* higher than Δ<sup>9</sup>-THC according to silica gel TLC (hexanes/EtOAc, 9:1) and final purification by semipreparative C18 HPLC, afforded **1** (4 mg, *t<sub>R</sub>* = 30 min), **2** (15 mg, *t<sub>R</sub>* = 29 min), fraction A (18 mg, *t<sub>R</sub>* = 22 min), and fraction B (6 mg, *t<sub>R</sub>* = 24 min).

Final purification of fractions A and B through semipreparative chiral HPLC afforded **3** (0.5 mg, *t<sub>R</sub>* = 3 min), **4** (6 mg, *t<sub>R</sub>* = 3.5 min), **5** (3.8 mg, *t<sub>R</sub>* = 4.8 min), **6** (0.7 mg, *t<sub>R</sub>* = 15 min), **7** (0.6 mg, *t<sub>R</sub>* = 14 min) and **8** (1.3 mg, *t<sub>R</sub>* = 20 min) and **9** (1.5 mg, *t<sub>R</sub>* = 4 min), **10** (2 mg, *t<sub>R</sub>* = 4.5 min), and **11** (1 mg, *t<sub>R</sub>* = 17 min), respectively.

Fractions with *R<sub>f</sub>* similar to or lower than Δ<sup>9</sup>-THC according to silica gel TLC (hexanes/EtOAc, 75:25) were combined and purified by flash silica gel chromatography (hexanes, 100%), followed by final purification by semipreparative silica HPLC, to afford Δ<sup>9</sup>-THC (250 mg), Δ<sup>9</sup>-THCA (150 mg), CBNA (5 mg), and CBGA (40 mg).

Δ<sup>9</sup>-THC,<sup>26</sup> Δ<sup>9</sup>-THCA,<sup>26</sup> CBNA,<sup>30</sup> and CBGA<sup>28</sup> were identified by comparison with published data; however, this is the first time full NMR data are reported for CBNA.

**GC-MS Trimethylsilyl Derivatization.** Dried samples (ca. 100 μg) were treated with pyridine (5 μL, silylation grade, Pierce) and BSTFA [*N,O*-bis(trimethylsilyl)trifluoroacetamide] (100 μL, 98+%, Acros Organics), followed by heating at 75 °C for 1 h. After cooling to room temperature, CH<sub>2</sub>Cl<sub>2</sub> (0.9 mL) was added to the reaction mixture and the solution analyzed by GC-MS.

**β-Fenchyl Δ<sup>9</sup>-Tetrahydrocannabinolate (1):** colorless oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +363.2 (c 0.1, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3404, 2930, 1718, 1638, 1568, 1314, 1013 cm<sup>–1</sup>; for <sup>1</sup>H NMR and <sup>13</sup>C NMR, see Tables 1 and 2, respectively; HRESIMS *m/z* 495.3532 [M + H]<sup>+</sup> (calcd for C<sub>32</sub>H<sub>47</sub>O<sub>4</sub>, 495.3474).

**epi-Bornyl Δ<sup>9</sup>-Tetrahydrocannabinolate (2):** yellow oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +89.9 (c 0.1, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3404, 2941, 1718, 1638, 1568, 1457, 1015 cm<sup>–1</sup>; for <sup>1</sup>H NMR and <sup>13</sup>C NMR, see Tables 1 and 2, respectively; HRESIMS *m/z* 493.3322 [M – H]<sup>–</sup> (calcd for C<sub>32</sub>H<sub>45</sub>O<sub>4</sub>, 493.3318).

**α-Terpenyl Δ<sup>9</sup>-Tetrahydrocannabinolate (3):** yellow oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +115.6 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3404, 2941, 1718, 1610, 1568, 1457, 1015 cm<sup>–1</sup>; HRESIMS *m/z* 493.3304 [M – H]<sup>–</sup> (calcd for C<sub>32</sub>H<sub>45</sub>O<sub>4</sub>, 493.3318).

**4-Terpenyl Δ<sup>9</sup>-Tetrahydrocannabinolate (4):** yellow oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +118.0 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3404, 2941, 1718, 1610, 1568, 1457, 1189 cm<sup>–1</sup>; for <sup>1</sup>H NMR and <sup>13</sup>C NMR, see Tables 1 and 2, respectively; HRESIMS *m/z* 493.3335 [M – H]<sup>–</sup> (calcd for C<sub>32</sub>H<sub>45</sub>O<sub>4</sub>, 493.3318).

**α-Cadinyl Δ<sup>9</sup>-Tetrahydrocannabinolate (5):** yellow oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +175.6 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3410, 2915, 1718, 1610, 1568, 1457, 1110 cm<sup>–1</sup>; for <sup>1</sup>H NMR and <sup>13</sup>C NMR, see Tables 1 and 2, respectively; HRESIMS *m/z* 561.3958 [M – H]<sup>–</sup> (calcd for C<sub>37</sub>H<sub>55</sub>O<sub>4</sub>, 561.3944).

**γ-Eudesmyl Δ<sup>9</sup>-Tetrahydrocannabinolate (6):** colorless oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +125.1 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3410, 2915, 1718, 1610, 1568, 1457, 1110 cm<sup>–1</sup>; for <sup>1</sup>H NMR, see Table 1; HRESIMS *m/z* 561.3946 [M – H]<sup>–</sup> (calcd for C<sub>37</sub>H<sub>55</sub>O<sub>4</sub>, 561.3944).

**γ-Eudesmyl Cannabigerolate (7):** colorless oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +136.2 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 220, 205 nm; IR (neat) ν<sub>max</sub> 3420, 2915, 1717, 1610, 1568, 1457, 1110 cm<sup>–1</sup>; for <sup>1</sup>H NMR, see Table 3; HRESIMS *m/z* 563.4120 [M – H]<sup>–</sup> (calcd for C<sub>37</sub>H<sub>55</sub>O<sub>4</sub>, 563.4100).

**4-Terpenyl Cannabinolate (8):** yellow oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +100.0 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 225, 205 nm; IR (neat) ν<sub>max</sub> 3446, 2920, 2815, 1716, 1636, 1541, 1457, 1418, 1067 cm<sup>–1</sup>; <sup>1</sup>H NMR and <sup>13</sup>C NMR, see Table 3; HRESIMS *m/z* 513.2963 [M + Na]<sup>+</sup> (calcd for C<sub>32</sub>H<sub>42</sub>O<sub>4</sub>Na, 513.2981).

**Bornyl Δ<sup>9</sup>-Tetrahydrocannabinolate (9):** yellow oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +156.2 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3404, 2941, 1718, 1638, 1568, 1457, 1015 cm<sup>–1</sup>; for <sup>1</sup>H NMR and <sup>13</sup>C NMR, Tables 1 and 2, respectively; HRESIMS *m/z* 493.3330 [M – H]<sup>–</sup> (calcd for C<sub>32</sub>H<sub>45</sub>O<sub>4</sub>, 493.3318).

**α-Fenchyl Δ<sup>9</sup>-Tetrahydrocannabinolate (10):** colorless oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +363.2 (c 0.1, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 230 nm; IR (neat) ν<sub>max</sub> 3404, 2930, 1718, 1638, 1568, 1314, 1013 cm<sup>–1</sup>; for <sup>1</sup>H NMR and <sup>13</sup>C NMR, Tables 1 and 2, respectively; HRESIMS *m/z* 495.3499 [M + H]<sup>+</sup> (calcd for C<sub>32</sub>H<sub>47</sub>O<sub>4</sub>, 495.3474).

**α-Cadinyl Cannabigerolate (11):** colorless oil; *R<sub>f</sub>* = 0.9 (hexanes/EtOAc, 98:2); [α]<sub>D</sub><sup>25</sup> +136.2 (c 0.05, CHCl<sub>3</sub>); UV (EtOH) λ<sub>max</sub> 312 (sh), 265, 220, 205 nm; IR (neat) ν<sub>max</sub> 3420, 2915, 1717, 1610, 1568, 1457, 1110 cm<sup>–1</sup>; for <sup>1</sup>H NMR and <sup>13</sup>C NMR, see Table 3; HRESIMS *m/z* 563.4122 [M – H]<sup>–</sup> (calcd for C<sub>37</sub>H<sub>55</sub>O<sub>4</sub>, 563.4100).

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**Supporting Information Available:** HRESIMS, GC-MS, GC-MS trimethylsilyl derivatization,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and selected 2D NMR spectra for compound **1**. HPLC chromatograms of isolated compounds. GC-MS data of isolated compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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