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FULL-LENGTH PAPER

Tuning the Lewis acid phenol *ortho*-prenylation as a molecular diversity tool

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Abstract A diversity-oriented approach for the synthesis of various structurally different prenylated alcohols from readily accessible and common precursors was developed. With varying approaches, this article describes some successful examples of a Friedel–Crafts alkylation using methoxyphenols and different prenyl alcohols (geraniol and (*E*,*E*)-farnesol). We demonstrated that just by varying the stoichiometry of the Lewis acid used, the course of the reaction can be shifted to produce the alkylated or the cyclized product. Eighteen unique products were obtained with good isolated yields by direct alkylation with or without a consecutive π-cationic cyclization.

Keywords Prenylated natural products · Phenols · Friedel–Crafts alkylation · Selective C-prenylation

Introduction

Prenylated natural products are an important class of secondary metabolites. Flavonoids [1,2], amino acids and peptides [3,4], quinones, and hydroquinones [5,6] are among the scaffolds that appear frequently prenylated. This abundant and diverse class of compounds can be divided into two sub-classes, namely those that are C-prenylated and those that are O-prenylated. The C-prenylated products seem to play more critical roles in the organisms that biosynthesized them. However, for years O-prenylated compounds have been considered merely biosynthetic intermediates towards C-prenylated derivatives. It is only in the last decade that these natural products have been recognized of interest and as valuable biologically active phytochemicals [7]. Prenylated quinones play a significant role in the regulation of essential biological processes, such as ubiquinone-ubiquinol (coenzyme Q) and cellular respiration [8], and are also part of the vitamin complexes E and K (Fig. 1).

Prenylated phenols are extensively distributed through nature. These compounds and their structurally modified members have shown promising biological activities. Some members of this compound family, such as grifolic acid, grifolin, and piperogalin (Fig. 2) have displayed remarkable activities as inhibitors of trypanosomatid proliferation [9]. Galopiperone (Fig. 2), a diprenylated chromane isolated from *Peperomia galioides* HBK (*Piperaceae*), exhibited potent antiparasitic activity against three species of *Leishmania* [10]. The prenylated antibiotic Ascofuranone, isolated from the fungus *Ascochyta viciae*, has exhibited antitumor activity and modulation of the immune system [11], and it has also displayed activity against *Trypanosoma brucei* [12] as an inhibitor of its alternative oxidase [13].

Recently, different isoprenylated phenols have been reported to exhibit antifungal [14], antitumor [15], anti-HIV [16], antioxidant [17], and anti-Alzheimer activities [18,19]. Additionally, isoprenylated dimethyl-benzopyranes have exhibited a wide spectrum of biological activities [20]. Other examples of these natural products with different scaffolds are Shikonin (Fig. 2), a very powerful antibacterial isoprenylated naphtoquinone [21], and Arnebinol (Fig. 2), an *ortho*-isoprenylated phenol that inhibits prostaglandin synthesis [22].

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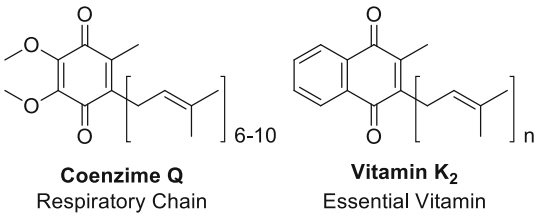


Fig. 1 Coenzyme Q and Vitamin K structures

An exhaustive search in the ChemNetBase® [23] shows that only 2.05 % of the identified natural products have an *ortho*-isoprenyl phenol scaffold. However, when reducing the search only to reported drugs, this percentage decreases to 0.55 %. This decrease is due to their scarcity from natural sources, their structural complexity that prohibits efficient chemical synthesis, and the lack of drug development.

To enable further studies of these biologically relevant metabolites [24], we reviewed the literature for synthetic routes. Multiple approaches have been explored to synthesize them, including the introduction of isoprenes through a benzylic coupling step [25], Claisen rearrangement [26], metal-halogen exchange, or metal-mediated coupling [27]. Because of the presence of many hydroxyl groups on the aromatic ring, which is often the case in many natural products, reported synthesis routes have major drawbacks in the production of these compounds. In this context, synthetic strategies capable to differentiate between similar aromatic hydroxyl groups would be advantageous to gain access to prenylated phenols which otherwise are difficult to obtain with existing methods. One approach to drive selectivity is through the regioselective chemical protection or functionalization of the hydroxyl groups. For example, in recent reports, meso-diols have been selectively alkylated using a chiral catalyst [28] or enzymes to produce chiral compounds [29].

Having in mind the diverse and noticeable activities of *ortho-prenylated* phenols, we decided to explore simple and modular strategies to prepare diverse collections of these compounds. Among the reported procedures, the Friedel–Crafts alkylation reaction allowed for the direct formation of the desired products using phenols and isoprenyl alcohols in the presence of a stoichiometric amount of a Lewis acid [30]. We report herein conditions to selectively generate alkylated products using $BF_3{\cdot}Et_2O$ as a reagent for its versatility, affordability, and commercial availability.

Results and discussions

Phenol mono-prenylation versus cyclization

In theory, the $BF_3{\cdot}Et_2O$ alkylation reaction involving isoprenols could produce either the desired alkylated product or a polycyclic product through a π-cationic cyclization mechanism.

The alkylation process can be rationalized through an electrophilic aromatic substitution (S_EAr) where the presence of a hydroxyl group is essential to serve as a strong aromatic ring activator and *ortho*-director, both properties required to obtain the desired products. To optimize the reaction conditions and favor the alkylated product over the cyclic one, an adequate and simple model substrate was needed. We selected *p*-methoxyphenol (mequinol) **1** as an initial substrate because its symmetry would reduce the number of possible isomeric products and is more stable compared to its corresponding hydroquinone.

Looking to optimize the yield and the selectivity towards the alkylated product, mequinol was reacted with geraniol **2** (alkylating agent) and $BF_3{\cdot}Et_2O$ in toluene at 4 °C [30] (Scheme 1).

Reactions varying the amount of mequinol **1** and $BF_3{\cdot}Et_2O$ were conducted and the results are shown in Table 1. The progress of the reactions was monitored using GC-MS, iden-

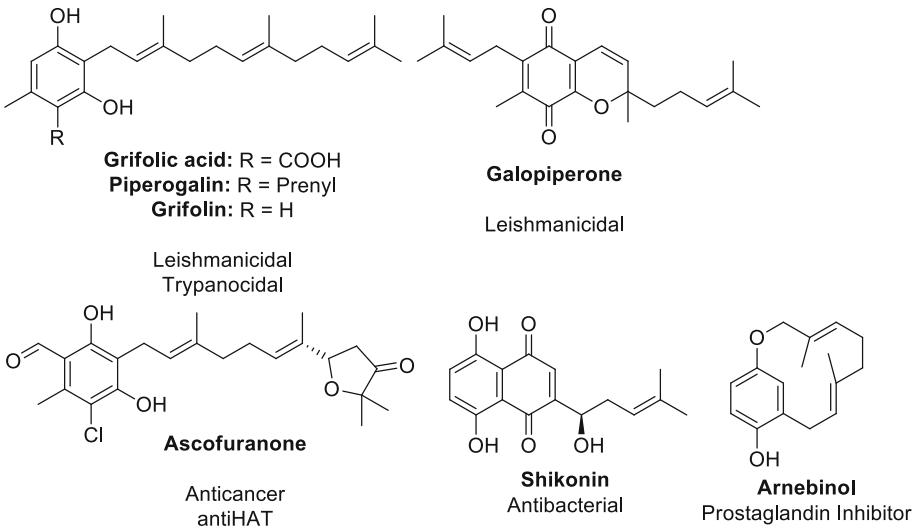


Fig. 2 Prenylated phenols and quinones

Scheme 1 Optimization of prenylation conditions

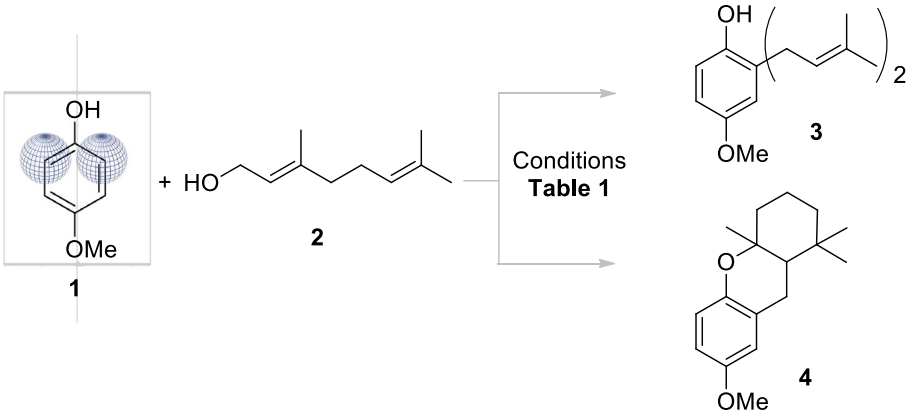


Table 1 Isoprenylation reaction optimization using $BF_3{\cdot}Et_2O$

Entry	Reaction conditions (eq.)			Product distribution (%)[a]		
	p-Methoxy phenol **1**	Geraniol **2**	$BF_3{\cdot}Et_2O$	*p*-Methoxy phenol **1**	**3**	4
1	1.00	1.00	0.30	50	50	0
2	1.30	1.00	0.30	67	33	0
3	1.70	1.00	0.30	67	33	0
4	2.00	1.00	0.30	71	29	0
5	1.00	1.00	0.60	25	0	75
6	1.00	1.00	0.90	18	0	82
7	1.00	1.00	1.20	14	0	86
8	2.00	1.00	0.60	71	0	29
9	2.00	1.00	0.90	71	0	29
10	2.00	1.00	1.20	71	0	29

[a] Determined by GC-MS

tifying products by their fragmentation patterns and using previously prepared standards to calculate product distribution. Geraniol **2** was used as the limiting reagent to avoid over prenylation (Table 1).

Entries 1–4 show the effect of increasing *p*-methoxyphenol **1** in the reaction outcome, where a direct correlation between the initial and recovered phenol was observed. Also, the amount of alkylated product **3** remained constant as the amount of phenol increased, without the formation of a cyclic product **4**. At the end, entry **1** provided the best conditions to isolate the desired *ortho*-prenyl product.

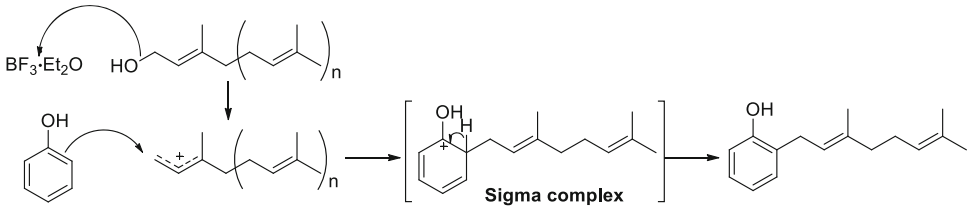
The importance of 0.3 equiv. of $BF_3{\cdot}Et_2O$ to obtain the monoalkylated product was evident since higher amount of $BF_3{\cdot}Et_2O$ led to cyclized product **4** (entries 5–7). When the amount of phenol **1** was doubled, the ratio between recovered phenol and cyclized product remained constant (entries 8–10). Overall, the reaction conditions can be modulated and product distribution can be controlled by varying the stoichiometry of $BF_3{\cdot}Et_2O$ used in the reaction.

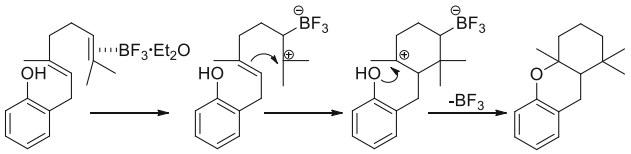
Based on these results, we propose the following reaction mechanism. The reaction starts with the formation of the allylic carbocation (electrophilic intermediate) which is generated by alcohol elimination upon binding to $BF_3{\cdot}Et_2O$. Then, the allyl carbocation reacts with the aromatic electrons of the π system forming a new carbocation intermediate (sigma complex) which then loses a proton leading to final product. Additionally, a thermodynamically more stable tertiary carbocation can be generated by proton transposition (carbocation rearrangement). If the temperature is kept low, the reaction then proceeds under kinetic control and the major product is obtained via the primary carbocation, while at higher temperatures the reaction is favored via the tertiary carbocation (Scheme 2).

To avoid the formation of polyalkylated products, maintaining a strict regiocontrol is key. Due to the aromatic ring activation by the alkyl groups in electrophilic aromatic substitution, the monoalkylated species are more reactive than the starting phenol itself. In our case, the regiocontrol is achieved by maintaining the isoprenyl alcohol:phenol equivalent ratio below one.

We found several examples in the literature where the alkylation reaction produces significant amounts of chromane [31]. This secondary reaction is disfavored when Lewis acids are used, particularly when catalytic amounts

Scheme 2 Phenol *ortho*-C-prenylation mechanism





Scheme 3 π-Cationic cyclization mechanism

are exceeded. When more than one equivalent of Lewis acid is used, $BF_3{\cdot}Et_2O$ coordinates with the π electrons of the double bond and subsequently attacks intramolecularly the nucleophilic centers present in the molecule (Scheme 3).

Dialkylated products

Direct dialkylation versus stepwise alkylation

In previous studies using Lewis acid-catalyzed alkylation conditions, polyalkylation was observed as a competitive side-reaction on the phenol group [32]. In fact, traces of two different dialkylated products were isolated on multigram scale reactions given in Table 1—entry 1 conditions. When the structure of the products were determined, it was confirmed that one was the 2,6-dialkylated phenol *(sym)* and the other the 2,5-dialkylated product (*anti*) (Fig. 3).

Aiming to obtain dialkylated products, two different pathways were studied adjusting the optimized reaction conditions: the direct double-alkylation and the stepwise procedure. The direct double-alkylation pathway involved the one-pot synthesis of the dialkylated product reacting one equivalent of **1** with two equivalents of **2**. For the stepwise alkylation procedure, one equivalent of **2** was reacted with the previously isolated alkylated product **3**. The results are summarized in Table 2.

Entries 11 and 12 show the effect of using 0.3 equivalents of $BF_3{\cdot}Et_2O$. The cyclized product was not favored and different alkylated products were detected, with the *sym* and *anti* products obtained in equal amounts (entry 11). Moreover, when the amount of the reagents was doubled, cyclized product **4** was favored (entries 13 and 14). Surprisingly, as shown in entry 16, when the amount of $BF_3{\cdot}Et_2O$ was doubled, only cyclized product **4** was formed and dialkylated *sym*-product was also produced (no *anti*-isomer present). Increasing the amount of **2** afforded same results (entries 17 and 18).

For the stepwise procedure, the alkylation conditions used in entry 1 were first tested on the monoalkylated product **3** (entry 19). The major component of the reaction mixture was starting material with a considerable percentage of dialkylated products, favoring the *sym*-isomer. The stepwise method was also investigated for the cyclization conditions shown in entry 7, and yet again the cyclized product was found as major component of the final reaction mixture (entry 20).

In order to alkylate cyclized product **4**, different experiments were performed using the alkylating conditions shown in entry 1. Either equal amount of **2** was used or the amount of the terpene was doubled. The results show almost no alkylation of **4**. It was clear that the alkylation is not favored for that substrate, being consistent with the Friedel–Crafts reaction mechanism where the OH directing group is critical to activate the adjacent carbon.

Reaction scope

We proceeded to investigate the scope of the optimized reaction conditions using farnesol as the alkylating reagent obtaining farnesylated phenol **6** and the tetracyclic analog **7** (Scheme 4).

Next, we aimed to expand the scope of the reaction using the optimized conditions on the methoxyphenol isomers (3-

Fig. 3 Possible dialkylated products

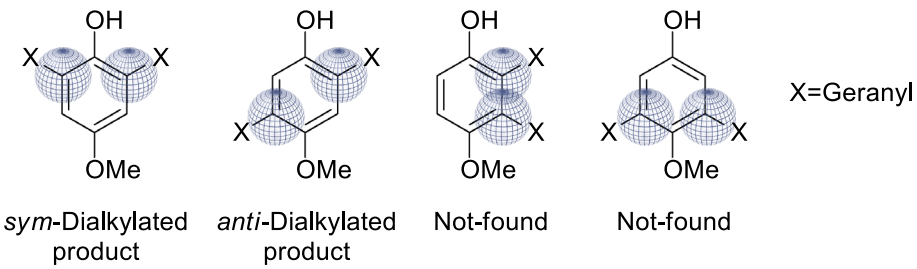
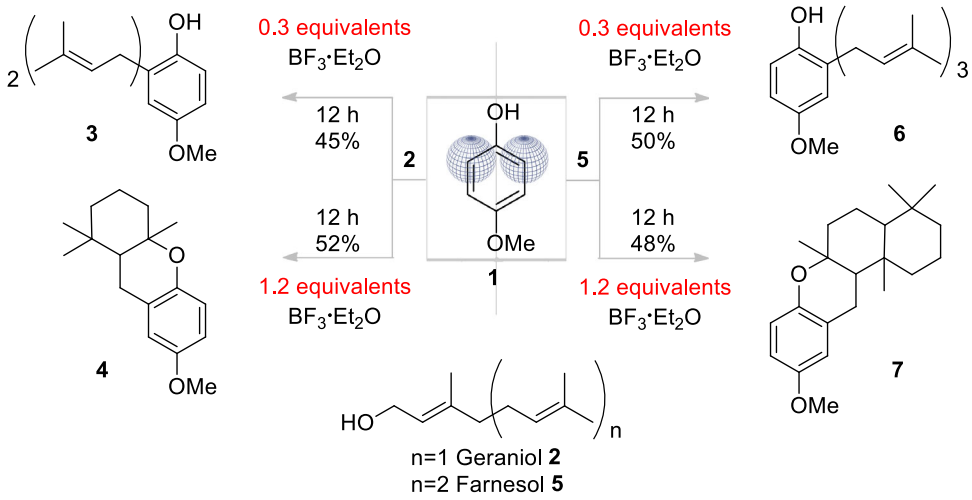


Table 2 Studies of 4-methoxyphenol dialkylation

Entry	Reaction conditions				Product distribution[a]			
	p-Methoxy phenol **1**	**3**	Geraniol **2**	$BF_3{\cdot}Et_2O$	**3**	**4**	*Sym*-product	*Anti*-product
11	1	–	2	0.3	65	3	17	15
12	1	–	2	0.6	9	80	10	2
13	1	–	3	0.3	67	8	14	11
14	1	–	3	0.6	3	94	3	0
15	1	–	2	1.2	0	94	6	0
16	1	–	2	2.4	0	82	18	0
17	1	–	3	1.2	0	89	11	0
18	1	–	3	2.4	0	80	20	0
19	–	1	1	0.3	54	12	26	8
20	–	1	1	1.2	3	85	9	3

[a] Determined by GC-MS

Scheme 4 Expansion to other substrates using *para*-methoxyphenol **1**, geraniol **2**, and farnesol **5**



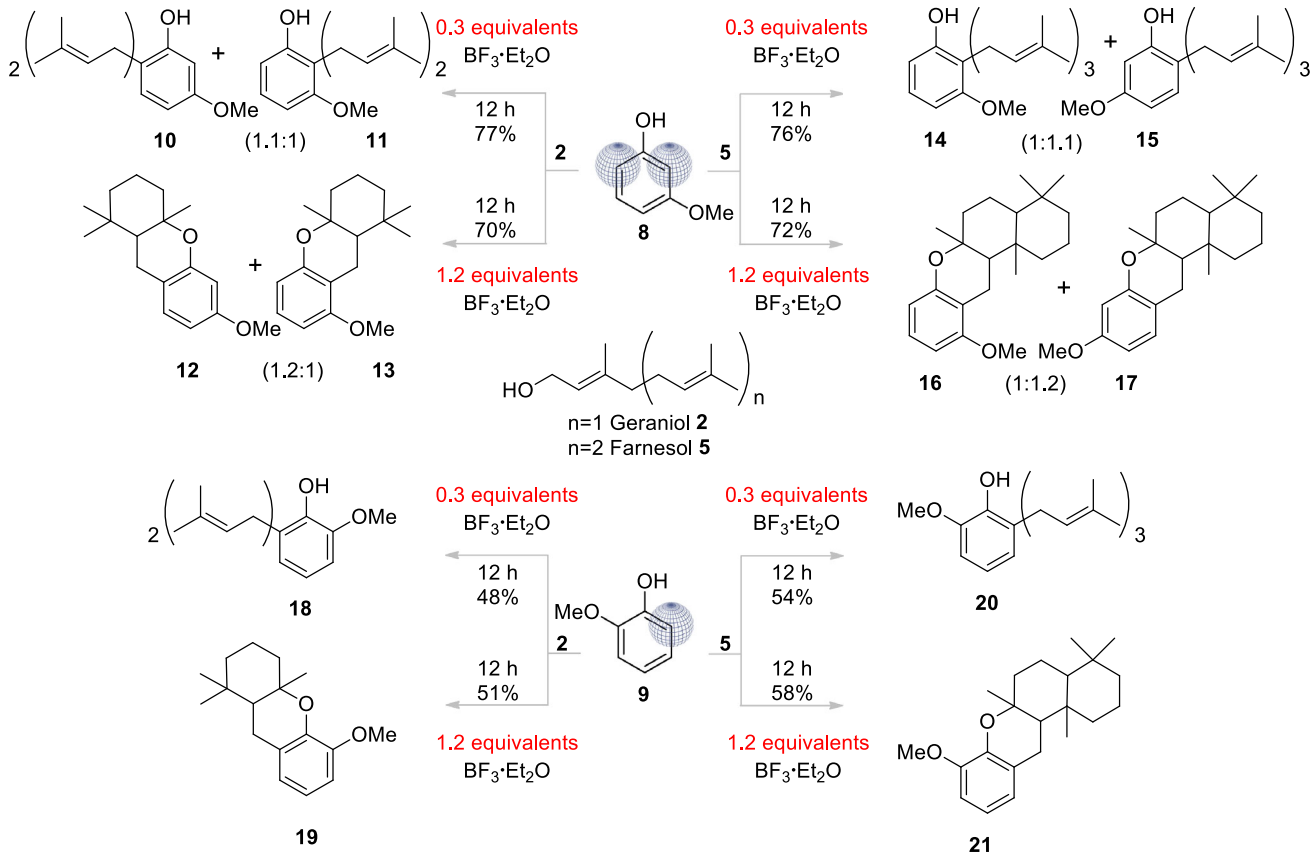
methoxyphenol **8** and 2-methoxyphenol **9**). These substrates have interesting biological properties as antiseptic [33] and local anesthetic agents [34].

When the reaction was applied to *meta*-methoxy phenol **8**, compounds **10**–**17** were obtained with higher yields than the compounds obtained using 4-methoxy phenol **1**. Using geraniol **2** as reagent, products **10** and **11** (1.1:1) were obtained, and when using farnesol **5**, analogs **14** and **15** (Scheme 5) were obtained also in the same ratio. Under cyclization conditions, a mixture of products **12** and **13** (1.2:1) was obtained when using geraniol **2**, and **16** and **17** (1:1.2) when using farnesol **5**. These results could be rationalized by the synergetic directing effect of the methoxy and hydroxyl groups. In particular, the *meta*-methoxy phenol **8** is non-symmetric and has two markedly different *ortho* positions which can be alkylated. The difference in reactivity is due to the greater activation of the C2-position by both functional groups (hydroxy and methoxy) on the aromatic ring.

When *ortho*-methoxy phenol **9** was reacted with geraniol **2** and farnesol **5**, exclusively monoalkylated products **18** and **20** were obtained, respectively (Scheme 5). The cyclization reactions of *ortho*-methoxy phenol produced **19** and **21** without noticeable amounts of byproducts. The selectivity observed in these 2 cases is because the methoxy group occupies one of the *ortho* positions.

In all cases, the similarities between the yields of the synthesized products with geraniol **2** or farnesol **5** provide evidence that the reactions are independent of the number of isoprenyl units on the substrate. The fact that the electrophile's nature did not affect the course of the reaction confirms that the diversity of the products depends on both the amount of $BF_3{\cdot}Et_2O$ and the phenol used.

The potential of this new procedure has been demonstrated synthesizing 18 unique, structurally diverse products in good yields, starting from three methoxyphenols and two isoprenyl alcohols under alkylation or cyclization conditions (Schemes 4, 5).



Scheme 5 Expansion to other substrates using *ortho*-methoxyphenol **9**, *meta*-methoxyphenol **8**, geraniol **2**, and farnesol **5**

Conclusions

Based on the Lewis acid Friedel–Crafts reaction, new conditions to generate alkylated or cyclized products were found. The distribution of the products was modulated by simply varying the amount of $BF_3{\cdot}Et_2O$, being the cyclized products the main component of the products when more than 0.3 equivalent of the reagent was used.

Dialkylation reaction conditions were also conducted for the production of *sym*- and *anti*-dialkylated products through different approaches. We found a one-pot procedure for the simple and rapid access to diverse products, while a stepwise strategy led exclusively to *sym*-dialkylated products.

Lastly, we expanded the diversity of the library by using geraniol **2** and farnesol **5** obtaining different methoxyphenol regioisomers confirming the ease of use and efficiency of our methodology.

Experimental

General information

^1H and ^{13}C NMR spectra were acquired on a Bruker Avance II 300 MHz (75.13 MHz) using $CDCl_3$ as solvent. Chemical shifts (δ) were reported in ppm downfield from tetramethylsilane (TMS) at 0 ppm as internal standard and coupling constants (J) are in hertz (Hz). Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 76.9 ppm. The following abbreviations are used to indicate NMR signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, p = pentuplet, br = broad signal. High-resolution mass spectra (ESI-HRMS) were recorded on a Bruker MicroTOF II with lock spray source. GC-MS analyses were carried out on a Perkin Elmer Autosystem XL equipped with Turbomass mass detector. Data were acquired with the Varian ChemStation for GC System program. IR spectra were obtained using an FT-IR Shimadzu spectrometer and only partial spectral data are listed. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Chemical reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted. Solvents were analytical grade or were purified by standard procedures prior to use. Yields were calculated for material judged homogeneous by thin layer chromatography (TLC) and nuclear magnetic resonance (^1H-NMR). All reactions were monitored by thin layer chromatography performed on silica gel

Table 3 Studied phenol alkylation conditions

Entry	*p*-Methoxyphenol **1**		Geraniol **2**		$BF_3{\cdot}Et_2O$	
	Mass (mg)	mmol	Mass (mg)	mmol	Vol (μL)	mmol
1	40	0.32	50	0.32	12	0.10
2	52	0.42	50	0.32	12	0.10
3	68	0.55	50	0.32	12	0.10
4	81	0.65	50	0.32	12	0.10
5	40	0.32	50	0.32	24	0.19
6	40	0.32	50	0.32	36	0.29
7	40	0.32	50	0.32	48	0.39
8	80	0.65	50	0.32	24	0.19
9	80	0.65	50	0.32	36	0.29
10	80	0.65	50	0.32	48	0.39
11	30	0.24	75	0.49	18	0.15
12	30	0.24	75	0.49	36	0.29
13	20	0.16	75	0.49	18	0.15
14	20	0.16	75	0.49	36	0.29
15	30	0.24	75	0.49	72	0.58
16	30	0.24	75	0.49	144	1.17
17	20	0.16	75	0.49	72	0.58
18	20	0.16	75	0.49	144	1.17
19	80[a]	0.32	50	0.32	12	0.10
20	80[a]	0.32	100	0.62	12	0.39

[a] Stepwise phenol dialkylation using *ortho*-monoalkylated 4-methoxyphenol as substrate

60 F_{254} pre-coated aluminum sheets, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 4-anisaldehyde. Column flash chromatography was performed using silica gel 60 (230–400 mesh).

Optimization of phenol mono-prenylation vs cyclization

Ten reactions of 1 mL final volume were conducted where the geraniol equivalent was constant varying the amount of reagents and substrates in accordance with Table 3. To a solution of *p*-methoxyphenol **1** in toluene at 0 °C, $BF_3{\cdot}Et_2O$ (10 % in anhydrous toluene) was added followed by the addition of geraniol **2**. The reaction mixture was continuously stirred at 4 °C overnight and quenched with H_2O (3 mL) and $NaHCO_3$ 5 % (1 mL). Two layers were formed and AcOEt (2 mL) was added over few minutes under continuous stirring. Finally, the organic layer was separated and a 1-μL aliquot was injected in the GC-MS under the conditions described below.

Optimization of phenol dialkylation

Ten reactions (1 mL final volume) were conducted keeping geraniol equivalents constant and varying the amount of reagents and substrates as shown in Table 3 (direct path, entries 11–18) and (stepwise path, entries 19–20). To a solution of *p*-methoxyphenol **1** or *ortho*-monoalkylated 4-methoxyphenol in toluene at 0 °C, $BF_3{\cdot}Et_2O$ (10 % in anhydrous toluene) was added followed by addition of geraniol **2**. The reaction mixture was continuously stirred at 4 °C overnight and the reagents were quenched with H_2O (3 mL) and $NaHCO_3$ 5 % (1 mL). Two layers were formed and AcOEt (2 mL) was added over few minutes under continuous stirring. Finally, the organic layer was separated and a 1-μL aliquot was injected in the GC-MS under the conditions described below.

GC-MS method The conditions for the GC assays were Column: VF-1ms (Varian Inc. 30m x 0.255mm) with helium as carrier gas. Oven temperature program was 70 °C (3 min), 10 °C/min to 310 °C and hold for 6 min.

General procedure for ortho-isoprenylated phenol synthesis

1.1 equivalents of the phenol substrate were dissolved in anhydrous toluene at 0 °C. Then, 0.3 equivalents of $BF_3{\cdot}Et_2O$ were added followed by the addition of 1 equivalent of the corresponding isoprenol. After 12 h of continuous stirring at 4 °C, the reaction was quenched with saturated $NaHCO_3$. The inorganic phase was extracted 3 times with AcOEt and the combined organic layers concentrated under vacuum. The residue was purified on a silica gel column (Hexane-AcOEt gradient).

Synthesis of (E)-2-(3,7-dimethylocta-2,6-diene-1-yl)-4-methoxyphenol (***3***) Following the general alkylation conditions for the *ortho*-isoprenylated phenol synthesis, *p*-methoxyphenol **1** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene (4 mL). Then, $BF_3{\cdot}Et_2O$ was slowly added (12 μL, 0.10 mmol) followed by the addition of geraniol **2** (50 mg; 0.32 mmol). After 12 h of continuous stirring at 4 °C, the reaction was worked up and purified to afford 37 mg of a yellowish oil (isolated yield: 45 %). ^{1}H-NMR ($CDCl_3$) δ 6.74 (d, 1H, $^3J_{HH}$ = 8.3, C6–H); 6.68 (d, 1H, $^4J_{HH}$ = 2.4, C3–H); 6.65 (dd, 1H, $^3J_{HH}$ = 8.2 and $^4J_{HH}$ = 2.5, C5–H); 5.30 (t, 1H, $^3J_{HH}$ = 6.5, C2′–H); 5.07 (t, 1H, $^3J_{HH}$ = 7.1 C6′–H); 4.74 (s, 1H, OH); 3.75 (s, 3H, Me–O); 3.33 (d, 2H, $^3J_{HH}$ = 7.0, C1′–H); 2.09 (m, 4H, C4′–H and C5′–H); 1.76 (s, 3H, C17–H); 1.68 (s, 3H, C16–H); and 1.60 (s, 3H, C15–H). ^{13}C-NMR ($CDCl_3$) δ 153.6 (C4, quaternary aromatic); 148.3 (C1, quaternary aromatic); 138.4 (C3′, olefinic quaternary); 131.9 (C7′, olefinic quaternary); 128.3 (C2, quaternary aromatic); 123.9 (C6′, CH olefinic); 121.5 (C2′, CH olefinic); 116.3 (C6, CH aromatic); 115.7 (C3, CH aromatic); 112.0 (C5, CH aromatic); 55.7 (C7, O–Me); 39.7 (C1′, CH_2); 29.8 (C4′, CH_2); 26.5 (C5′, CH_2); 25.7 (C8′, CH_3); 17.7 (C10′, CH_3); and 16.2 (C9′, CH_3). HRMS Calculated for $C_{17}H_{24}O_2Na$ ($M + Na^+$) 283.1669; found

283.1654. IR (film) υ_{max} 2969 (=CH−); 2928 (−CH_2−); 1664 (−C=C−) cm^{-1}.

Synthesis of 2,6-bis((E)-3,7-dimethylocta-2,6-dienyl)-4-methoxyphenol (sym-digeranylated product) and 2,5-bis((E)-3,7-dimethylocta-2,6-dienyl)-4-methoxyphenol (anti-digeranylated product) Scaling up the general alkylation conditions for the *ortho*-isoprenylated phenol synthesis, *p*-methoxyphenol **1** (370 mg; 1.35 mmol) was dissolved in anhydrous toluene (4 mL). Then, $BF_3{\cdot}Et_2O$ was slowly added (50 μL, 0.4 mmol) followed by the addition of geraniol **2** (208 mg; 1.35 mmol). After 12 h of continuous stirring at 4 °C, the reaction was worked up and purified to afford 100 mg of the *sym*-dialkylated product (isolated yield: 17 %) and 47 mg of the *anti*-dialkylated product (isolated yield: 8 %).

Sym-digeranylated product, ^{1}H-NMR ($CDCl_3$) δ 6.56 (s, 1H, C6–H); 5.31 (t, 2H, $^3J_{HH}$ = 7.2, C2′–H and C2″–H); 5.10–5.06 (m, 2H, C6′−H y C6″−H); 4.94 (s, 1H, OH); 3.74 (s, 3H, C11–H); 3.32 (d, 2H, $^3J_{HH}$ = 6.1, C1′–H, and C1″–H); 2.14–1.99 (m, 8H, C4-H, C5′–H, C4″, and C5″–H); 1.75 (s, 6H, C9′–H, and C9″–H); 1.68 and 1.60 (s, 12H, C8′–H, C10′–H, C10″–H and C8″–H). ^{13}C-NMR ($CDCl_3$) δ 153.2 (C4, quaternary aromatic); 146.6 (C1, quaternary aromatic); 138.0 (C3′ and C3″, olefinic quaternary); 131.9 (C7′ and C7″, olefinic quaternary); 128.3 (C2 and C6, quaternary aromatic); 124.0 (C6′ and C6″, CH olefinic); 121.9 (C2′ and C2″, CH olefinic); 113.0 (C3 and C5); 55.6 (C11, O–Me); 39.7 (C4′ and C4′, CH_2); 29.7 (C1′ and C1″, CH_2); 26.5 (C5′ and *C*6′, CH_2); 25.7 (C10′ and C10″, CH_3); 17.7 (C8′ and C8″, CH_3); and 16.2 (C9′ and C9″, CH_3). HRMS Calculated for $C_{27}H_{40}O_2Na$ (M + Na^+) 419.2921; found 419.2906. IR (film) υ_{max} 2969 (=CH−); 2928 (−CH_2−); 1664 (−C=C−) cm^{-1}.

Anti-digeranylated product, ^{1}H-NMR ($CDCl_3$) δ 6.62 (s, 1H, C6–H); 6.60 (s, 1H, C3–H); 5.34–5.26 (m, 2H, C2′ − H y C2″−H); 5.13–5.06 (m, 2H, C6′ − H y C6″−H); 4.69 (s, 1H, OH); 3.79 (s, 3H, C11–H); (t, 1H, $^3J_{HH}$ = 7.1, C13–H); 4.74 (s, 1H, OH); 3.75 (s, 3H, C7–H); 3.32 (d, 2H, $^3J_{HH}$ = 7.1, C1′−H); 3.26 (d, 2H, $^3J_{HH}$ = 7.3, C1″−H); 2.14 to 1.99 (m, 8H, C4-H, C5′−H, C4″ and C5″−H); 1.76 (s, 3H, C9′−H); 1.68 and 1.60 (s, 15H, C8′−H, C10′−H, C9″−H, C10″ − H, and C8″−H). ^{13}C-NMR ($CDCl_3$) δ 151.3 (C4, quaternary aromatic); 147.9 (C1, quaternary aromatic); 138.2 (C3′, olefinic quaternary); 136.2 (C3″, olefinic quaternary); 131.9 and 131.4 (C7′, C7″, exchangeable, olefinic quaternary); 129.2 (C5, quaternary aromatic); 124.4 (C6′ and C6″, CH olefinic) 122.3 (C2″, CH olefinic); 121.9 (C2′, CH olefinic); 129.2 (C5, quaternary aromatic); 117.1 (C6, CH aromatic); 112.6 (C3, quaternary aromatic); 56.2 (C11, O–Me); 39.8 and 39.7 (C4′, C4″, exchangeable, CH_2); 29.9 (C1′, CH_2); 27.7 (C1″, CH_2); 26.7 and 26.5 (C5′, C5″, exchangeable, CH_2); 25.7 and 17.7 (C8′, C8″ and C10′, C10″; exchangeable, CH_3); 16.2 and 16.0 (C9′,C9″, exchangeable, CH_3). HRMS Calculated for $C_{27}H_{40}O_2Na$(M + Na^+) 419.2921; found 419.2906 IR (film) υ_{max} 2969 (=CH−); 2928 (−CH_2−); 1664 (−C=C−) cm^{-1}.

Synthesis of 4-methoxy-2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-triene-1-yl) phenol (***6***) Following the general alkylation conditions for the *ortho*-isoprenylated phenol synthesis, *p*-methoxyphenol **1** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene (4 mL). Then, $BF_3{\cdot}Et_2O$ was slowly added (12 μL, 0.10 mmol) followed by the addition of farnesol **5** (50 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 53 mg of a yellowish oil (isolated yield: 50 %).

^{1}H-NMR ($CDCl_3$) δ 6.74 (d, 1H, $^3J_{HH}$ = 8.5, C6–H); 6.70–6.62 (m, 2H, C3–H, and C5–H); 5.31 (t, 1H, $^3J_{H2'-H3'}$ = 7.2, C2′–H); 5.09 (m, 2H, C6′–H, and C10′–H); 4.77 (s, 1H, OH); 3.75 (s, 3H, Me–O); 3.34 (d, 2H, $^3J_{H1'-H2'}$ = 7.3, C1′–H); 2.21–1.94 (m, 8H, C4′–H, C5′–H, C8′–H, and C9′–H); 1.77 (s, 3H, C13′–H); 1.68 (s, 3H, C12′–H); and 1.60 (s, 6H, C15′–H y C14′–H). ^{13}C-NMR ($CDCl_3$) δ 153.6 (C4, quaternary aromatic); 148.3 (C1, quaternary aromatic); 138.5 (C3′, olefinic quaternary); 135.5 (C7′, olefinic quaternary); 131.3 (C11′, olefinic quaternary); 128.2 (C2, quaternary aromatic); 124.4 (C10′, CH olefinic); 123.7 (C6′, CH olefinic); 121.5 (C2′, CH olefinic); 116.3 (C6, CH aromatic); 115.7 (C3, CH aromatic); 112.0 (C5, CH aromatic); 55.7 (O–Me, CH_3); 39.7 (C4′ and C8′, CH_2); 29.9 (C1′, CH_2); 26.7 and 26.5 (C5′ and C9′ exchangeable, CH_2); 25.7 (C12′, CH_3); 17.7 (C15′, CH_3); 16.2 and 16.1 (C13′ and C14′ exchangeable, CH_3). HRMS Calculated for $C_{22}H_{32}O_2Na$ (M + Na^+) 351.2295; found 351.2296. IR (film) υ_{max} 3437 (O–H); 2959 (=CH−); 2928 (−CH_2−); 1660 (−C=C−) cm^{-1}.

*Synthesis of (E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-5-methoxyphenol (**10**) and (E)-2-(3,7-dimethylocta-2,6-diene-1-yl)-3-methoxy phenol (**11**)* Following the general alkylation conditions for the *ortho*-isoprenylated phenol synthesis, *m*-methoxyphenol **8** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene (4 mL). Then, $BF_3{\cdot}Et_2O$ was slowly added (12 μL, 0.10 mmol) followed by the addition of geraniol **2** (50 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 64 mg of a yellowish oil (isolated yield: 77 %). Product distribution 1:1.1.
*Compound **10***, ^{1}H-NMR ($CDCl_3$) δ 7.00 (d, 1H, $^3J_{H3-H4}$ = 8.4, C3–H); 6.44 (dd, 1H, $^3J_{H4-H3}$ = 8.4, $^4J_{H4-H6}$ = 2.6, C4–H); 6.43 (s, 1H, C6–H); 5.35 (s, 1H, OH); 5.30 (t, 1H, $^3J_{H2'-H3'}$ = 7.1, C2′–H); 5.09 (m, 1H, C6′–H); 3.77 (s, 3H, Me–O); 3.32 (d, 2H, $^3J_{H1'-H2'}$ = 7.1, C1′–H); 2.11 (m, 4H, C4′–H, and C5′–H); 1.77 (s, 3H, C9′–H); 1.70 (s, 3H, C8′–

H); and 1.61 (s, 3H, C10′–H). ^{13}C-NMR ($CDCl_3$) δ 159.3 (C1, quaternary aromatic); 155.3 (C5, quaternary aromatic); 138.3 (C3′, olefin quaternary); 132.0 (C7′, olefin quaternary); 130.3 (C3, CH aromatic); 123.9 (C6′, CH olefin); 122.1 (C2′, CH olefin); 119.0 (C2, quaternary aromatic); 106.1 (C4, CH aromatic); 102.0 (C6, CH aromatic); 55.3 (Me–O, CH_3); 39.7 (C4′, CH_2); 29.1 (C1′, CH_2); 26.4 (C5′, CH_2); 25.7 (C8′, CH_3); 17.7 (C10′, CH_3); and 16.1 (C9′, CH_3). HRMS Calculated for $C_{17}H_{24}O_2Na$ ($M + Na^+$) 283.1669; found 283.1668. IR (film) υ_{max} 3450 (O–H); 2959 (=CH−); 2930 ($-CH_2-$); 1603 (−C=C−) cm^{-1}.

Compound ***11***, ^{1}H-NMR ($CDCl_3$) δ 7.05 (t, 1H, $^3J_{HH} = 8.2$, C5–H); 6.48 (d, 2H, $^3J_{HH} = 8.2$, C4–H y C6–H); 5.32 (s, 1H, OH); 5.24 (t, 1H, $^3J_{HH} = 6.9$, C2′–H); 5.06 (m, 1H, C6′–H); 3.81 (s, 3H, Me–O); 3.42 (d, $^3J_{HH} = 6.9$, C1′–H); 2.05 (m, 4H, C4′–H, and C5′–H); 1.80 (s, 3H, C9′–H); 1.67 (s, 3H, C8′–H); and 1.58 (s, 3H, C10′–H). ^{13}C-NMR ($CDCl_3$) δ 157.9 (C1, quaternary aromatic); 155.7 (C3, quaternary aromatic); 138.1 (C3′, olefinic quaternary); 131.9 (C7′, olefinic quaternary); 127.1 (C5, CH aromatic); 123.9 (C6′, CH olefinic); 121.9 (C2′, CH olefinic); 115.2 (C2, quaternary aromatic); 109.0 (C4, CH aromatic); 103.1 (C6, CH aromatic); 55.8 (Me–O, CH_3); 39.7 (C4′, CH_2); 26.5 (C5′, CH_2); 25.7 (C8′, CH_3); 22.2 (C1′, CH_2); 17.7 (C10′, CH_3); and 16.2 (C9′, CH_3). HRMS Calculated for $C_{17}H_{24}O_2Na$ ($M + Na^+$) 283.1669; found 283.1669. IR (film) υ_{max} 3506 (O–H); 2966 (=CH−); 2924 ($-CH_2-$) cm^{-1}.

Synthesis of 3-methoxy-2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-triene-1-yl) phenol (14) and 5-methoxy-2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-triene-1-yl) phenol (***15***) Following the general alkylation conditions for the *ortho*-isoprenylated phenol synthesis, *m*-methoxyphenol **8** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene (4 mL). Then, $BF_3{\cdot}Et_2O$ was slowly added (12 μL, 0.10 mmol) followed by the addition of farnesol **5** (71 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 80 mg of a yellowish oil (isolated yield: 76 %). Product distribution 1:1.2.

Compound ***14***, ^{1}H-NMR ($CDCl_3$): $\delta = 7.05$ (t, 1H, $^3J_{HH} = 8.2$, C5–H); 6.47 (d, 2H, $^3J_{HH} = 8.2$, C4–H, and C6–H); 5.31 (s, 1H, OH); 5.24 (t, 1H, $^3J_{HH} = 7.1$, C2′–H); 5.08 (m, 2H, C6′–H, and C10′–H); 3.80 (s, 3H, Me–O); 3.42 (d, $^3J_{HH} = 7.1$, C1′–H); 2.05 (m, 8H, C4′–H, C5′–H, C8′–H and C9′–H); 1.81 (s, 3H, C13′–H); 1.67 (s, 3H, C12′–H); and 1.59 (s, 6H, C15′–H, and C14′–H). ^{13}C-NMR ($CDCl_3$) δ 158.0 (C1, quaternary aromatic); 155.6 (C3, quaternary aromatic); 138.1 (C3′, olefinic quaternary); 135.4 (C7′, olefinic quaternary); 131.3 (C11′, olefinic quaternary); 127.1 (C5, CH aromatic); 124.4 (C10′, CH olefinic); 123.8 (6’, CH olefinic); 121.9 (C2′, CH olefinic); 115.2 (C2, quaternary aromatic); 109.0 (C4, CH aromatic); 103.1 (C6, CH aromatic); 55.8 (C7, CH_3); 39.7 (C4′ and C8′, CH_2); 26.7 and 26.4 (C5′ and C9′ exchangeable, CH_2); 25.7 (C12′, CH_3); 22.2 (C1′, CH_2); 17.7 (C15′, CH_3); 16.2 (C14′, CH_3); and 16.0 (C13′, CH_3). HRMS Calculated for $C_{22}H_{33}O_2$ ($M+H^+$) 329.2475; found 329.2477. IR (film) υ_{max} 3520 (O–H); 2964 (=CH−); 1605 (−C=C−) cm^{-1}.

Compound ***15***, ^{1}H-NMR ($CDCl_3$) δ 6.98 (d, 1H, $^3J_{H3-H4} = 8.3$, C3–H); 6.42 (dd, 1H, $^3J_{H4-H3} = 8.4$, $^4J_{H4-H6} = 2.6$, C4–H); 6.41 (s, 1H, C6–H); 5.31 (t, 1H, $^3J_{H2'-H1'} = 7.1$, C2′–H); 5.23 (s, 1H, OH); 5.10 (m, 2H, C6′–H y C10′–H); 3.76 (s, 3H, Me–O); 3.30 (d, 2H, $^3J_{H1'-H2'} = 6.9$, C1′–H); 2.10 (m, 8H, C4′–H, C5′–H, C8′–H, and C9′–H); 1.77 (s, 3H, C13′–H); 1.68 (s, 3H, C12′–H); and 1.60 (s, 6H, C15′–H, and C14′–H). ^{13}C-NMR ($CDCl_3$) δ 159.4 (C1, quaternary aromatic); 155.4 (C5, quaternary aromatic); 138.4 (C3′, olefinic quaternary); 135.6 (C7′, olefinic quaternary); 131.3 (C11′, olefinic quaternary); 130.3 (C3, CH aromatic); 124.4 (C10′, CH olefinic); 123.7 (C6′, CH olefinic); 122.1 (C2′, CH olefinic); 118.9 (C2, quaternary aromatic); 106.1 (C4, CH aromatic); 102.0 (C6, CH aromatic); 55.3 (Me–O, CH_3); 39.7 (C4′ and C8′, CH_2); 29.2 (C1′, CH_2); 26.7 and 26.4 (C5′ and C9′ exchangeable, CH_2); 25.7 (C12′, CH_3); 17.7 (C15′, CH_3); 16.2 and 16.1 (C13′ and C14′ exchangeable, CH_3). HRMS Calculated for $C_{22}H_{33}O_2$ ($M+H^+$) 329.2475; found 329.2476. IR (film) υ_{max} 3520 (O–H); 2964 (=CH−); 1605 (−C=C−) cm^{-1}.

Synthesis of (E)-2-(3,7-dimethylocta-2,6-diene-1-yl)-6-methoxy phenol (***18***) Following the general alkylation conditions for the *ortho*-isoprenylated phenol synthesis, *o*-methoxyphenol **9** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene (4 mL). Then, $BF_3{\cdot}Et_2O$ was slowly added (12 μL, 0.10 mmol) followed by the addition of geraniol **2** (50 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 41 mg of a yellowish oil (isolated yield: 48 %). ^{1}H-NMR ($CDCl_3$) δ 6.84 (d, 1H, $^3J_{H4-H5} = 8.2$, C5–H); 6.68 (m, 2H, C3–H, and C4–H); 5.55 (s, 1H; OH); 5.34 (t, 1H, $^3J_{HH} = 7.1$, C2′–H); 5.12 (m, 1H, C6′–H); 3.89 (s, 3H, O–Me); 3.30 (d, $^3J_{HH} = 7.2$, C1′–H); 2.08 (m, 4H, C4′–H, and C5′–H); 1.72 (s, 3H, C9′–H); 1.70 (s, 3H, C8′–H) y 1.62 (s, 3H, C10′–H). ^{13}C-NMR ($CDCl_3$) δ 146.4 (C6, quaternary aromatic); 143.6 (C1, quaternary aromatic); 136.0 (C3′, olefinic quaternary); 133.7 (C7′, olefinic quaternary); 131.5 (C2, aromatic quaternary); 124.2 (C6′, CH olefinic); 123.4 (C2′, CH olefinic); 120.8 (C4, CH aromatic); 114.2 (C5, CH aromatic); 110,9 (C3, CH aromatic); 55.9 (Me–O, CH_3); 39.7 (C4′, CH_2); 33.8 (C1′, CH_2); 26.7 (C5′, CH_2); 25.7 (C8′, CH_3); 17.7 (C10′, CH_3); and 16.1 (C9′, CH_3). HRMS Calculated for $C_{17}H_{25}O_2$ ($M+H^+$) 261.1849; found 261.1850. IR (film) υ_{max} 3445 (O–H); 2958 (=CH−); 2926 ($-CH_2-$); 1606 (−C=C−) cm^{-1}.

Synthesis of 2-methoxy-6-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-triene-1-yl) phenol (***20***) Following the general alkylation conditions for the *ortho*-isoprenylated phenol synthesis, *o*-methoxyphenol **9** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene (4 mL). Then, $BF_3{\cdot}Et_2O$ was slowly added (12 μL, 0.10 mmol) followed by the addition of farnesol **5** (57 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 57 mg of a yellowish oil (isolated yield: 54 %). ^{1}H-NMR ($CDCl_3$) δ 6.84–6.64 (m, 3H, C3–H, C4–H, and C5–H); 5.46 (s, 1H; OH); 5.33 (t, 1H, $^3J_{HH}$ = 7.1, C2′–H); 5.11 (m, 2H, C6′H, and C10′–H); 3.87 (s, 3H, Me–O); 3.29 (d, $^3J_{HH}$ = 7.4, C1′–H); 2.06 (m, 8H, C4′–H, C5′–H, C8′–H, and C9′–H); 1.71 (s, 3H, C13′–H); 1.68 (s, 3H, C12′–H); and 1.60 (s, 6H, C15′–H and C14′–H). ^{13}C-NMR ($CDCl_3$) δ 146.4 (C6, quaternary aromatic); 143.6 (C1, quaternary aromatic); 136.1 (C3′, olefinic quaternary); 135.1 (C7′, olefinic quaternary); 133.7 (C11′, quaternary aromatic); 131.3 (C6, quaternary aromatic); 124.4 (C10′, CH olefinic); 124.1 (C6′, CH olefinic); 123.4 (C2′, CH olefinic); 120.8 (C4, CH aromatic); 114.2 (C5, CH aromatic); 110,9 (C3, CH aromatic); 55.8 (Me–O, CH_3); 39.7 (C4′ and C8′, CH_2); 33.8 (C1′, CH_2); 26.8 and 26.6 (C5′ and C9′ exchangeable, CH_2); 25.7 (C12′, CH_3); 17.7 (C15′, CH_3); 16.2 (C13′, CH_3); and 16.0 (C14′, CH_3). HRMS Calculated for $C_{22}H_{33}O_2$ ($M + H^{+)}$ 329.4957; found 329.4956. IR (film) υ_{max} 3450 (O–H); 2959 (=CH−); 2930 (−CH_2−); 1603 (−C=C−) cm^{-1}.

General procedure for cyclized ortho-prenylated phenol synthesis

1.1 equivalents of *p*-methoxy phenol were dissolved in anhydrous toluene at 0 °C. Then, 1.2 equivalents of $BF_3{\cdot}Et_2O$ were added followed by the addition of 1 equivalent of the corresponding isoprenol. After 12 h at 4 °C and continuous stirring, the reaction was quenched with saturated $NaHCO_3$. The inorganic phase was extracted 3 times with AcOEt and the combined organic layers concentrated under vacuum. The residue was purified on a silica gel column (Hexane-AcOEt gradient).

Synthesis of 7-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (***4***) Following the general alkylation conditions for cyclized ortho-prenylated phenol synthesis, *p*-methoxy phenol **1** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene at 0 °C. Then, $BF_3{\cdot}Et_2O$ (48 μL, 0.38 mmol) was added followed by the addition of geraniol **2** (50 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 43 mg of a yellowish oil (isolated yield: 52 %). ^{1}H-NMR ($CDCl_3$) δ 6.73–6.36 (m, 3H, C5–H, C6–H, and C8–H); 3.75 (s, 3H, Me–O); 2.80 to 2.45 (m, 2H, C9–H); 2.20 to 1.40 (m, 7H, C2–H to C4–H, and C9a–H); 1.20 (s, 3H, C12–H); 1.00 and 0.90 (s, 3H, C10–H, and C11–H, exchangeable). ^{13}C-NMR ($CDCl_3$) δ 153.0 (C7, quaternary aromatic); 147.3 (C5a, quaternary aromatic); 123.2 (C8a, quaternary aromatic); 117.5 (C5, CH aromatic); 114.2 (C6, CH aromatic); 113.2 (C8, CH aromatic); 76.8 (C4a, C quaternary); 55.5 (Me–O, CH_3); 48.1 (C9a, C quaternary); 41.6 and 40,0 (C2 and C4, exchangeable, CH_2); 33.4 (C1, C quaternary); 32.1 and 20,7 (C10 and C11 exchangeable, CH_3); 23.7 (C9; CH_2); 19.8 (C3, CH_2) and 19.7 (C12, CH_3). HRMS Calculated for $C_{34}H_{48}O_4Na$ (2M + Na^+) 543.3445; found 543.3430. IR (film) υ_{max} 2969 (=CH−); 2928 (−CH_2−) cm^{-1}.

Synthesis of 10-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6,6a,12,12a,12b-decahydro-1H-benzo[a]xanthene (***7***) Following the general alkylation conditions for cyclized ortho-prenylated phenol synthesis, *p*-methoxy phenol **1** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene at 0 °C. Then, $BF_3{\cdot}Et_2O$ (48 μL, 0.38 mmol) was added followed by the addition of farnesol **5** (71 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 50 mg of a yellowish oil (isolated yield: 48 %). ^{1}H-NMR ($CDCl_3$) δ 6.73–6.60 (m, 3H, C8–H, C9–H, and C11–H); 3.74 (s, 3H, Me–O); 2.80 to 2.60 (m, 2H, C12–H); 2.20–0.85 (m, 24H, C1–H to C6a–H, and C12a–H to C16–H). ^{13}C-NMR ($CDCl_3$) δ 153.0 (C10, quaternary aromatic); 147.2 (C7a, quaternary aromatic); 122.9 (C11a, quaternary aromatic); 117.4 (C8, CH aromatic); 113.9 (C9, CH aromatic); 113.4 (C11, CH aromatic); 75.9 (C6a, C quaternary); 56.2 (C4a, C quaternary); 55.7 (Me–O, CH_3); 52.2 (C12a, C quaternary); 41.9 to 19.6 (C1–C4, C5–C6 and C12–C16). HRMS Calculated for $C_{22}H_{32}O_2Na$ (M + Na^+) 351.2295; found 351.2295. IR (film) υ_{max} 2967 (=CH−); 2931 (−CH_2−); 1460 (C=C) cm^{-1}.

Synthesis of 6-methoxy-1,1,4a-trimethyl-2,3,4,4a,9.9a-hexahydro-1H-xanthene (***12***) *and 8-methoxy-1,1,4a-trimethyl-2,3,4,4a,9.9a-hexahydro-1H-xanthene* (***13***) Following the general alkylation conditions for cyclized ortho-prenylated phenol synthesis, *m*-methoxyphenol **8** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene at 0 °C. Then, $BF_3{\cdot}Et_2O$ (48 μL, 0.38 mmol) was added followed by the addition of geraniol **2** (50 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 58 mg of a yellowish oil (isolated yield: 70 %). Product distribution 1:1.2.
Compound ***12***, ^{1}H-NMR ($CDCl_3$) δ 6.96 (d, 1H, $^3J_{HH}$ = 7.9, C8–H); 6.42 (m, 2H, C5–H, and C7–H); 3.75 (s, 3H, Me–O); 2.78 to 2.45 (m, 2H, C9–H); 2.20 to 1.40 (m, 7H, C1–H to C4–H, and C9a–H); 1.21 (s, 3H, C12–H); 1,01 and 0,91 (s, 3H, C10–H and C11–H, exchangeable). ^{13}C-NMR ($CDCl_3$) δ 159.0 (C5a, quaternary aromatic); 154.0 (C6, quaternary aromatic); 130,1 (C3, CH aromatic); 123.6 (C8, CH aromatic); 120.7 (C8a, quaternary aromatic); 106.1 (C7, CH aromatic); 100.6 (C5, CH aromatic); 74.8 (C4a, C quater-

nary); 55.2 (Me–O, CH_3); 48.3 (C9a, CH); 41.5 and 40.0 (C2 and C4 exchangeable, CH_2); 33.4 (C1, C quaternary); 32.1 and 20,7 (C10 and C11 exchangeable, CH_3); 22.5 (C9; CH_2); 20.7 (C3, CH_2) and 19.8 (C12, CH_3). HRMS Calculated for $C_{17}H_{24}O_2Na$ (M + Na^+) 283.1668; found 283.1669. IR (film) υ_{max} 2974 (=CH−); 2932 (−CH_2−) cm^{-1}.

Compound ***13***, ^{1}H-NMR ($CDCl_3$) δ 6.93 (t, 1H, $^3J_{HH}$= 8.0, C6–H); 6.35 (m, 2H, C5–H y C7–H); 3.74 (s, 3H, Me–O); 2.78 to 2.45 (m, 2H, C9–H); 2.20 to 1.00 (m, 7H, C1–H to C4–H, and C9a–H); 1.22 (s, 3H, C12–H); 1,00 and 0,90 (s, 3H, C10–H, and C11–H, exchangeable). ^{13}C-NMR ($CDCl_3$) δ 159.0 (C5a, quaternary aromatic); 157.6 (C8, quaternary aromatic); 127.1 (C6, CH aromatic); 114.8 (C8a, quaternary aromatic); 106.8 (C7, CH aromatic); 101.7 (C5, CH aromatic); 76.2 (C4a, C quaternary); 55.7 (Me–O, CH_3); 48.3 (C9a, CH); 41.7 and 39.6 (C4 y C3 exchangeable, CH_2); 33.9 and 21,4 (C10 and C11, exchangeable, CH_3); 24.3 (C9; CH_2); 19.8 (C12, CH_3); and 18.1 (C3, CH_2). HRMS Calculated for $C_{17}H_{24}O_2Na$ (M + Na^+) 283.1668; found 283.1667. IR (film) υ_{max} 2975 (=CH−); 2932 (−CH_2−) cm^{-1}.

Synthesis of 11-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6, 6a,12,12a,12b-decahydro-1H-benzo[α]xanthene (***16***) *and 9-methoxy-4,4,6a,12b-tetramethyl-2, 3, 4, 4a, 5, 6, 6a,12,12a, 12b-decahydro-1H-benzo[a]xanthene* (*17*) Following the general alkylation conditions for cyclized ortho-prenylated phenol synthesis, *m*-methoxy phenol **8** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene at 0 °C. Then, $BF_3{\cdot}Et_2O$ (48 μL, 0.38 mmol) was added followed by the addition of farnesol **5** (71 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 75 mg of a yellowish oil (isolated yield: 72 %). Product distribution 1:1.1.

Compound ***16***, ^{1}H-NMR ($CDCl_3$) δ 7.04 (t, 1H, $^3J_{HH}$ = 7.8, C9–H); 6.38 (m, 2H, C8–H y C10–H); 3.81 (s, 3H, Me–O); 2.74 to 2.62 (m, 2H, C12–H); and 2.25 to 0.85 (m, 24H, C1–H to C6a–H, and C12a–H to C16–H). ^{13}C-NMR ($CDCl_3$) δ 158.6 (C7a, quaternary aromatic); 156.8 (C11, quaternary aromatic); 128.7 (C9, CH aromatic); 115.3 (C11a, quaternary aromatic); 104.9 (C10, CH aromatic); 103.0 (C8, CH aromatic); 76.2 (C6a, C quaternary); 55.3 (Me–O, CH_3); 41.6 to 14.9 (C1 to C6 and C12 to C16). HRMS Calculated for $C_{22}H_{32}O_2Na$ (M + Na^+) 351.2295; found 351.2295. IR (film) υ_{max} (cm^{-1}) = 2966 (=CH−); 2942 (−CH_2−); 1484 (−C=C−).

Compound ***17***, ^{1}H-NMR ($CDCl_3$) δ 6.94 (d, 1H, $^3J_{HH}$ = 8.0, C11–H); 6.37 (m, 2H, C8–H and C10–H); 3.75 (s, 3H, C7–H); 2.75 to 2.50 (m, 2H, C8–H); and 2.25 to 0,85 (m, 24H, C1–H to C6a–H, and C12a–H to C16–H). ^{13}C-NMR ($CDCl_3$) δ 159.1 (C7a, quaternary aromatic); 153.9 (C9, quaternary aromatic); 129.8 (C8, CH aromatic); 113.3 (C11a, quaternary aromatic); 106.8 (C10, CH aromatic); 101.5 (C11, CH aromatic); 76.2 (C6a, C quaternary); 55.2 (Me–O; CH_3); 46.2 to 16.1 (C1 to C6 and C12 to C16). HRMS Calculated for $C_{22}H_{32}O_2Na$ (M + Na^+) 351.2295; found 351.2294. IR (film) υ_{max} 2969 (=CH−); 2938 (−CH_2−); 1483 (−C=C−) cm^{-1}.

Synthesis of 5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (***19***) Following the general alkylation conditions for cyclized ortho-prenylated phenol synthesis, *o*-methoxy phenol **9** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene at 0 °C. Then, $BF_3{\cdot}Et_2O$ (48 μL, 0.38 mmol) was added followed by the addition of geraniol **2** (71 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was worked up and purified to afford 42 mg of a yellowish oil (isolated yield: 51 %). ^{1}H-NMR ($CDCl_3$) δ 6.60–6.60 (m, 3H, C6–H, C7–H, and C8–H); 3.85 (s, 3H, Me–O); 2.78 to 2.50 (m, 2H, C9–H); 2.20 to 1.20 (m, 7H, C2–H to C4–H, and C9a–H); 1.26 (s, 3H, C12–H); 1.02 (s, 3H, C10–H*); and 0.92 (s, 3H, 11–H*). ^{13}C-NMR ($CDCl_3$) δ 147.2 (C5, quaternary aromatic); 144.9 (C5a, quaternary aromatic); 132.0 (C8a, quaternary aromatic); 110.9 (C7, CH aromatic); 107.9 (C8, CH aromatic); 107.6 (C6, CH aromatic); 76.2 (C4a, C quaternary); 56.2 (Me–O, CH_3); 45.7 (C9a, C quaternary); 36.2 and 35.2 (C2 and C4, exchangeable, CH_2); 33.6 (C1, C quaternary); 31.0 (C9; CH_2); 29.5 and 20,7 (C10 and C11, exchangeable, CH_3); and 19.8 (C12, CH_3). HRMS Calculated for $C_{17}H_{24}O_2Na$ (M + Na^+) 283.1669; found 283.1664. IR (film) υ_{max} 2974 (=CH−); 2932 (−CH_2−) cm^{-1}.

Synthesis of 8-methoxy-4,4,6a,12b-tetramethyl-2,3,4,4a,5,6, 6a,12,12a,12b-decahydro-1H-benzo[a]xanthene (***21***) Following the general alkylation conditions for cyclized ortho-prenylated phenol synthesis, *o*-methoxy phenol **9** (40 mg; 0.32 mmol) was dissolved in anhydrous toluene at 0 °C. Then, $BF_3{\cdot}Et_2O$ (48 μL, 0.38 mmol) was added followed by the addition of farnesol **5** (50 mg; 0.32 mmol). After 12 h at 4 °C, the reaction was finished, worked up, and purified to afford 61 mg of a yellowish oil (isolated yield: 58 %). ^{1}H-NMR ($CDCl_3$) δ 6.90–6.50 (m, 3H, C9–H, C10–H, and C11–H); 3.85 (s, 3H, Me–O); 2.78–2.45 (m, 2H, C12–H); 2.20 to 0.88 (m, 24H, C1–H to C6a–H, and C12a–H to C16–H). ^{13}C-NMR ($CDCl_3$) δ 148.3 (C8, quaternary aromatic); 144.1 (C7a, quaternary aromatic); 133.4 (C11a, quaternary aromatic); 111.5 (C10, CH aromatic); 108.3 (C11, CH aromatic); 106,9 (C9, CH aromatic); 76.2 (C6a, C quaternary); 56.2 (Me–O, CH_3); 48.0 to 16.2 (C1 to C6 and C12 to C16). HRMS Calculated for $C_{22}H_{32}O_2Na$ (M + Na^+) 351.2295; found 351.2293. IR (film) υ_{max} 2966 (=CH−); 2942 (−CH_2−); 1484 (−C=C−) cm^{-1}.

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