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Synthesis of Cannabigerol and Cannabigerol Derivatives

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Abstract

The synthesis of cannabigerol—a cannabinoid with significant pharmaceutical potential—is described. The synthesis involves four stages. In the first step, (E)-non-3-en-2-one reacts with dimethyl malonate to yield a cyclic enone, which is subsequently oxidized with bromine to produce the olivetol ester. This ester then undergoes an alumina-catalyzed coupling reaction with geraniol, followed by ester hydrolysis to obtain cannabigerol. By modifying the chain length of the enone in the initial step and employing allylic alcohols other than geraniol, a range of cannabigerol derivatives can be synthesized, including the natural product cannabigerovarin.

Keywords: cannabigerol; cannabigerovarin; resorcinol methyl esters; electrophilic aromatic alkylation; cannabinoids; geraniol; allylic alcohols

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1. Introduction

The cannabis plant (Cannabis sativa), native to Central Asia, has been cultivated and utilized by numerous cultures throughout history. It exists in various forms, each characterized by unique botanical and chemical properties. This diversity has contributed to the plant's complexity and its wide range of biological effects, making it a subject of significant scientific interest [1]. At the heart of cannabis's pharmacological potential are cannabinoids—a class of compounds unique to this plant. Among them, Δ^9-tetrahydrocannabinol (**1**, Δ^9-THC) and cannabidiol (**2**, CBD) are the most well known (Figure 1). Δ^9-THC (**1**) is primarily responsible for the psychoactive effects of cannabis, altering perception and mood, whereas CBD (**2**) lacks psychoactive properties and has drawn increasing attention for its potential therapeutic applications [2]. Cannabinoids exert their effects through interactions with the endocannabinoid system (ECS), a regulatory system present in mammals that influences physiological processes such as pain sensation, immune function, mood, and appetite [3]. Over 100 distinct cannabinoids have been identified, each with a unique chemical structure and pharmacological profile. While some have been extensively studied, many remain poorly understood, representing a promising frontier for biomedical research. One cannabinoid that has recently gained attention is cannabigerol (**3**, CBG, Figure 1). Despite being classified as a minor cannabinoid due to its typically low

concentrations in the plant, CBG (**3**) exhibits several notable properties [4]. Like CBD (**2**), it is non-psychoactive, and it has shown potential for therapeutic activity through interactions with both the ECS and other receptor systems [5]. Notably, CBG (**3**) displays a unique affinity for components of the "extended endocannabinoid system," including vanilloid receptors that are involved in neural signaling. This interaction profile has opened up promising avenues for therapeutic applications, including anti-inflammatory effects [6,7], neuroprotection [8,9], treatment of glaucoma [10], and potential anticancer activity [11,12].

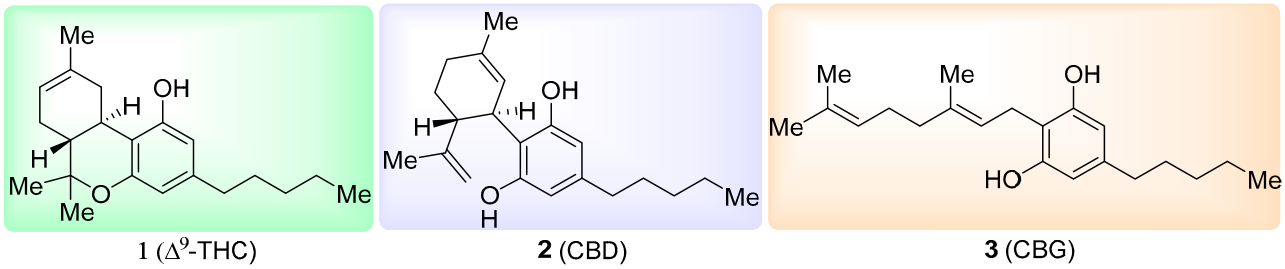
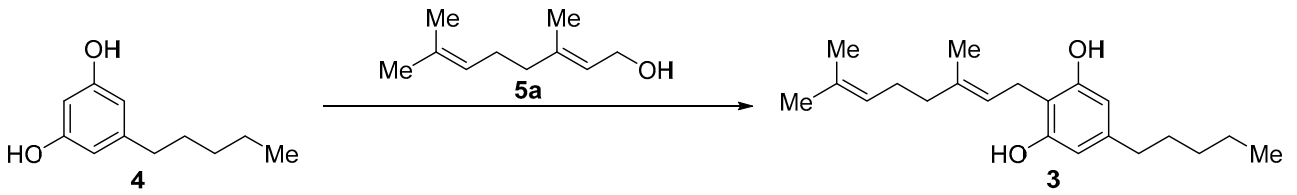


Figure 1. Structures of Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD), and cannabigerol (CBG).

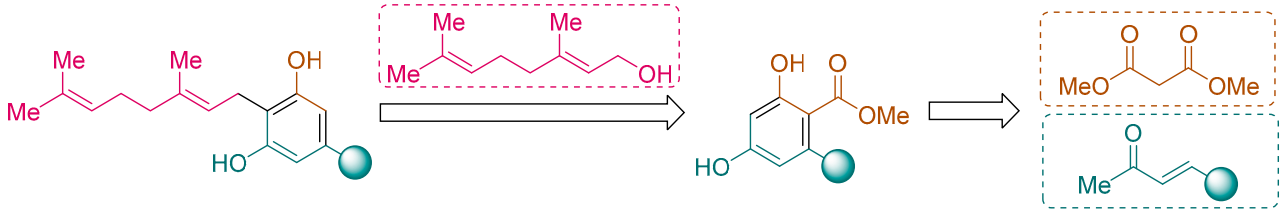
However, due to its low natural abundance, isolating CBG (**3**) from the cannabis plant presents significant challenges. As a result, there is growing interest in the development of synthetic methods for the production of CBG (**3**). Despite its importance, synthetic approaches to CBG (**3**) remain limited, with most reported examples appearing in the patent literature [13]. These often involve low product yields and require complex purification procedures. In 1985, the Mechoulam group reported a synthesis based on a Friedel–Crafts allylation of olivetol (**4**) with geraniol (**5a**), promoted by boron trifluoride etherate in dichloromethane at room temperature. Although operationally straightforward, this method resulted in low isolated yields and was not suitable for the industrial-scale production of CBG (**3**) (Scheme 1) [14]. A more recent example is a 2020 synthesis by the Magolan group, which employed acidic alumina to catalyze the coupling of olivetol (**4**) and geraniol (**5a**) under reflux in dichloroethane. This method yielded CBG (**3**) in 62%; however, it also led to the formation of polyalkylated side products, complicating purification and limiting scalability (Scheme 1) [15]. The Merli group also reported the synthesis of CBG (**3**) from the same precursors under acidic conditions in chloroform, although in this case, the yield of CBG (**3**) was notably low (Scheme 1) [16]. Similarly, Kuzuyama and collaborators carried out the coupling of olivetol (**4**) and geraniol (**5a**) using *Streptomyces* prenyltransferases as chemoenzymatic catalysts, yielding CBG (**3**), albeit on a millimolar scale [17]. Building on these precedents, we aimed to develop a straightforward and cost-effective methodology for the synthesis of CBG (**3**) and its derivatives, with the ultimate goal of scaling up the process to the pilot plant level.



5a (0.9 equiv), $BF_3{\cdot}OEt_2$ (20 equiv), SiO_2 (2 g/mol), DCM, 23 °C, 48 h (29%)	Mechoulam, 1985
5a (1.5 equiv), $Al_2O_{3\,(ac)}$ (2.0 g/mmol), DCE, 84 °C, 6 h (62%)	Magolan, 2020
5a (1.75 equiv), *p*-TsOH (10 mol%), $CHCl_3$, 23 °C, 12 h (15%)	Merli, 2021

Scheme 1. Selected recent examples of synthesis of cannabigerol (CBG) [14–16].

Our proposed synthetic strategy consists of two main steps: first, a malonic synthesis in which methyl malonate reacts with enones of varying chain lengths; and second, an acid-activated alumina-catalyzed coupling of resorcinol methyl ester derivatives with geraniol. This approach builds upon previously reported methodologies, either for small-scale syntheses using acidic alumina as a catalyst [15], or for carrying out the alkylation of the methyl ester of olivetolic acid [13], which in the latter case prevents the formation of polyalkylated products (Scheme 2).



Scheme 2. Retrosynthetic analysis for cannabigerol (CBG) and cannabigerol derivatives.

2. Materials and Methods

2.1. General Information

Reagents and solvents were of reagent grade and purchased from commercial suppliers [Sigma-Aldridh (Saint Louis, MO, USA), Fisher Scientific (Kandel, Germany)], and used as received. Low-resolution mass spectra (LRMS) were acquired using electron impact ionization (EI) at 70 eV, employing either an Agilent MS5973N mass spectrometer equipped with a Scientific Instrument Services (SIS) direct insertion probe (model 73DIP-1), or an Agilent GC/MS5973N system operating under similar conditions. Fragment ions are reported as mass-to-charge ratios (m/z), with relative abundances (%) provided in parentheses. High-resolution mass spectrometry (HRMS) analyses were also performed using EI at 70 eV on an Agilent 7200 instrument, which features a time-of-flight (TOF) analyzer. Samples were introduced via either a direct insertion probe or an Agilent GC7890B gas chromatograph (Agilent, Santa Clara, CA, USA). Nuclear magnetic resonance (NMR) spectra were recorded using Bruker AV300 Oxford and Bruker AV400 spectrometers (Bruker, Karlsruhe, Germany). Proton NMR (^{1}H NMR) spectra were obtained at 300 or 400 MHz, while carbon NMR (^{13}C NMR) spectra were recorded at 75 or 100 MHz. Deuterated solvents DMSO-d_6 and $CDCl_3$ were used, with tetramethylsilane (TMS) as the internal reference (0.00 ppm). The spectral data are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad signal; coupling constants (J) are given in Hz; and signal integration is included. Proton-decoupled ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. CH, CH_2, and CH_3 signals were further assigned using DEPT-135 experiments. Thin-layer chromatography (TLC) was carried out on Merck (Sigma-Aldrich, Saint Louis, MO, USA) pre-coated aluminum sheets (silica gel 60 with F254 fluorescent indicator). Spots were visualized using phosphomolybdic acid (PMA) staining, and retention factors (R_fs) were determined under these conditions. Flash column chromatography was conducted on silica gel 60 (230–400 mesh) manually packed into glass columns. Melting points were determined with a Reichert Thermovar (Depew, NY, USA) hot plate apparatus and were uncorrected. HPLC analysis was performed on an Agilent InfinityLab Poroshell 120 EC-C18 1260 2.7 µm 100 × 3 mm column, using an Agilent 1260 HPLC. The mobile phase consisted of formic acid (0.1%) in acetonitrile, with a flow rate of 0.4 mL/min. The HPLC flow was directed into the UV detector and set up at 228 nm wavelength.

2.2. Preparation and Characterization of Compounds

2.2.1. Synthesis of Hydroxycyclohexenone Derivatives **8**

General Procedure. To a solution of dimethyl malonate 6 (13.2 g, 11.4 mL, 100.0 mmol) in methanol (80 mL) was successively added a 5.8 M solution of NaOMe in methanol (16.0 mL, 92.8 mmol) and the corresponding enone 7 (72.0 mmol) at 0 °C. After that, the resulting reaction mixture was heated at 65 °C for 18 h. Then, the solvent was evaporated under vacuum (15 Torr). The residue was dissolved first in 50 mL of dichloromethane, followed by the addition of 50 mL of water. After stirring for 15 min, the organic phase was discarded and the aqueous phase was acidified with a 3.0 M aqueous HCl solution to pH 2. The resulting turbid aqueous phase was extracted with dichloromethane (3 × 100 mL), dried over magnesium sulfate, and the solvent was evaporated (15 Torr), giving rise to the expected compounds 8 in high purity, which were used in the next reaction step without the need for further purification.

Methyl 2-Hydroxy-6-methyl-4-oxocyclohex-2-ene-1-carboxylate (**8a**) [18]: following the general procedure, compound 8a was obtained from pent-3-en-2-one (7a, 7.11 g, 8.25 mL, 72.0 mmol) as a yellow solid (8.00 g, 43.47 mmol, 61%): $C_9H_{12}O_4$; mp 127–128 °C (hexane/CH_2Cl_2, lit. 122–123 °C [18]); [HPLC (Agilent IndinityLab Poroshell 120 EC-C18 1260 column, acetonitrile/formic acid = 99.9/0.1, 0.4 mL/min, 228 nm) t = 3.47 min (98.75%)]; R_f 0.22 (hexane/EtOAc 1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.44 (br s, 1H), 5.23 (s, 1H), 3.64 (s, 3H), 3.11 (d, J = 10.9 Hz, 1H), 2.40–2.23 (m, 3H), 0.96 (d, J = 6.1 Hz, 3H); LRMS (EI) m/z 184 (M^+, 15%), 169 (28), 153 (18), 125 (23), 114 (39), 101 (25), 84 (23), 69 (100), 55 (19), 43 (26); HRMS (EI-TOF) calcd. for $C_9H_{12}O_4$ 184.0736; found 184.0736.

Methyl 2-Hydroxy-4-oxo-6-propylcyclohex-2-ene-1-carboxylate (**8b**): following the general procedure, compound 8b was obtained from hept-3-en-2-one (7b, 8.48 g, 10.05 mL, 72.0 mmol) as a yellow solid (13.51 g, 63.72 mmol, 88.5%): $C_{11}H_{16}O_4$; mp 95–96 °C (hexane/CH_2Cl_2); [HPLC (Agilent IndinityLab Poroshell 120 EC-C18 1260 column, acetonitrile/formic acid = 99.9/0.1, 0.4 mL/min, 228 nm) t = 10.87 min (99.13%)]; R_f 0.27 (hexane/EtOAc 1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (br s, 1H), 5.23 (s, 1H), 3.64 (s, 3H), 3.16 (d, J = 10.8 Hz, 1H), 2.40 (dd, J = 16.0, 3.8 Hz, 1H), 2.33–2.18 (m, 2H), 1.33–1.19 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H); LRMS (EI) m/z 212 (M^+, 10%), 181 (20), 169 (100), 153 (11), 137 (73), 127 (33), 113 (24), 97 (82), 84 (29), 69 (31), 55 (41), 43 (44); HRMS (EI-TOF) calcd. for $C_{11}H_{16}O_4$ 212.1049; found 212.1047.

Methyl 2-Hydroxy-4-oxo-6-pentylcyclohex-2-ene-1-carboxylate (**8c**) [19]: following the general procedure, compound 8c was obtained from non-3-en-2-one (7c, 10.50 g, 12.38 mL, 72.0 mmol) as a pale yellow solid (14.00 g, 58.32 mmol, 81.0%): $C_{13}H_{20}O_4$; mp 82–83 °C (hexane/CH_2Cl_2, lit. 98–100 °C [19]); [HPLC (Agilent IndinityLab Poroshell 120 EC-C18 1260 column, acetonitrile/formic acid = 99.9/0.1, 0.4 mL/min, 228 nm) t = 13.25 min (97.41%)]; R_f 0.35 (hexane/EtOAc 1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.09 (br s, 1H), 5.18 (s, 1H), 3.62 (s, 3H), 3.13 (d, J = 10.7 Hz, 1H), 2.39 (dd, J = 16.1, 3.9 Hz, 1H), 2.29–2.13 (m, 2H), 1.30–1.18 (m, 8H), 0.85 (t, J = 6.9 Hz, 3H); LRMS (EI) m/z 240 (M^+, 3%), 169 (100), 157 (11), 137 (49), 125 (33), 95 (26), 84 (13), 69 (13), 55 (22), 43 (15); HRMS (EI-TOF) calcd. for $C_{13}H_{20}O_4$: 240.1362; found 240.1352.

Methyl 6-Heptyl-2-hydroxy-4-oxocyclohex-2-ene-1-carboxylate (**8d**) [20]: following the general procedure, compound 8d was obtained from undec-3-en-2-one (7d, 12.10 g, 13.44 mL, 72.0 mmol) as a pale yellow solid (15.24 g, 56.88 mmol, 79.0%): $C_{15}H_{24}O_4$; mp 71–72 °C (hexane/CH_2Cl_2, lit. 85–87 °C [20]); [HPLC (Agilent IndinityLab Poroshell 120 EC-C18 1260 column, acetonitrile/formic acid = 99.9/0.1, 0.4 mL/min, 228 nm) t = 14.84 min (97.73%)]; R_f 0.29 (hexane/EtOAc 1:3); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.38 (br s, 1H), 5.23 (s, 1H), 3.63 (s, 3H), 3.20–3.12 (m, 1H), 2.45–2.36 (m, 1H), 2.33–2.17 (m, 2H), 1.29–1.20 (m, 12H), 0.85 (t, J = 6.7 Hz, 3H); LRMS (EI) m/z 268 (M^+, 2%),169 (100), 153 (12),

137 (43), 95 (20), 69 (12), 55 (12), 43 (19); HRMS (EI-TOF) calcd. for $C_{15}H_{24}O_4$: 268.1675; found 268.1669.

2.2.2. Synthesis of Resorcinol Methyl Ester Derivatives **9**

General Procedure. To a solution of the corresponding enone 8 (40.0 mmol) in dimethyl formamide (40 mL) was added a solution of bromine (6.40 g, 2.05 mL, 40.0 mmol) in dimethyl formamide (20 mL) at 0 °C. The resulting reaction mixture was heated at 150 °C for 18 h. Then, it was cooled down to reach room temperature and after that, a 0.4 M solution of $Na_2S_2O_3$ (12.64 g, 80.0 mmol) in water (200 mL) was added and stirred for 24 h at the same temperature. The reaction mixture was extracted with *tert*-butyl methyl ether (3 × 50 mL), and the combined organic phases were washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, and the solvent was evaporated under vacuum (15 Torr). The resulting residue was dissolved in a 1:1 hexane ethyl acetate solution (100 mL), filtered through a silica gel pad, and washed the 1:1 hexane ethyl acetate solution (3 × 100 mL). The solvent was evaporated under vacuum (15 Torr), and the residue was dissolved in dichloromethane (10 mL), warming up the solution to 30 °C, followed by the slow addition of hexane (80 mL). The resulting cloudy solution was cooled down to −10 °C, and after 1 h, the solid formed was filtered off and dried to yield pure resorcinol derivatives 9.

Methyl 2,4-Dihydroxy-6-methylbenzoate (**9a**) [21]: following the general procedure, compound 9a was obtained from enone **8a** (7.36 g, 40.0 mmol) as a white solid (3.93 g, 21.6 mmol, 54%): $C_9H_{10}O_4$; mp 170–172 °C (hexane/CH_2Cl_2, lit. 173–174 °C [21]); R_f 0.21 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.82 (s, 1H), 6.30 (dd, *J* = 2.6, 0.5 Hz, 1H), 6.25 (dd, *J* = 2.6, 0.8 Hz, 1H), 4.93 (br s, 1H), 3.93 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 165.1 (C), 160.6 (C), 143.9 (C), 111.5 (CH), 105.5 (C), 101.3 (CH), 51.9 (CH_3), 24.2 (CH_3); LRMS (EI) *m*/*z* 182 (M^+, 45%), 150 (100), 122 (55), 94 (15), 69 (13), 43 (11); HRMS (EI-TOF) calcd. for $C_9H_{10}O_4$ 182.0579; found 182.0575.

Methyl 2,4-Dihydroxy-6-propylbenzoate (**9b**) [21]. Following the general procedure, compound 9b was obtained from enone **8b** (8.48 g, 40.0 mmol) as a white solid (4.95 g, 23.6 mmol, 59%): $C_{11}H_{14}O_4$; mp 152–153 °C (hexane/CH_2Cl_2, lit. 152–156 °C [21]); R_f 0.26 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.90 (s, 1H), 6.33 (d, *J* = 2.6 Hz, 1H), 6.27 (d, *J* = 2.6 Hz, 1H), 6.11 (br s, 1H), 3.94 (s, 3H), 2.87–2.76 (m, 2H), 1.59–1.51 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 164.8 (C), 160.6 (C), 148.8 (C), 111.2 (CH), 104.9 (C), 101.4 (CH), 52.1 (CH_3), 38.8 (CH_2), 24.8 (CH_2), 14.3 (CH_3); LRMS (EI) *m*/*z* 210 (M^+, 32%), 178 (100), 150 (30), 121 (31), 69 (11), 43 (13); HRMS (EI-TOF) calcd. for $C_{11}H_{14}O_4$ 210.0892; found 210.0891.

Methyl 2,4-Dihydroxy-6-pentylbenzoate (**9c**) [21]: following the general procedure, compound 9c was obtained from enone **8c** (9.60 g, 40.0 mmol) as a yellow solid (5.99 g, 25.2 mmol, 63%): $C_{13}H_{18}O_4$; mp 105–106 °C (hexane/CH_2Cl_2, lit. 105–106 °C [21]); R_f 0.28 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (s, 1H), 6.59 (br s, 1H), 6.32 (d, *J* = 2.6 Hz, 1H), 6.27 (d, *J* = 2.6 Hz, 1H), 3.93 (s, 3H), 2.87–2.78 (m, 2H), 1.57–1.46 (m, 2H), 1.36–1.29 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 164.9 (C), 160.6 (C), 149.1 (C), 111.1 (CH), 104.9 (C), 101.4 (CH), 52.0 (CH_3), 36.8 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 22.5 (CH_2), 14.1 (CH_3); LRMS (EI) *m*/*z* 238 (M^+, 48%), 206 (65), 182 (75), 150 (100), 121 (25), 94 (12), 69 (20), 43 (25); HRMS (EI-TOF) calcd. for $C_{13}H_{18}O_4$ 238.1205; found 238.1199.

Methyl 2-Heptyl-2,4-dihydroxybenzoate (**9d**) [20]: following the general procedure, compound 9d was obtained from enone **8d** (10.72 g, 40.0 mmol) as a yellow solid (4.25 g, 16.0 mmol, 40%): $C_{15}H_{22}O_4$; mp 95–96 °C (hexane/CH_2Cl_2, lit. 71.5–72 °C [20]); R_f 0.33 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.84 (s, 1H), 6.31 (d, *J* = 2.5 Hz, 1H),

6.28 (br s, 1H), 6.26 (d, *J* = 2.5 Hz, 1H), 3.93 (s, 3H), 2.88–2.78 (m, 2H), 1.57–1.45 (m, 2H), 1.35–1.27 (m, 8H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 165.0 (C), 160.6 (C), 149.0 (C), 110.9 (CH), 104.9 (C), 101.4 (CH), 51.9 (CH_3), 36.9 (CH_2), 31.85 (CH_2), 31.8 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3); LRMS (EI) *m*/*z* 266 (M^+, 35%), 234 (29), 192 (12), 182 (100), 163 (37), 150 (59), 121 (18), 69 (17), 43 (39); HRMS (EI-TOF) calcd. for $C_{15}H_{22}O_4$ 266.1522; found 266.1517.

2.2.3. Synthesis of Cannabigerol Methyl Ester Derivatives **10**

General Procedure. To a solution of the corresponding resorcinol derivative 9 (5.0 mmol) and alcohol 5 (5.00 mmol) in toluene (5.0 mL) was added acid alumina (10.0 g). The resulting reaction mixture was heated at 110 °C for 8 h. Then, acid alumina was filtered off and washed with ethyl acetate (3 × 25 mL). The solvent was evaporated under vacuum (15 Torr) and the residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compounds **10**.

Methyl (*E*)-2,4-Dihydroxy-3-(3,7-dimethylocta-2,6-dien-1-yl)-6-methylbenzoate (**10aa**) [22]. Following the general procedure, compound **10aa** was obtained from resorcinol derivative **9a** (0.91 g, 5.0 mmol) and geraniol (**5a**, 0.772 g, 0.87 mL, 5.0 mmol) as a yellow solid (0.811 g, 2.55 mmol, 51%): $C_{19}H_{26}O_4$; mp 90–91 °C (hexane/CH_2Cl_2, lit. 46–47 °C [22]); R_f 0.75 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.13 (s, 1H), 6.24 (d, *J* = 0.8 Hz, 1H), 5.82 (br s, 1H), 5.34–5.24 (m, 1H), 5.12–5.01 (m, 1H), 3.93 (s, 3H), 3.44 (d, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.12–2.07 (m, 4H), 1.82 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (C), 162.6 (C), 159.5 (C), 140.9 (C), 139.2 (C), 132.1 (C), 123.8 (CH), 121.4 (CH), 111.4 (CH), 111.3 (C), 105.1 (C), 51.9, 39.7 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 24.2 (CH_3), 22.1 (CH_2), 17.7 (CH_3), 16.2 (CH_3); LRMS (EI) *m*/*z* 318 (M^+, <1%), 299 (55), 261 (20), 229 (100), 215 (11), 187 (13), 175 (42), 123 (13), 91 (11), 69 (48), 41 (35); HRMS (EI-TOF) calcd. for $C_{19}H_{26}O_4$ 318.1831; found 318.1825.

Methyl (*E*)-2,4-Dihydroxy-3-(3,7-dimethylocta-2,6-dien-1-yl)-6-propylbenzoate (**10ba**): following the general procedure, compound **10ba** was obtained from resorcinol derivative **9b** (1.05 g, 5.0 mmol) and geraniol (**5a**, 0.772 g, 0.87 mL, 5.0 mmol) as a yellow solid (0.916 g, 2.65 mmol, 53%): $C_{21}H_{30}O_4$; mp 82–83 °C (hexane/CH_2Cl_2); R_f 0.77 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.05 (s, 1H), 6.25 (s, 1H), 5.86 (s, 1H), 5.35–5.25 (m, 1H), 5.12–5.03 (m, 1H), 3.94 (s, 3H), 3.45 (d, *J* = 7.3 Hz, 2H), 2.85–2.76 (m, 2H), 2.16–2.02 (m, 4H), 1.82 (q, *J* = 1.0 Hz, 3H), 1.69 (d, *J* = 1.3 Hz, 3H), 1.60 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.58–1.52 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C), 162.5 (C), 159.5 (C), 145.5 (C), 139.1 (C), 132.0 (C), 123.8 (CH), 121.5 (CH), 111.5 (C), 110.9 (CH), 104.6 (C) 51.8 (CH_3), 39.7 (CH_2), 38.8 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 24.9 (CH_2), 22.1 (CH_2), 17.7 (CH_3), 16.2 (CH_3), 14.3 (CH_3); LRMS (EI) *m*/*z* 346 (M^+, <1%), 314 (20), 271 (15), 245 (100), 223 (13), 191 (69), 123 (16), 69 (14), 41 (21); HRMS (EI-TOF) calcd. for $C_{21}H_{30}O_4$ 346.2144; found 346.2147.

Methyl (*E*)-2,4-Dihydroxy-3-(3,7-dimethylocta-2,6-dien-1-yl)-6-pentylbenzoate (**10ca**) [23]: following the general procedure, compound **10ca** was obtained from resorcinol derivative **9c** (1.19 g, 5.0 mmol) and geraniol (**5a**, 0.772 g, 0.87 mL, 5.0 mmol) as a yellow solid (1.065 g, 2.85 mmol, 57%): $C_{23}H_{34}O_4$; mp 60–61 °C (hexane/CH_2Cl_2); R_f 0.79 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.03 (s, 1H), 6.23 (s, 1H), 5.83 (s, 1H), 5.29–5.24 (m, 1H), 5.05 (m, 1H), 3.92 (s, 3H), 3.43 (d, *J* = 7.2 Hz, 2H), 2.80 (t, J = 7.5 Hz, 2H), 2.13–2.02 (m, 4H), 1.81 (d, *J* = 1.2 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.59–1.56 (m, 2H), 1.37–1.29 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C), 162.5 (C), 159.5 (C), 145.8 (C), 138.9 (C), 131.9 (C), 123.8 (CH), 121.5 (CH), 111.5 (C), 110.8 (CH), 104.5 (C) 51.8 (CH_3), 39.7 (CH_2), 36.8 (CH_2), 32.1 (CH_2), 31.6 (CH_2), 26.4 (CH_2), 25.6 (CH_3), 22.5 (CH_2), 22.1 (CH_2), 17.7 (CH_3), 16.2 (CH_3), 14.1 (CH_3); LRMS (EI) *m*/*z* 373 (M^+-1, 6%), 342

(23), 299 (19), 273 (100), 251 (17), 219 (92), 123 (21), 91 (9), 69 (24), 41 (29); HRMS (EI-TOF) calcd. for $C_{23}H_{34}O_4$ 374.2457; found 374.2453.

Methyl (*E*)-6-Heptyl-2,4-Dihydroxy-(3,7-dimethylocta-2,6-dien-1-yl)benzoate (**10da**): following the general procedure, compound **10da** was obtained from resorcinol derivative **9d** (1.33 g, 5.0 mmol) and geraniol (**5a**, 0.772 g, 0.87 mL, 5.0 mmol) as a yellow solid (0.984 g, 2.45 mmol, 49%): $C_{25}H_{38}O_4$; mp 74–75 °C (hexane/CH_2Cl_2); R_f 0.80 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.07 (s, 1H), 6.24 (s, 1H), 5.88 (s, 1H), 5.28 (dt, *J* = 6.4, 4.2 Hz, 1H), 5.14–5.01 (m, 1H), 3.93 (s, 3H), 3.44 (d, *J* = 7.1 Hz, 2H), 2.88–2.74 (m, 2H), 2.09 (q, *J* = 6.3 Hz, 4H), 1.82 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.53 (d, *J* = 6.9 Hz, 2H), 1.35–1.24 (m, 8H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C), 162.5 (C), 159.5 (C), 145.8 (C), 139.1 (C), 132.0 (C), 123.8 (CH), 121.5 (CH), 111.4 (C), 110.8 (CH), 104.6 (C), 51.8 (CH_3), 39.7 (CH_2), 36.8 (CH_2), 31.9 (CH_2), 31.85 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 22.7 (CH_2), 22.1 (CH_2), 17.7 (CH_3), 16.2 (CH_3), 14.1 (CH_3); LRMS (EI) *m*/*z* 402 (M^+, 3%), 370 (8), 358 (11), 292 (18), 247 (100), 175 (15), 164 (15), 143 (47), 125 (22), 99 (13), 83 (15), 69 (19), 59 (25), 43 (73); HRMS (EI-TOF) calcd. For $C_{25}H_{38}O_4$: 402.2770; found 402.2743.

Methyl (*E*)-3-(But-2-en-1-yl)-2,4-dihydroxy-6-pentylbenzoate (**10cb**): following the general procedure, compound **10cb** was obtained from resorcinol derivative **9c** (1.19 g, 5.0 mmol) and crotyl alcohol (**5b**, 0.360 g, 0.31 mL, 5.0 mmol) as a red solid (0.833 g, 2.85 mmol, 57%): $C_{17}H_{24}O_4$; mp 38–40 °C (hexane/CH_2Cl_2); R_f 0.72 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.04 (s, 1H), 6.26 (s, 1H), 5.97 (br s, 1H), 5.66–5.58 (m, 2H), 3.94 (s, 3H), 3.41 (q, *J* = 2.0 Hz, 2H), 2.86–2.77 (m, 2H), 1.69 (dt, *J* = 4.8, 1.6 Hz, 3H), 1.58–1.48 (m, 2H), 1.39–1.28 (m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C), 162.6 (C), 159.2 (C), 146.0 (C), 128.4 (CH), 126.7 (CH), 110.9 (C), 110.7 (CH), 104.6 (CH_3), 51.9 (CH_2), 36.8 (CH_2), 32.1 (CH_2), 31.6 (CH_2), 26.0 (CH_2), 22.5 (CH_2), 17.8 (CH_3), 14.1 (CH_3); LRMS (EI) *m*/*z* 292 (M^+, 56%), 260 (100), 231 (95), 219 (48), 204 (17), 189 (21), 176 (77), 147 (46), 105 (10), 91 (21), 77 (18), 55 (23), 43 (30); HRMS (EI-TOF) calcd. for $C_{17}H_{24}O_4$ 292.1675; found 292.1663.

Methyl 3-Cinnamyl-2,4-dihydroxy-6-pentylbenzoate (**10cc**): following the general procedure, compound **10cc** was obtained from resorcinol derivative **9c** (1.19 g, 5.0 mmol) and cinnamyl alcohol (**5c**, 0.670 g, 0.64 mL, 5.0 mmol) as a yellow solid (1.25 g, 3.55 mmol, 71%): $C_{22}H_{26}O_4$; mp 57–59 °C (hexane/CH_2Cl_2); R_f 0.78 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.09 (s, 1H), 7.39–7.19 (m, 6H), 6.53–6.33 (m, 2H), 6.27 (s, 1H), 3.95 (s, 3H), 3.63 (dd, *J* = 6.3, 1.4 Hz, 2H), 2.91–2.76 (m, 2H), 1.61–1.49 (m, 2H), 1.42–1.30 (m, 4H), 0.98–0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 162.8 (C), 158.8 (C), 146.2 (C), 137.3 (C), 130.8 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 127.1 (CH), 126,5 (CH), 126.2 (CH), 110.7 (C), 110.6 (CH), 104.9 (C), 51.9 (CH_3), 36.8 (CH_2), 32.1 (CH_2), 31.6 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); LRMS (EI) *m*/*z* 354 (M^+, 16%), 322 (30), 231 (100), 175 (11), 147 (13), 115 (11), 91 (26), 43 (12); HRMS (EI-TOF) calcd. for $C_{22}H_{26}O_4$: 354.1831; found 354.1844.

Methyl 2,4-Dihydroxy-6-pentyl-3-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl) benzoate (**10cd**): following the general procedure, compound **10cd** was obtained from resorcinol derivative **9c** (1.19 g, 5.0 mmol) and farnesol (**5d**, 1.112 g, 1.25 mL, 5.0 mmol) as a yellow solid (1.060 g, 2.40 mmol, 48%): $C_{28}H_{42}O_4$; mp 95–97 °C (hexane/CH_2Cl_2); R_f 0.74 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.10 (s, 1H), 6.32–6.20 (m, 2H), 5.38–5.27 (m, 1H), 5.12 (dddq, *J* = 7.2, 4.5, 2.8, 1.5 Hz, 2H), 3.94 (s, 3H), 3.46 (d, *J* = 7.2 Hz, 2H), 2.86–2.77 (m, 2H), 2.17–1.98 (m, 8H), 1.87–1.82 (m, 3H), 1.71 (t, *J* = 1.4 Hz, 3H), 1.66–1.59 (m, 6H), 1.53 (tt, *J* = 7.0, 3.6 Hz, 2H), 1.42–1.31 (m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C), 162.7 (C), 159.4 (C), 145.7 (C), 138.2 (C), 135.4 (C), 131.2 (C), 124.5 (CH), 123.8 (CH), 121.6 (CH), 111.8 (C), 110.8 (CH), 104.4 (C), 51.8 (CH_3), 39.8 (CH_2), 39.7 (CH_2), 36.8 (CH_2), 32.2 (CH_2), 31.6 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 22.6

(CH_2), 22.1 (CH_2), 17.7 (CH_3), 16.2 (CH_3), 16.0 (CH_3), 14.1 (CH_3); LRMS (EI) *m*/*z* 442 (M^+, 7%), 411 (13), 341 (36), 299 (13), 273 (99), 251 (43), 219 (100), 191 (30), 175 (13), 147 (15), 135 (14), 121 (25), 109 (14), 95 (11), 81 (20), 69 (53), 41 (22); HRMS (EI-TOF) calcd. For $C_{28}H_{42}O_4$: 442.3083; found 442.3072.

2.2.4. Synthesis of Cannabigerol Derivatives **11**

General Procedure. To a solution of the corresponding resorcinol derivative 9 (1.0 mmol) and geraniol **5a** (0.154 g, 0.173 mL, 1.00 mmol) in toluene (1.0 mL) was added acid alumina (2.0 g). The resulting reaction mixture was heated at 110 °C for 8 h. Then, acid alumina was filtered off and washed with ethyl acetate (3 × 10 mL). The solvent was evaporated under vacuum (15 Torr) and the resulting cannabigerol methyl ester derivative 10 was used in the next reaction step without further purification. Then, a solution of KOH (0.450 g, 8.0 mmol) in water (4.0 mL), and the corresponding cannabigerol methyl ester derivative 10 (1.0 mmol) in methanol (3.0 mL) was heated at 65 °C for 8 h, and after that, it was cooled down to room temperature and water (5 mL) and ethyl acetate (5 mL) was added. The resulting mixture was acidified with concentrated hydrochloric acid aqueous solution to pH 3. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate and the solvent was evaporated under vacuum (15 Torr). The resulting residue was dissolve in heptane (1.0 mL) at 80 °C, and after that, the solution was allowed to reach room temperature, and then it was cooled down at -10 °C. After 2 h, the crystalline solid formed was filtered off and dried to yield pure resorcinol derivatives 11.

(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-5-methylbenzene-1,3-diol (**11aa**) [15]: following the general procedure, compound **11aa** was obtained from resorcinol methyl ester derivative **9a** (0.128 g, 1.0 mmol) as a yellow solid (0.122 g, 0.47 mmol, 47%): $C_{17}H_{24}O_2$; mp 85–86 °C (heptane); R_f 0.60 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 2H), 5.34–5.23 (m, 1H), 5.12–5.05 (m, 3H), 3.41 (d, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 2.17–2.04 (m, 4H), 1.83 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (C), 138.9 (C), 137.5 (C), 132.0 (C), 123.8 (CH), 121.7 (CH), 110.5 (C), 109.1 (CH), 39.7 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 22.2 (CH_2), 21.0 (CH_3), 17.7 (CH_3), 16.2 (CH_2); LRMS (EI) *m*/*z* 260 (M^+, 14%), 217 (5), 163 (21), 149 (20), 137 (100), 123 (21), 69 (17), 61 (50); HRMS (EI-TOF) calcd. For $C_{17}H_{24}O_2$: 260.1776; found 260.1771.

(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-5-propylbenzene-1,3-diol (cannabigerovarin, **11ba**) [24]: following the general procedure, compound **11ba** was obtained from resorcinol methyl ester derivative **9b** (0.210 g, 1.0 mmol) as an orange solid (0.118 g, 0.41 mmol, 41%): $C_{19}H_{28}O_2$; mp 73–74 °C (heptane, lit. 52–53 °C [24]); R_f 0.63 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 2H), 5.32–5.26 (m, 1H), 5.10–4.97 (m, 3H), 3.41 (d, *J* = 7.1 Hz, 2H), 2.45 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.10 (d, *J* = 6.1 Hz, 4H), 1.83 (q, *J* = 1.0 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.63–1.52 (m, 5H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (C), 142.5 (C), 139.0 (C), 132.1 (C), 123.8 (CH), 121.7 (CH), 110.6 (C), 108.4 (CH), 39.7 (CH_2), 37.6 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 24.2 (CH_2), 22.3 (CH_2), 17.7 (CH_3), 16.2 (CH_3), 13.9 (CH_3); LRMS (EI) *m*/*z* 288 (M^+, 12%), 203 (27), 191 (14), 177 (10), 165 (100), 123 (20), 69 (14), 41 (19); HRMS (EI-TOF) calcd. For $C_{19}H_{28}O_2$: 288.2089; found 288.2095.

(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-5-pentylbenzene-1,3-diol (cannabigerol, **3**) [15]: following the general procedure, cannabigerol (**3**) was obtained from resorcinol methyl ester derivative **9c** (0.238 g, 1.0 mmol) as a yellow solid (0.161 g, 0.51 mmol, 51%): $C_{21}H_{32}O_2$; mp 49–50 °C (heptane); R_f 0.61 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (s, 2H), 5.31–5.23 (m, 1H), 5.16 (s, 2H), 5.09–5.01 (m, 1H), 3.39 (d, *J* = 7.1 Hz, 2H), 2.48–2.40 (m, 2H), 2.17–2.00 (m, 4H), 1.80 (d, *J* = 1.3 Hz, 3H), 1.67 (d, *J* = 1.4 Hz, 3H), 1.61–1.48 (m, 5H), 1.34–1.25 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (C), 142.8 (C),

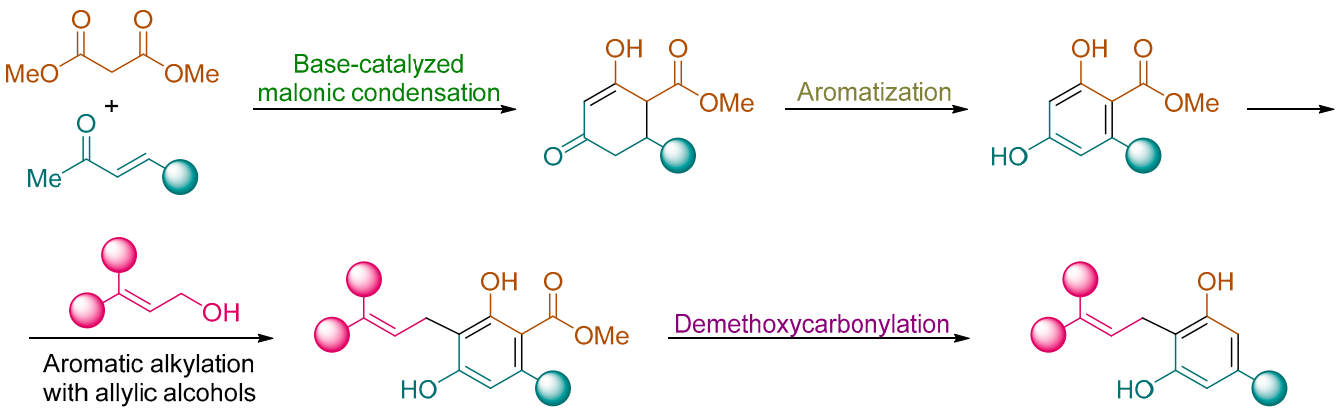
139.0 (C), 132.1 (C), 123.8 (CH), 121.7 (CH), 110.6 (C), 108.4 (CH), 39.7 (CH_2), 35.5 (CH_2), 31.5 (CH_2), 30.8 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 22.6 (CH_2), 22.3 (CH_2), 17.7 (CH_3), 16.2 (CH_3), 14.1 (CH_3); LRMS (EI) *m*/*z* 316 (M^+, 15%), 381 (30), 273 (5), 247 (16), 231 (31), 219 (11), 193 (100), 136 (10), 123 (15), 69 (9), 41 (9); HRMS (EI-TOF) calcd. For $C_{21}H_{32}O_2$: 316.2402; found 316.2384.

(*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-5-heptylbenzene-1,3-diol (**11da**): following the general procedure, compound **11da** was obtained from resorcinol methyl ester derivative **9d** (0.266 g, 1.0 mmol) as a yellow solid (0.179 g, 0.52 mmol, 52%): $C_{23}H_{36}O_2$; mp 62–63 °C (heptane); R_f 0.62 (hexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 2H), 5.33–5.22 (m, 3H), 5.12–5.04 (m, 1H), 3.41 (d, *J* = 7.1 Hz, 2H), 2.47 (dd, *J* = 8.8, 6.7 Hz, 2H), 2.20–2.04 (m, 4H), 1.83 (s, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.56 (m, *J* = 8.1 Hz, 2H), 1.34–1.26 (m, 8H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (C), 142.8 (C), 139.0 (C), 132.1 (C), 123.78 (CH), 121.7 (CH), 110.6 (C), 108.3 (CH), 39.7 (CH_2), 35.6 (CH_2), 31.8 (CH_2), 31.2 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 22.7 (CH_2), 22.3 (CH_2), 17.7 (CH_3), 16.2 (CH_3), 14.1 (CH_3); LRMS (EI) *m*/*z* 344 (M^+, 1%), 275 (14), 259 (42), 221 (100), 136 (13), 123 (22), 69 (14), 57 (11), 43 (21); HRMS (EI-TOF) calcd. For $C_{23}H_{36}O_2$: 344.2715; found 344.2708.

Copies of ^{1}H-NMR, ^{13}C-NMR spectra of compounds **3**, **8**, **9**, **10,** and **11**., in addition to HPLC chromatograms of compounds **8** are available in Supplementary Materials.

3. Results and Discussion

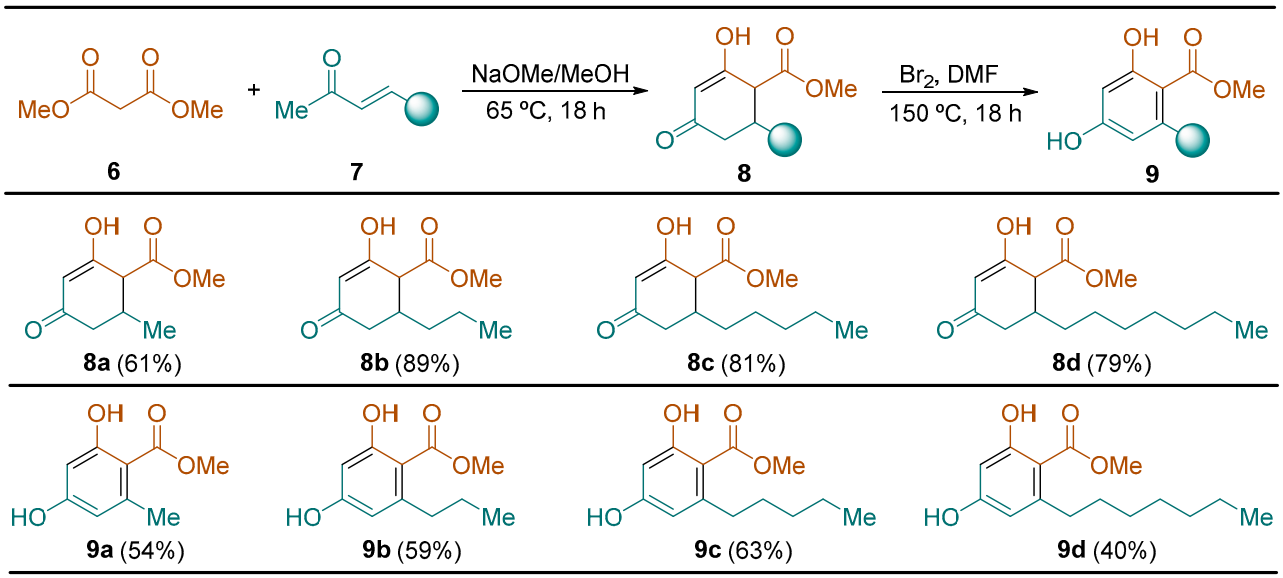
Based on the previous background, the synthetic strategy we will follow toward the synthesis of cannabigerol (CBG) and its derivatives is depicted in Scheme 3. This scheme clearly illustrates the four synthetic operations involved in the transformation, using dimethyl malonates, methyl enones, and allylic alcohols as starting materials.



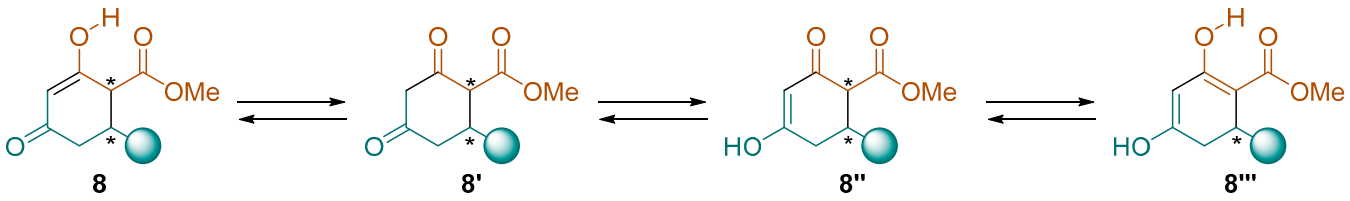
Scheme 3. Synthetic strategy for the synthesis of cannabigerol (CBG) and cannabigerol derivatives.

3.1. Synthesis of Hydroxycyclohexenone and Resorcinol Methyl Ester Derivatives **8** *and* **9**

The synthesis of cannabigerol derivatives began with the base-catalyzed condensation of dimethyl malonate (**6**) with aliphatic 3-alken-2-ones **7** in methanol at 65 °C [25]. The expected hydroxycyclohexenone derivatives **8** were obtained in high yields ranging from 61% to 89%, with hept-3-en-2-one (**7b**) providing the highest yield (Scheme 4). Notably, these compounds precipitated as solid residues upon solvent removal and were readily purified by recrystallization. This approach streamlines the synthesis process and provides a practical method for obtaining the desired compounds on a larger scale. The characterization of compounds **8** proved challenging, as the ^{13}C NMR spectra displayed more signals than expected [18]. Spectral data for compounds **8** do not correspond to pure compounds, probably due to the presence of diastereomeric and/or tautomeric forms (Scheme 5).



Scheme 4. Synthesis of hydroxycyclohexenones and resorcinol methyl ester derivatives **8** and **9**, respectively, starting from dimethyl malonate **6** and enones **7**.



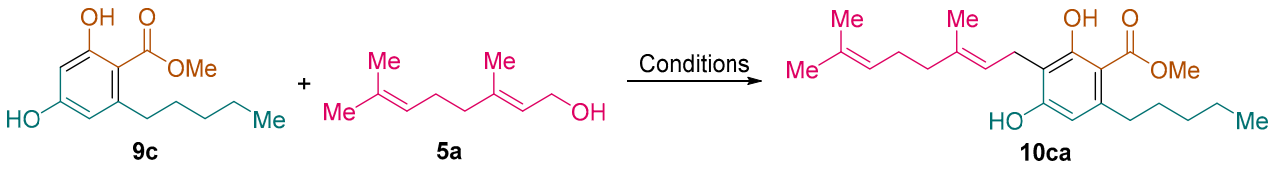
Scheme 5. Tautomers of compounds **8**.

The oxidation of the cyclic enones **8** with bromine in DMF [19] generally afforded the corresponding aromatic resorcinol derivatives **9** in moderate yields (Scheme 4). The heptyl-substituted compound **9d** was the only exception, being obtained in a lower yield (40%). Following aqueous sodium thiosulfate work-up, the products **9** were again isolated as solids and could be purified by recrystallization, thus eliminating the need for column chromatography. As an alternative oxidation procedure, we attempted to carry out the transformation using a catalytic amount of I_2 in DMSO as solvent [26]; however, the yields were not improved, nor was the purification of the reaction products facilitated.

3.2. Synthesis of Cannabigerol Methyl Ester Derivatives **10**

We then focused on optimizing the reaction conditions for the coupling of resorcinol methyl ester derivatives **9** with allylic alcohols **5**. As model substrates, we selected compound **9c** and geraniol (**5a**) to give ester derivative **10ca**. Three acid catalysts previously reported as effective coupling promoters—namely the Lewis acid $BF_3{\cdot}OEt_2$ [14], and the Brønsted acids p-TsOH [16] and acidic alumina [$Al_2O_{3(ac)}$] [15]—were evaluated in DCE (Table 1, entries 1–6). Interestingly, only acidic alumina demonstrated catalytic activity (Table 1, entries 5 and 6). Subsequently, a variety of solvents were screened (Table 1, entries 5–12), with toluene yielding the highest conversion rates (Table 1, entries 11 and 12). Attempts to lower the catalyst loading (Table 1, entries 13 and 14) led to reduced conversions. Finally, two additional reactions were carried out under the conditions of entry 11, but with varying stoichiometric ratios of **9c** and **5a**. Unexpectedly, the conversion levels remained comparable to those observed in entries 11 and 12 (Table 1, entries 15 and 16).

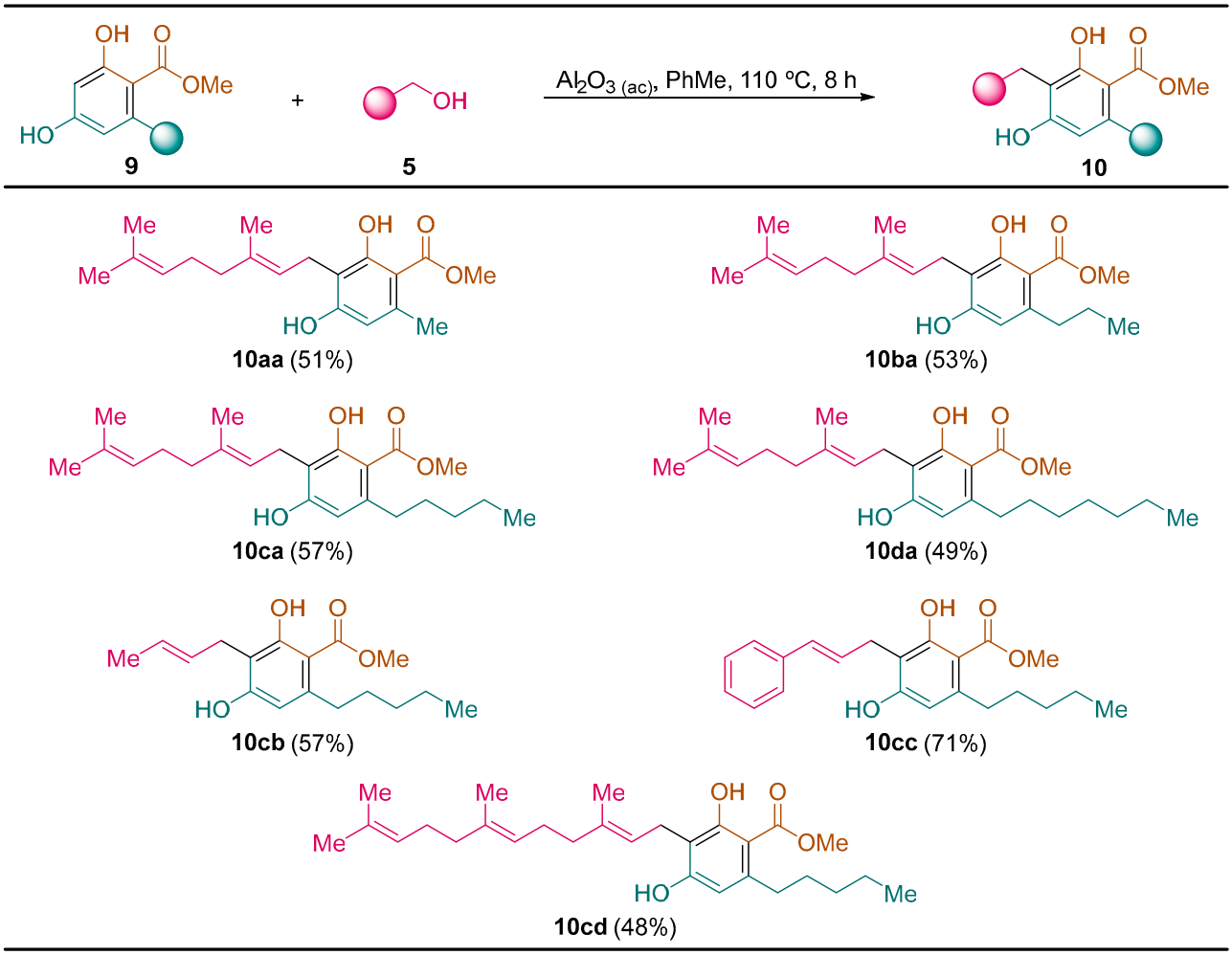
Table 1. Optimization of the reaction conditions in the synthesis of cannabigerol methyl ester derivatives **10** [1].



Entry	Solvent	Catalyst	T (°C)	t (h)	Conversion (%) [2]
1	DCE	$BF_3{\cdot}OEt_2$ (20 mol%)	23	8	<5
2	DCE	$BF_3{\cdot}OEt_2$ (20 mol%)	23	18	<5
3	DCE	*p*-TsOH (10 mol%)	23	8	<5
4	DCE	*p*-TsOH (10 mol%)	23	18	<5
5	DCE	$Al_2O_{3(ac)}$ (2.0 g/mmol)	84	8	72
6	DCE	$Al_2O_{3(ac)}$ (2.0 g/mmol)	84	18	85
7	DCM	$Al_2O_{3(ac)}$ (2.0 g/mmol)	45	8	<5
8	DCM	$Al_2O_{3(ac)}$ (2.0 g/mmol)	45	18	<5
9	CH_3CN	$Al_2O_{3(ac)}$ (2.0 g/mmol)	82	8	57
10	CH_3CN	$Al_2O_{3(ac)}$ (2.0 g/mmol)	82	18	59
11	$PhCH_3$	$Al_2O_{3(ac)}$ (2.0 g/mmol)	110	8	91
12	$PhCH_3$	$Al_2O_{3(ac)}$ (2.0 g/mmol)	110	18	92
13	$PhCH_3$	$Al_2O_{3(ac)}$ (1.5 g/mmol)	110	18	79
14	$PhCH_3$	$Al_2O_{3(ac)}$ (1.0 g/mmol)	110	18	70
15 [3]	$PhCH_3$	$Al_2O_{3(ac)}$ (2.0 g/mmol)	110	8	90
16 [4]	$PhCH_3$	$Al_2O_{3(ac)}$ (2.0 g/mmol)	110	8	91

[1] All the reactions were performed using 1.0 equivalent of **9c** and 1.0 equivalent of **5a**. [2] Conversions were determined by ^{1}H NMR analysis of the crude reaction mixtures. [3] The reaction was performed using 1.0 equivalent of **9c** and 1.5 equivalents of **5a**. [4] The reaction was performed using 1.5 equivalents of **9c** and 1.0 equivalent of **5a**.

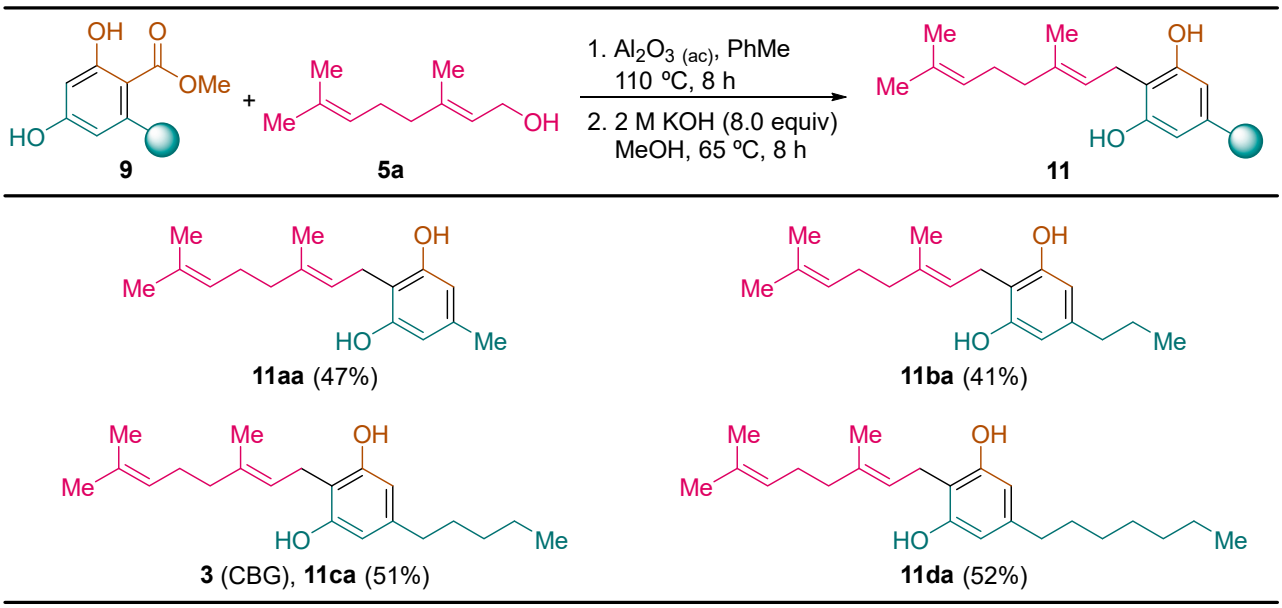
We next explored the scope of the reaction between geraniol (**5a**) and various resorcinol methyl ester derivatives **9** under the optimized conditions described in Table 1, entry 11 (toluene as solvent, acidic alumina as coupling promoter, 110 °C, 8 h). The expected cannabigerol methyl ester derivatives **10aa**–**10da** were obtained in moderate yields ranging from 49% to 57% after column chromatography purification. Notably, these reactions were performed on a gram scale, although the products were not purified by recrystallyzation (Scheme 6). To further expand the reaction scope, alkylation at the C-5 position of resorcinol methyl ester **9c** [the precursor of CNB (**3**)] was attempted using different alcohols. However, successful coupling was observed only with crotyl alcohol (**5b**), cinnamyl alcohol (**5c**), and farnesol (**5d**), affording the corresponding products **10cb**, **10cc**, and **10cd**, respectively (Scheme 6). It is worth highlighting that the highest yield was obtained for compound **10cc**, resulting from the coupling with cinnamyl alcohol (**5c**). Unfortunately, other alkanols, benzylic alcohols, and allylic alcohols with a Z-configuration were ineffective under these conditions.



Scheme 6. Synthesis of cannabigerol methyl ester derivatives **11** from resorcinol derivaties **9** and allylic alcohols **5**.

3.3. Synthesis of Cannabigerol Derivatives **11**

The final step in the proposed synthesis of the cannabigerol derivatives (Scheme 3) involved the demethoxycarbonylation of methyl esters **10**. To avoid the need for column chromatography purification required for the characterization of these synthetic intermediates, and with the aim of performing the transformations cost-effectively on a multigram scale, we attempted a two-step process starting from resorcinol methyl ester derivatives **9** and geraniol (**5a**). After coupling on acidic alumina, the crude products **10** were not purified; instead, the unrefined reaction mixtures were directly subjected to the subsequent demethoxycarbonylation step. This well-established transformation was carried out by treating the esters with a 2 M aqueous KOH solution in methanol at 65 °C for 8 h. Conversion rates were excellent (85–95%), and the target cannabigerol derivatives **11** were obtained in moderate yields through recrystallization from heptane (Scheme 7). Although the isolated yields were modest, calculated from the initial methyl esters **9** and geraniol (**5a**), they are reasonable considering the two-step process involved. Notably, the final cannabinoids displayed high levels of purity. The cannabigerol derivative **11da** is a new compound that has not been previously described; therefore, complete characterization is provided in the *Materials and Methods* section.



Scheme 7. Synthesis of cannabigerol derivatives **11** from resorcinol methyl esters **9** and geraniol **5a** in a two-step process.

3.4. Recovering of Acidic Alumina

Catalyst recovery is of great importance in industrial processes, both to reduce costs and to minimize environmental impact. In the key alkylation step of the synthetic strategy presented here (Scheme 6), a substantial amount of acidic alumina (2.0 g/mmol) is required for the coupling of allylic alcohols **5** with resorcinol methyl ester derivatives **9**. To assess the feasibility of recovering and reactivating the alumina for reuse as a promoter in these aromatic alkylations, we selected the model reaction between compound **9c** and geraniol (**5a**), as described in Table 1. Following its use in the initial reaction, the spent acidic alumina was collected and treated with an aqueous 3 M hydrochloric acid solution. After stirring for 2 h, the alumina was filtered, dried, and then calcined at 600 °C in a muffle furnace. Once cooled, the regenerated alumina was reused in the same reaction, maintaining high activity as a coupling promoter for up to four cycles—showing a gradual decrease in conversion from 91% in the first cycle to 83% in the fourth (Figure 2). However, beyond the fourth cycle, a significant drop in catalytic performance was observed.

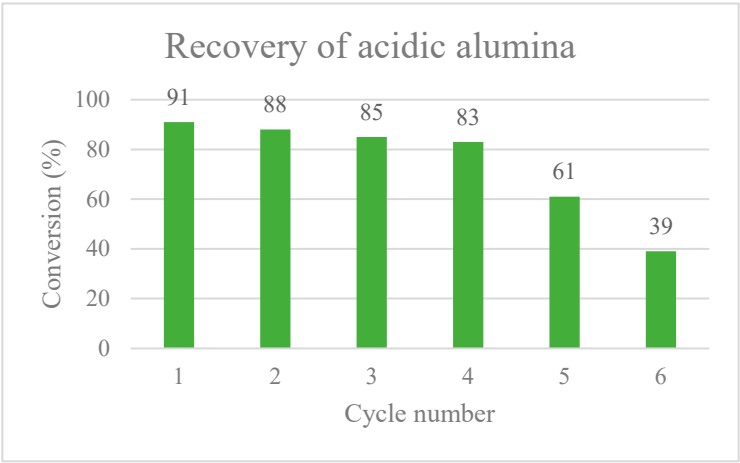


Figure 2. Recycling studies of acidic alumina in the coupling of compounds **9c** and **5a** under the conditions depicted in entry **11** of Table 1.

4. Conclusions

Cannabigerol (**3**) and its derivatives **11** can be synthesized from dimethyl malonate, alk-3-en-2-ones, and geraniol. The synthetic sequence involves the base-catalyzed condensation of dimethyl malonate with alk-3-en-2-ones, followed by the aromatization of the resulting 3-hydroxycyclohexenones, aromatic alkylation with geraniol promoted by acidic alumina, and final demethoxycarbonylation. The target compounds were obtained in good overall yields and purified by recrystallization, eliminating the need for costly column chromatography. This synthetic methodology is straightforward, operationally simple, and readily scalable to the pilot-plant level.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org6030031/s1, copies of ^{1}H-NMR, ^{13}C-NMR spectra of compounds **3**, **8**, **9**, **10,** and **11**. HPLC chromatograms of compounds **8**.

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Data Availability Statement: The data presented in this study are available in this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CBD	Cannabidiol
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ECS	Endocannabinoid system
GC	Gas chromatography
HRMS	High-resolution mass spectroscopy
LRMS	Low-resolution mass spectroscopy
NMR	Nuclear magnetic resonance
THC	Tetrahydrocannabinol
TOF	Time of flight

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