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Article

Efficient Synthesis of Cannabigerol, Grifolin, and Piperogalin via Alumina-Promoted Allylation

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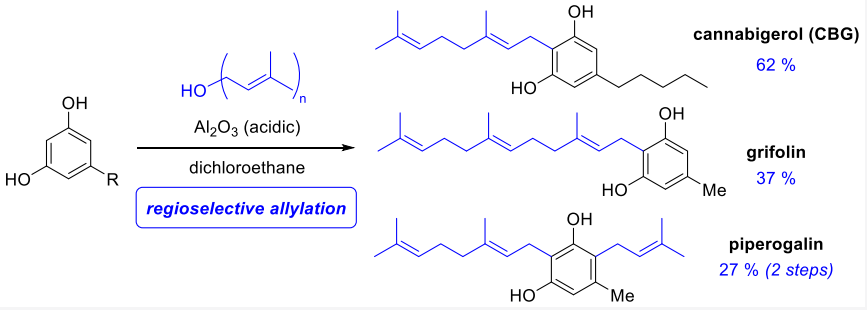


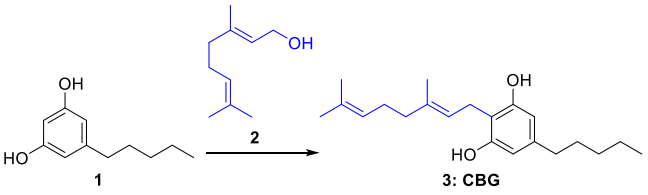
ABSTRACT: The synthesis of three phenolic natural products has been accomplished with unprecedented efficiency using a new alumina-promoted regioselective aromatic allylation reaction. Cannabigerol and grifolin were prepared in one step from the inexpensive 5-alkyl-resorcinols olivetol and orcinol. Piperogalin was synthesized, for the first time, via two sequential allylations of orcinol with geraniol and prenol.

Cannabigerol (CBG, **3**) is a nonpsychotropic minor cannabinoid produced by *Cannabis sativa*.[1] CBG is reported to be an α2-adrenoceptor agonist, a $5HT_{1A}$ receptor antagonist,[2] and an activator of TRPV1 and TRPV2 ion channels.[3] It has also been shown to stimulate appetite,[4] act as a neuroprotective agent in mouse models of Huntington's disease,[5] inhibit colon carcinogenesis,[6] act as an anti-inflammatory in the context of colitis,[7] and inhibit nausea.[8] A 2008 report by Appendino and co-workers demonstrated that **3** and other cannabinoids had potent antimicrobial activity against *Staphylococcus aureus*.[9] We recently became interested in further exploring the antimicrobial potential of **3** and its synthetic analogues.[10] This required efficient synthetic access to the CBG scaffold.

RESULTS AND DISCUSSION

Two syntheses of **3** have been previously reported, both proceeding via C-alkylation of olivetol (**1**) with geraniol (**2**) (Scheme 1). In 1995, Baek and co-workers treated these two substrates with boron trifluoride etherate on silica in CH_2Cl_2 to afford **3** in 29% yield (Scheme 1).[11] One year later, Morimoto and co-workers reported the use of *p*-toluenesulfonic acid in $CHCl_3$ to obtain **3** from the same two substrates in 40% yield,[12] following a similar procedure to one described in 1969 by Mechoulam and Yagen.[13] However, in our hands, both of these methods produced lower yields than those reported (Scheme 1). Our inability to achieve appreciable yields following the procedure of Baek and co-workers might be attributed to variability between the silica used in our laboratories.

Scheme 1. Previous Syntheses of CBG



	Conditions	Reported Yield	Our Yield
Baek, 1995 *ref. 11*	$BF_3{\cdot}EtO_2$, SiO_2, CH_2Cl_2, r.t.,	29 %	0-5 %
Morimoto, 1996 *ref.12*	TsOH CH_3Cl, r.t.	40 %	28 %

These results prompted an investigation into alternative reaction conditions for this process. In the context of heterogeneous synthetic methods development research,[14,15]

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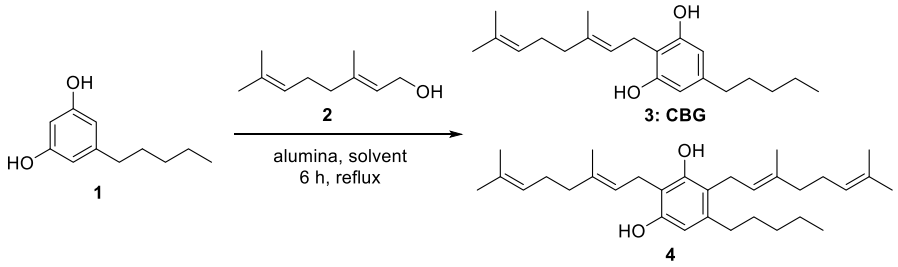
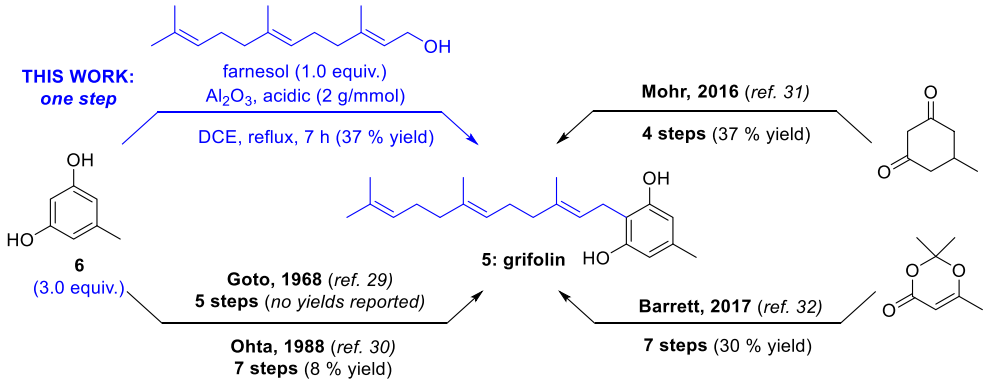
Table 1. Optimization of Alumina-Promoted CBG Synthesis



entry	alumina type	alumina amt (g)	solvent	1 (mmol)	2 (mmol)	3 (%)[a]	4 (%)[a]
1	acidic	2	hexanes	1	1	34	11
2	neutral	2	hexanes	1	1	12	2
3	basic	2	hexanes	1	1	4	1
4	acidic	2	hexanes	1	1.5	39	13
5	acidic	2	hexanes	1.5	1	53	12
6	acidic	1	hexanes	1.5	1	22	13
7	acidic	2	heptanes	1.5	1	15	13
8	acidic	2	DCE	1.5	1	67 (62[b])	10
9	acidic	2	CH_3CN	1.5	1	9	2
10	acidic	2	MeOH	1.5	1	0	0
11	none	0	DCE	1.5	1	0	0

[a]Yield determined by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [b]Isolated yield after chromatography.

Scheme 2. Current Synthesis and Four Previous Syntheses of Grifolin (5)



we recently identified the pairing of activated acidic alumina with hydrophobic solvents such as hexanes or 1,2-dichloroethane (DCE) as useful conditions for promoting an indole alkylation reaction.[16] When analogous conditions were applied to the reaction of **1** with **2**, a relatively selective and clean formation of **3** in 34% yield (Table 1, entry 1) was observed. The only other observable product was digeranylated compound **4**, in 11% yield. The optimization of this process is summarized in Table 1. Acidic alumina was found to be superior to basic and neutral aluminas (entries 1−3) and DCE was found to be a preferred solvent (entries 6−10). Byproduct **4**, which was formed in 10% yield could be readily removed using silica chromatography. Ultimately, **3** was obtained in 62% isolated yield using the following reaction conditions (entry 8): treatment of **2** with excess **1** (1.5 equiv) in DCE at reflux temperature (83 °C) for 6 h in the presence of acidic alumina (2 g/mmol with respect to **2**). This constitutes the most efficient synthesis of this natural product reported to date. Notably, CBG is of industrial significance as a substrate for a bioenzymatic synthesis of tetrahydrocannabinol (THC).[17]

Cannabigerol is structurally analogous to grifolin (**5**), a natural product isolated in 1950 by Hirata from the mushroom *Grifola confluens* (Scheme 2).[18] Bioactivity investigations of **5** have shown it to be a tyrosinase inhibitor,[19] an antioxidant,[20] an antihistamine agent,[21] an antitumor agent,[22−25] an antimicrobial,[15] hypocholesterolemic,[26] a carbonic anhydrase inhibitor,[27] and an inhibitor of nitric oxide production.[28] We hypothesized that a simple one-step synthesis of **5** was possible using a process analogous to the cannabigerol synthesis. Indeed, after a cursory optimization of substrate ratios it was found that a refluxing mixture of farnesol (1.0 mmol), orcinol (**6**, 3.0 mmol), and acidic alumina (2.0 g) in DCE afforded **5** in 37% isolated yield after a 7 h reaction time (Scheme 2). This simple one-step process compares favorably with four previous syntheses of this compound, which utilized reaction sequences ranging from four to seven steps (Scheme 2).[29−32]

Seeking to further demonstrate the utility of this alumina-promoted allylation reaction, a third natural product, piperogalin (**8**), was selected for synthesis. Pierogalin was isolated in 1995 from *Peperomia galioides*[33] and later from *Peperomia obtusifolia* but had yet to be accessed via chemical

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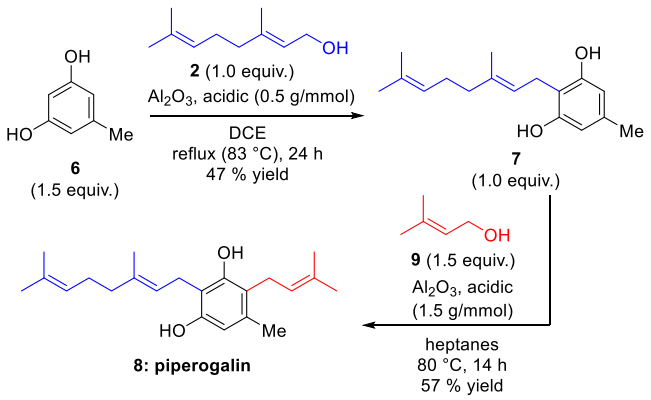
synthesis (Scheme 3).[34] Compound **8** showed antiparasitic activity against *Leishmania* and *Trypanosoma cruzi*.[35] As

Scheme 3. Synthesis of Piperogalin



illustrated in Scheme 3, the two-step sequence began with a geranylation of **6**. In this case, the reaction was run on a 4 mmol scale with a reduced alumina loading of 0.5 g/mmol to facilitate magnetic stirring of the heterogeneous reaction mixture. The reaction required 24 h in refluxing DCE and afforded cannabigerocin (**7**) in 47% isolated yield. Next, prenylation of **7** was initially low yielding in DCE and required some effort to optimize solvent, reaction temperature, and substrate ratios. Ultimately, **8** was obtained in 57% yield when the reaction was run in heptanes, with 1.5 equiv of prenol (**9**)and 1.5 g/mmol of alumina relative to **7**, and the temperature was maintained at 80 °C for 14 h. Considerably reduced yields were observed when the reaction was performed at 98 °C, the reflux temperature of heptanes, as **8** appeared to be prone to further reactions resulting in complex mixtures of unidentified byproducts evident in the crude ^{1}H NMR spectrum. Overall, this regioselective geranylation and prenylation sequence offered the first total synthesis of **8** in 27% overall yield in two steps from **6**.

In conclusion, we have demonstrated the utility of a new regioselective alumina-promoted allylation reaction of resorcinols that has enabled efficient syntheses of the natural products cannabigerol, grifolin, and piperogalin. While the mechanism of this reaction remains under examination in our laboraotry, we suspect that the allylation occurrs via an alumina-templated electrophilic aromatic substitution process. Mechanistic investigations and broad explorations of the scope of this allylation chemistry are underway will be reported in future manuscripts, as will the application of this chemistry to the synthesis of novel cannabinoid analogues in the context of preclinical drug discovery.

EXPERIMENTAL SECTION

General Experimental Procedures. Alumina was purchased from Millipore Sigma (activated, acidic, Brockmann I, catalogue no. 199966; activated neutral, Brockmann I, catalogue no. 199974; activated, basic, Brockmann I, catalogue no. 199443). Activated aluminas are typically sold at the Brockmann I grade, which corresponds to a water content of 1−1.5%. Freshly purchased alumina was used in this study. Reduced reaction yields were obtained when using alumina that had been stored under air for several months. High reaction yields could be regained by drying alumina at 200 °C under high vacuum for several hours prior to use.

Substrates were purchased from AKScientific and used as obtained. Solvents were purchased from Fisher Scientific, reagent grade, and used without further purification. ^{1}H NMR spectra were acquired at 700 MHz with a default digital resolution (Brüker parameter: FIDRES) of 0.15 Hz/point. Coupling constants, therefore, have uncertainties of ±0.30 Hz. Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) with reference to residual $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.16). Peak multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. Reaction progress was monitored by TLC (EMD Chemicals, Inc., silica gel 60 F254). TLC plates were developed via capillary action in hexanes−EtOAc solvent mixtures, visualized under UV light followed by *p*-anisaldehyde stain. An automated flash chromatography system (Teledyne CombiFlash R_f 200) was used for the purification of compounds on silica gel (40−60 μM particle size).

*Cannabigerol (**3**).* To a solution of geraniol (**2**,173.5 μL, 1.0 mmol) and olivetol (**1**, 270.4 mg, 1.5 mmol) in DCE (5 mL) was added acidic alumina (2.0 g). The heterogeneous mixture was stirred at reflux temperature for 6 h, then cooled to ambient temperature, and filtered through a Celite plug. The filter cake was rinsed with EtOAc (3 × 10 mL portions), and the filtrate was concentrated in vacuo to afford a yellow oil. This residue was purified via chromatography using silica gel eluted with hexanes and EtOAc. Product-rich fractions were pooled and evaporated to afford **1** (162 mg, 62%) as a yellow oil: R_f = 0.49 (EtOAc−hexanes, 30:70); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.25 (2H, s), 5.27 (1H, td, *J* = 7.1, 1.0 Hz), 5.05 (3H, m), 3.39 (2H, d, *J* = 7.1 Hz), 2.46 (2H, t, *J* = 7.8 Hz), 2.11 (2H, q, *J* = 7.4 Hz), 2.06 (2H, d, *J* = 7.4 Hz), 1.81 (3H, s), 1.68 (3H, s), 1.60 (3H, s), 1.56 (2H, q, *J* = 7.2 Hz), 1.36−1.28 (4H, m), 0.89 (3H, t, *J* = 6.9 Hz); DEPTQ ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.9 (C), 142.9 (C), 139.1 (C), 132.2 (C), 123.9 (CH), 121.8 (CH), 110.7 (C), 108.5 (CH), 39.8 (CH_2), 35.7 (CH_2), 31.6 (CH_2), 30.9 (CH_2), 26.5 (CH_2), 25.8 (CH_3), 22.7 (CH_2), 22.4 (CH_2), 17.8 (CH_3), 16.3 (CH_3), 14.2 (CH_3). These NMR spectroscopic data matched those in a previous report.[36]

*Grifolin, (E)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-5-methylbenzene-1,3-diol (**5**).* To a solution of farnesol (251 μL, 1.0 mmol) and orcinol (**6**, 372 mg, 3.0 mmol) in DCE (5 mL) was added acidic alumina (2.0 g). The heterogeneous mixture was stirred at reflux temperature for 7 h, then cooled to ambient temperature, and filtered through a Celite plug. The filter cake was rinsed with EtOAc (3 × 10 mL portions), and the filtrate was concentrated in vacuo to afford a yellow oil. This residue was purified via chromatography using silica gel eluted with hexanes and EtOAc. Product-rich fractions were pooled, and the solvent was evaporated to afford **5** (121 mg, 37%) as a yellow oil: R_f = 0.57 (EtOAc−hexanes, 25:75); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.25 (2H, s), 5.48 (2H, s), 5.29 (1H, t, *J* = 7.0 Hz), 5.12 (2H, q, *J* = 7.1 Hz), 3.42 (2H, d, *J* = 7.1 Hz), 2.21 (3H, s), 2.10 (2H, q, *J* = 6.9 Hz), 2.09−2.07 (4H, m), 2.01−1.99 (2H, m), 1.83 (3H, s), 1.70 (3H, s), 1.63 (3H, s), 1.61 (3H, s); DEPTQ ^{13}C NMR (176 MHz, $CDCl_3$) δ 154.9 (C), 138.9 (C), 137.5 (C), 135.7 (C), 131.4 (C), 124.5 (CH), 123.7 (CH), 121.9 (CH), 110.7 (C), 109.2 (CH), 39.8 (CH_2), 39.8 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 25.8 (CH_3), 22.3 (CH_2), 21.1 (CH_3), 17.8 (CH_3), 16.3 (CH_3), 16.1 (CH_3). These NMR spectroscopic data matched those in two previous reports.[30,37]

*Cannabigerorcin, (E)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-5-methylbenzene-1,3-diol (**7**).* To a solution of geraniol (**2**, 838 μL, 4.0 mmol) and orcinol (**6**, 617 mg, 6.0 mmol) in DCE was added acidic alumina (2.0 g). The heterogeneous mixture was stirred at reflux temperature for 24 h, cooled to ambient temperature, and filtered through a Celite plug. The filter cake was rinsed with EtOAc (3 × 15 mL portions), and the filtrate was concentrated in vacuo to afford a yellow oil. This residue was purified via chromatography using a silica gel eluted with hexanes and EtOAc. Product-rich fractions were pooled, and the solvent was evaporated to afford **7** (492 mg, 47%) as a yellow oil: R_f = 0.41 (EtOAc−hexanes, 25:75); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.24 (2H, s), 5.28−5.26 (1H, m), 5.07 (2H, s), 5.05 (1H, d, *J* = 6.9 Hz), 3.39 (2H, d, *J* = 7.1 Hz), 2.21 (3H, s), 2.10 (2H, dd, *J* = 7.3, 6.9 Hz), 2.06 (2H, dd, *J* = 8.7, 6.3 Hz), 1.81 (3H, s), 1.68 (4H, s), 1.59 (3H, s); DEPTQ ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.8 (C), 139.0 (C), 137.6 (C), 132.1 (C), 123.8

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(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), 21.1 (CH_3), 17.7 (CH_3), 16.2 (CH_3). These NMR spectroscopic data matched those in two previous reports.[38,39]

*Piperogalin, (E)-2-(3,7-Dimethylocta-2,6-dien-1-yl)-5-methyl-4-(3-methylbut-2-en-1-yl)benzene-1,3-diol (**8**).* To a solution of cannabigerorcin (**7**, 78 mg, 0.3 mmol) and prenol (**9**, 20.3 μL, 0.2 mmol) in heptanes (3.0 mL) was added acidic alumina (300 mg). The reaction was heated to 80 °C for 14 h, cooled to ambient temperature, and filtered through a Celite pad. The filter cake was rinsed with EtOAc (3 × 10 mL), and the filtrate was concentrated in vacuo to afford a yellow oil. This residue was purified via chromatography using silica gel eluted with hexanes and EtOAc. Product-rich fractions were pooled, and the solvent was evaporated to afford **8** (37.5 mg, 57%) as a yellow oil: R_f = 0.46 (EtOAc−hexanes, 1:6); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.27 (1H, s), 5.38 (1H, s), 5.25 (1H, t, *J* = 7.0 Hz), 5.14 (1H, t, *J* = 6.4 Hz), 5.06 (1H, t, *J* = 6.4 Hz), 4.90 (1H, s), 3.40 (2H, d, *J* = 7.0 Hz), 3.29 (2H, d, *J* = 7.0 Hz), 2.21 (3H, s), 2.11 (2H, q, *J* = 7.5 Hz), 2.07−2.04 (2H, m), 1.81 (3H, s), 1.80 (3H, s), 1.73 (3H, s), 1.68 (3H, s), 1.59 (3H, s); DEPTQ ^{13}C NMR (176 MHz, $CDCl_3$) δ 153.6 (C), 152.8 (C), 138.8 (C), 135.4 (C), 133.7 (C), 132.1 (C), 124.0 (CH), 122.6 (CH), 122.1 (CH), 118.2 (C), 111.5 (C), 109.9 (CH), 39.8 (CH_2), 26.5 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 25.7 (CH_2), 22.7 (CH_2), 20.0 (CH_3), 18.0 (CH_3), 17.8 (CH_3), 16.3 (CH_3). These NMR spectroscopic data matched both reports of isolated natural piperogalin.[33,34]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00131.

Copies of ^{1}H and ^{13}C NMR spectra of all compounds synthesized (PDF)

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Notes

The authors declare the following competing financial interest(s): J.M., N.G.J. and X.Z. are inventors on a patent application on the use of alumina to synthesize functionalized phenols.

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