

SYNTHESIS AND NMR STRUCTURE DETERMINATION OF NEW LINEAR GERANYLPHENOLS BY DIRECT GERANYLATION OF ACTIVATED PHENOLS.

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ABSTRACT

The known geranylhydroquinone **2**, geranylorcinol **4** and the derivative (*E*)-4-(3,7-dimethylocta-2,6-dienyl)-5-methylbenzene-1,3-diol **5**, were prepared by Electrophilic Aromatic Substitution (EAS) reactions between the corresponding phenol derivatives containing electron-donor substituents and geraniol using $\text{BF}_3 \cdot \text{OEt}_2$ as a catalyst. In addition, spectroscopic NMR information for **4** and **5** is complemented. Furthermore, the new (*E*)-2-(3,7-dimethylocta-2,6-dienyl)benzene-1,3,5-triol (geranylphloroglucinol) **13**, (*E*)-2-(3,7-dimethylocta-2,6-dienyl)-1,3,5-trimethoxybenzene **14**, (*E*)-2-(3,7-dimethylocta-2,6-dienyl)-6-methoxyphenol **15**, (*E*)-3-(3,7-dimethylocta-2,6-dienyl)-2-methoxyphenol **16**, (*E*)-5-(3,7-dimethylocta-2,6-dienyl)-2-methoxyphenol **17**, (*E*)-4-(3,7-dimethylocta-2,6-dienyl)benzene-1,3-diol **18**, (*E*)-3-(3,7-dimethylocta-2,6-dienyl)benzene-1,2-diol **19**, (*E*)-4-(3,7-dimethylocta-2,6-dienyl)-5-isopropyl-2-methylphenol **20**, (*E*)-2-(3,7-dimethylocta-2,6-dienyl)-4-isopropyl-3-methylphenol **21**, (*E*)-2-(3,7-dimethylocta-2,6-dienyl)-4-isopropyl-5-methylphenol **22**, and (*E*)-2-tert-butyl-4-(3,7-dimethylocta-2,6-dienyl)-5-methylphenol **23** were also prepared with this synthesis strategy. All the synthesized compounds were fully characterized and their structures were established by IR, MS and mainly NMR spectroscopic dates.

Keywords: Linear geranylphenols, synthesis, NMR spectroscopy.

INTRODUCTION

The subgroups of linear geranylquinones or geranylhydroquinones are represented by an important number of compounds, for example 2-geranylbenzoquinone (**1**) isolated from Ascidian *Synoicum castellatum* [1] and 2-geranylhydroquinone (**2**) isolated from tree *Cordia alliodora* [2], *Phacelia crenulata* [3-5], *Aplidium antillense* [6] and the tunicate *Amaroucium multiplicatum* [7]. Both natural products are present in higher plants, but also have been reported in marine urochordates [8].

2-geranylbenzoquinone (**1**) exhibits interesting biological activities such as toxicity against *Gambusia affinis* and *Artemia salina*, antimicrobial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans*, *Micrococcus luteus* and *Bacillus subtilis* [9]. Also the compound **1** has been reported as a potent skin sensitizer for guinea pigs, proving to be a fairly reliable indicator of allergenicity against human skin [3]. In addition, it has antimicrobial activity against *Serratia marcescens*, *Morganella morganii*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus fecalis* and antimicrobial activity against methicillin-resistant *Staphylococcus aureus* [9]. Cytotoxicity against mouse P388 cells and cytotoxicity against human KB cells has also been reported for this compound [6], as well as inhibition of soybean arachidonate 15-lipoxygenase and antioxidant activity in rat liver microsomes assessed as inhibition of lipid peroxide formation [7]. Furthermore, 2-geranylhydroquinone (**2**) has been synthesized as a drug and it has been reported to have some value as radioprotective and anti-cancer protective agents [10-11].

Additionally, the evaluation of Cancer-Preventive Activity and Structure-Activity Relationships (SAR) of 3-demethylubiquinone Q2 (**3**), isolated from the Ascidian *Aplidium glabrum* [12], and the geranylhydroquinone synthetic analogues were informed. All the compounds tested were able to inhibit JB6 Cl41 cell transformation, to induce apoptosis, AP-1, and NF-KB activity, and to inhibit p53 activity [13]. On the other hand, the geranylhydroquinone derivatives **4** and **5** (figure 1) showed antimicrobial and antifungal activities [14-15].

The geranylmethoxyphenol **6** (isolated from *Piper crassinervium* Kunth) showed antioxidant activity [16], whereas the linear geranylmethoxyphenol/acetates **7-9** (see figure 1), isolated from *Phacelia ixodes* [5], showed a biological activity which allows to repel and in some cases, to kill phytophagous insects and plant pathogens [17].

Recently, our research group reported the synthesis and *in vitro* cytotoxic activity against cells of PC-3 prostate cancer, MCF-7 and MDA-MB-231 breast carcinoma of compounds **1**, **2** and some methoxylated geranylphenol derivatives in μM concentrations.

These compounds were obtained by Electrophilic Aromatic Substitution (EAS) reactions between geraniol and the phenols 1,4-hydroquinone and *p*-methoxyphenols using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst. [18] [19].

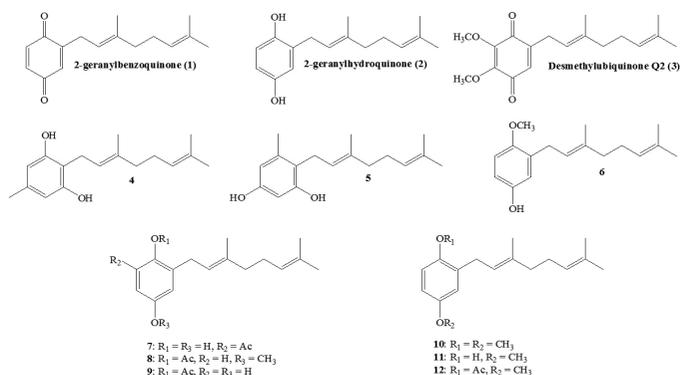


Figure 1. Structure of some active linear geranylquinone and geranylphenols.

On another hand, several factors highlight the urgent need for the development of new strategies for the control of phytopathogen fungus *Botrytis cinerea* and other plagues affecting important Chilean agricultural crops. They include the emergence of *Botrytis* strains resistant to fungicides, the high cost of chemical control and the limited availability of fungicides. In addition, it should be considered the strong worldwide trend towards sustainable development and environmentally friendly substances. Therefore, our interest is to gain a broader insight about the biological properties of these substances against plant pathogens which are important for the local national industry. On the basis of previously described and considering the structure-activity relationship with the derivatives **6-12**, in this opportunity we report the synthesis of **2**, **4-5** and the new **13-23** linear geranylmethoxyphenol derivatives (figure 2) by direct geranylation reactions of activated phenols, between geraniol and orcinol, phloroglucinol, guaiaicol, resorcinol, catechol, carvacrol, 4-isopropyl-3-methylphenol and 2-tert-butyl-5-methylphenol using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst. In addition, the structural determinations of these new eleven compounds were established by chemical and spectroscopic properties and the effect in the inhibition of the growth of *B. cinerea* will be informed later.

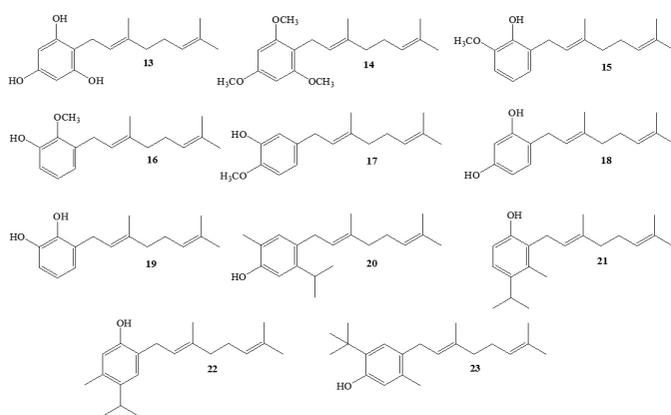


Figure 2. Structure of new linear geranylphenol derivatives.

RESULTS AND DISCUSSION

Our first objective was the preparation of compounds **2**, **4-5**, using the coupling method previously described by us [18, 19] with geraniol and commercially available hydroquinone and orcinol, respectively. In this case, 2-geranylhydroquinone **2** was obtained with 28 % yield, whereas the compounds **4** and **5** were obtained with 12.6 % and 27.6 % yields, respectively. The physical and spectroscopic properties of compounds **4** and **5** were consistent with those previously reported [14, 15]. In addition, for the case of geranylorcinol structure derivatives, these were fully characterized by our research group, where the position of geranyl chain was established by selective 1D NOESY and 2D HMBC experiments, according to interactions shown in figure 3.

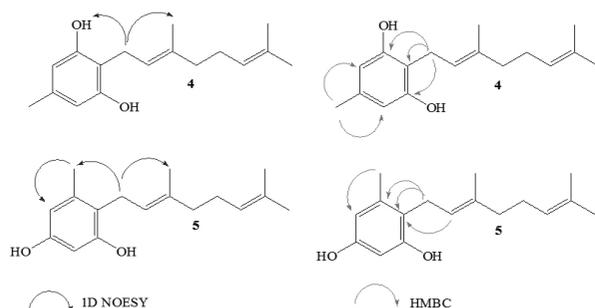
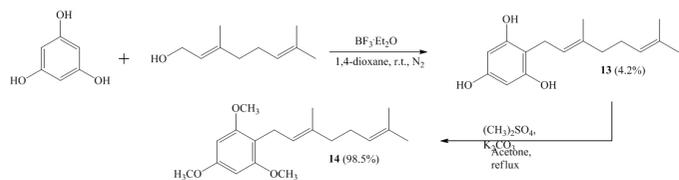


Figure 3. Observed correlations 1D NOESY and 2D ^1H - ^{13}C HMBC in the NMR experiments for the compounds **4** and **5**, which confirm the position and geometrical orientation of double bond in the geranyl chain.

The synthesis of compound **13** (*geranylphloroglucinol* proposed name by us in analogy with the name of *geranylorcinol*) was development by direct geranylation reactions between phloroglucinol (benzene-1,3,5-triol) and geraniol with a 4,2 % yield. Later, the compound **13** was methylated with dimethylsulfate in acetone as was previously described by us for other compounds [18]. The trimethoxylated derivative **14** was obtained with a 98.5 % yield. These reactions are shown in scheme 1.



Scheme 1: Synthesis of geranylphloroglucinol **13** and their trimethoxylated derivative **14**.

The determination of structure of **13** was mainly established by the NMR aromatic signal at $d_{\text{H}} = 5.93$ ppm, where was observed a singlet for two hydrogen

H-4 and H-6, confirming the unique possibility of aromatic mono-substitution. Additionally, the signal at $d_{\text{H}} = 3.30$ ppm to assigned at H-2' (d, $J = 6.9$ Hz, 2H) shows $^3J_{\text{H-C}}$ coupling with C-1 and C-3 ($d_{\text{C}} = 155.7$ ppm) and $^2J_{\text{H-C}}$ coupling with C-2 ($d_{\text{C}} = 106.3$ ppm), these HMBC correlations are shown in figure 4. In order to establish the *E* geometry in double bond position at C-2'-C-3' of the geranyl chain, selective 1D NOESY NMR experiments were registered for the compound **13**. These correlations are shown in figure 4, where the most important of those correspond to the correlation observed between the H-2' and the hydrogens of methyl group in C-3' position. For the derivative **14**, in ^1H NMR spectra the two singlet signal at $d_{\text{H}} = 3.92$ ppm (3H, OCH_3) and $d_{\text{H}} = 3.79$ ppm (6H, 2 x OCH_3) confirm the presence of trimethoxylated derivative.

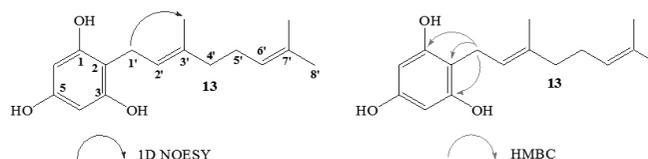
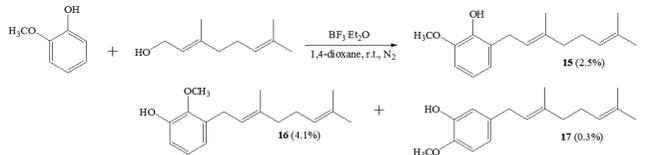


Figure 4. Observed correlations 1D NOESY and 2D ^1H - ^{13}C HMBC in the NMR experiments for the compound **13**, which confirm the position and geometrical orientation of double bond in the geranyl chain.

The following step consisted in the preparation of compound **15**. Nevertheless, the regio-isomers **16** and **17** also were obtained according to scheme 2.



Scheme 2: Synthesis of derivatives **15**, **16** and **17** by direct geranylation between geraniol and guaiacol (2-methoxyphenol) catalyzed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$.

The substitution position of geranyl chain in aromatic ring was established in base at NMR data spectra, mainly from the 2D HMBC and selective 1D NOESY correlations. For the compound **15**, the signal at $d_{\text{H}} = 3.39$ ppm (d, $J = 6.6$ Hz, 2H, H-1') showed $^3J_{\text{H-C}}$ coupling with C-1 ($d_{\text{C}} = 143.3$ ppm) and $^2J_{\text{H-C}}$ coupling with C-2 ($d_{\text{C}} = 127.5$ ppm), while other HMBC correlations are shown in figure 5. In the compound **16**, the signal at $d_{\text{H}} = 3.29$ ppm (d, $J = 7.2$ Hz, 2H, H-1') showed $^3J_{\text{H-C}}$ coupling with C-2 ($d_{\text{C}} = 146.4$ ppm) and $^2J_{\text{H-C}}$ coupling with C-3 ($d_{\text{C}} = 133.7$ ppm), additionally, other HMBC correlations are shown in figure 5. In addition, for the compound **17** the signal at $d_{\text{H}} = 3.26$ ppm (d, $J = 7.2$ Hz, 2H, H-1') showed $^3J_{\text{H-C}}$ coupling with C-6 ($d_{\text{C}} = 114.6$ ppm), with C-4 ($d_{\text{C}} = 119.5$ ppm) and $^2J_{\text{H-C}}$ coupling with C-5 ($d_{\text{C}} = 135.2$ ppm), additionally, other HMBC correlations are shown in figure 5.

In order to establish the *E* geometry in double bond position at C-2'-C-3' of the geranyl chain, selective 1D NOESY NMR experiments were registered for the compounds **15**, **16** and **17**. These correlations are shown in figure 5, where the most important of those correspond to the observed between the H-2' of geranyl chain with the hydrogens of the CH_3 -C3' and between some substituents in aromatic nucleus.

On the other hand, the direct geranylation between resorcinol and geraniol produced the compound **18** with 11.9 % yield. The structure and pattern of the aromatic monosubstitution of this compound were established from NMR data spectra. In ^1H NMR spectrum, the signals at $d_{\text{H}} = 6.92$ ppm (d, $J = 8.8$ Hz, 1H, H-5) and $d_{\text{H}} = 6.37$ - 6.35 ppm (m, 2H, H-2 and H-4) confirm the presence of a tri-substituted aromatic system. The position of geranyl chain substitution in the aromatic nucleus was determined from the 2D HMBC and selective 1D NOESY techniques. The signal at $d_{\text{H}} = 3.27$ ppm (d, $J = 7.2$ Hz, 2H, H-1') showed heteronuclear $^3J_{\text{H-C}}$ coupling with C-3 ($d_{\text{C}} = 154.8$ ppm) and C-5 ($d_{\text{C}} = 130.3$ ppm) and $^2J_{\text{H-C}}$ coupling with C-4 ($d_{\text{C}} = 124.0$ ppm). Other HMBC correlations are shown in the figure 6. Additionally, the signal assigned at H-1' (3.27 ppm, d, $J = 7.2$ Hz, 2H) showed long range NOE interaction with aromatic H-5 (6.92 ppm, d, $J = 8.8$ Hz, 1H) confirming the geranyl chain position and CH_3 -C3' (1.72 ppm, s, 3H) that indicate the geometrical orientation of double bond in C2'-C3', as shown in figure 6.

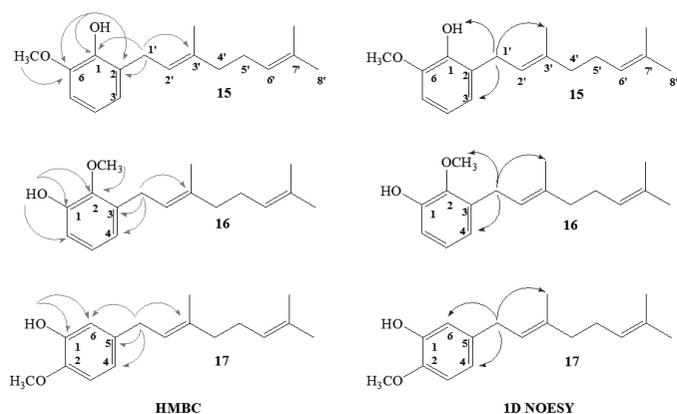


Figure 5. Main 2D HMBC and 1D NOESY observed correlations that allowed differentiate and determine the regio-isomer structures **15**, **16** and **17**.

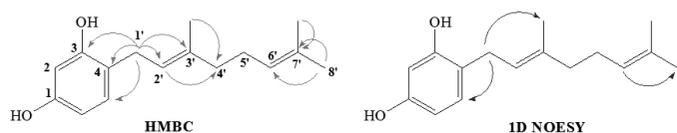


Figure 6. 2D ^1H - ^{13}C HMBC and 1D NOESY observed correlations in the NMR experiments for the compound **18**, which confirm the aromatic substitution position and geometrical orientation of double bond in the geranyl chain.

For the synthesis of compound **19**, pyrocatechol and geraniol were used. In this opportunity, the geranyl chain was substituted in *ortho* position respect to hydroxyl group at the aromatic nucleus; as in the previous cases, the structure of compound **19** and geranyl chain position were confirmed by NMR data spectra. In ^1H NMR spectrum the signals at $d_{\text{H}} = 6.79 - 6.72$ (m, 2H, H-5 and H-6) and 6.66 (d, $J = 7.0$ Hz, 1H, H-4) ppm confirm the presence of a tri-substituted aromatic system. From 2D HMBC spectrum, the signal at $d_{\text{H}} = 3.37$ ppm (d, $J = 7.1$ Hz, 2H, H-1') showed heteronuclear $^3J_{\text{H-C}}$ coupling with C-2 ($d_{\text{C}} = 141.9$ ppm) and C-4 ($d_{\text{C}} = 121.4$ ppm) and $^2J_{\text{H-C}}$ coupling with C-3 ($d_{\text{C}} = 127.4$ ppm). HMBC correlations are shown in the figure 7. Additionally, the signal assigned to H-1' (3.37 ppm, d, $J = 7.1$ Hz, 2H) showed long range NOE interaction with aromatic H-4 (6.66 ppm, d, $J = 7.0$ Hz, 1H) confirming the geranyl chain position and with single signal $\text{CH}_3\text{-C}3'$ (1.78 ppm, s, 3H) that indicate the geometrical orientation of double bond in C2'-C3', as shown in figure 7.

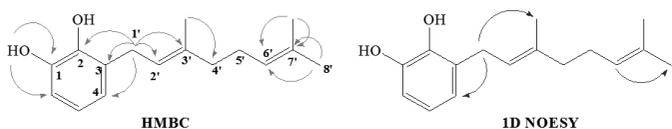
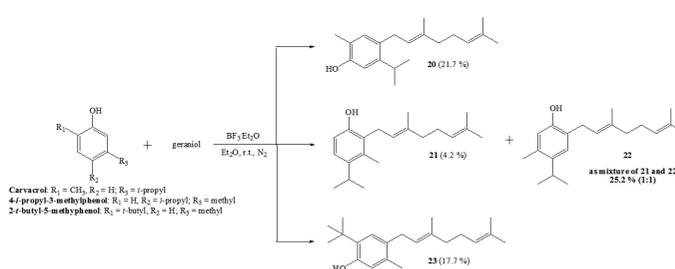


Figure 7. Principal 2D ^1H - ^{13}C HMBC and 1D NOESY observed correlations in the NMR experiments for the compound **19**, these confirm the aromatic substitution position and geometrical orientation of double bond in the geranyl chain.

Later, the compounds **20**, **21**, **22** and **23** were obtained by direct geranylation between carvacrol, 4-*i*-propyl-3-methylphenol, 2-*t*-butyl-5-methylphenol and geraniol under identical conditions for the three cases. Nevertheless, in the latter case, ethyl ether was used as dissolvent instead of dioxane (to see scheme 3). These compounds were obtained with 21.7 %, 4.2 % and 17.7 % yield, respectively. In addition, the **21-22** mixture was obtained with a 25.2 % yield, when the 4-*i*-propyl-3-methylphenol reacted with geraniol according to the scheme 3.



Scheme 3: Synthetic route for the obtaining of derivatives **20-23** by direct geranylation reaction between, carvacrol, 4-*i*-propyl-3-methylphenol and 2-*t*-butyl-5-methylphenol and geraniol in Et_2O catalyzed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$.

The structural determination of these compounds was mainly established by NMR data spectra. Thus, for compound **20**, the signals at $d_{\text{H}} = 6.88$ ppm (s, 1H, H-3) and 6.69 ppm (s, 1H, H-6) indicate the aromatic substitution pattern, confirming that the geranyl fragment was incorporated in *para* orientation with respect to hydroxyl group. Additionally, $^3J_{\text{H-C}}$ HMBC correlations were observed between H-1' ($d_{\text{H}} = 3.27$ ppm, d, $J = 6.8$ Hz) with C-3 ($d_{\text{C}} = 131.9$ ppm), C-5 ($d_{\text{C}} = 146.1$ ppm) and C-3' ($d_{\text{C}} = 135.3$ ppm) on the other hand, $^2J_{\text{H-C}}$ correlation with C-4 ($d_{\text{C}} = 130.8$ ppm) and C-2' ($d_{\text{C}} = 124.1$ ppm) also were observed (to see figure 8). Additionally, long range interactions (NOE) between H-1' with H-3 ($d_{\text{H}} = 6.88$ ppm, s, 1H) and $\text{CH}_3\text{-C}3'$ ($d_{\text{H}} = 1.71$ ppm, s, 3H) were observed which confirmed the geometrical *E* orientations around of double bond C2'-C3' and geranyl fragment position in the aromatic nuclei (to see figure 8)

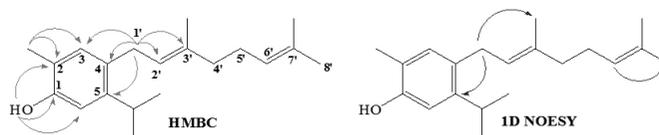


Figure 8. Main 2D ^1H - ^{13}C HMBC and 1D NOESY observed correlations in the NMR experiments for the compound **20**, these confirm the aromatic substitution position and geometrical orientation of double bond in the geranyl chain.

When 4-*i*-propyl-3-methylphenol was reacted with geraniol catalyzed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ under ethereal solution, the compounds **21** and **22** were obtained. After work-up and posterior flash conventional C.C. purification and separation, only the compound **21** was accessible in pure form with a 4.2 % yield. However, the mixture of compounds **21-22** was mainly obtained with a 25.2 % yield. The proportion of compounds **21/22** = 1:1 present in the mixture was determined from ^1H NMR spectrum, considering the average values of integration area for signal assigned to the aromatic hydrogens. H-1' and $\text{CH}(\text{CH}_3)_2$ signals were clearly identified in the ^1H NMR spectrum onto the mixture.

The structure of compound **21** was easily identified due to the pattern of aromatic substitution shown in the spectrum of ^1H RMN. Two doublet signal at $d_{\text{H}} = 7.01$ ppm (d, $J = 8.4$ Hz, 1H, H-5) and $d_{\text{H}} = 6.67$ ppm (d, $J = 8.4$ Hz, 1H, H-6) confirmed that the geranyl chain was incorporated in *ortho* position with respect to hydroxyl group, specifically, in C-2. Additionally, $^3J_{\text{H-C}}$ HMBC correlations were observed between H-1' ($d_{\text{H}} = 3.41$ ppm, d, $J = 6.6$ Hz) with C-1 ($d_{\text{C}} = 151.1$ ppm) and C-3 ($d_{\text{C}} = 131.7$ ppm). Additionally, $^2J_{\text{H-C}}$ correlation with C-2 ($d_{\text{C}} = 125.9$ ppm) and C-2' ($d_{\text{C}} = 122.1$ ppm) were also observed (to see figure 9).

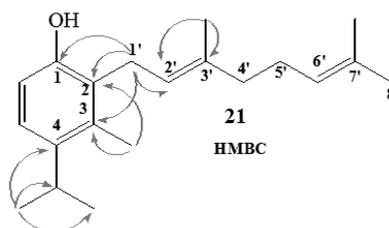


Figure 9. Main 2D ^1H - ^{13}C HMBC observed correlations in the NMR spectrum for the compound **21**, which confirm the aromatic substitution position of the geranyl chain.

The structural assignment of compound **22** was established by comparison from ^1H NMR spectrum of pure **21** with the mixture **21/22**. Thus, in the ^1H NMR spectrum of mixture the signals at $d_{\text{H}} = 6.96$ ppm (s, 1H) and 6.62 ppm (s, 1H) were assigned to the H-3 and H-6, respectively, indicating the aromatic substitution pattern. Additionally, the ^1H NMR signal at $d_{\text{H}} = 5.04$ ppm (s, 1H);

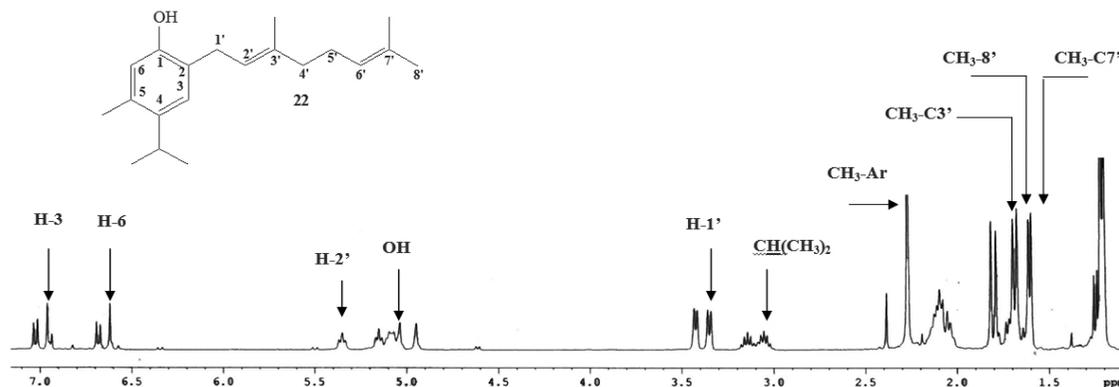


Figure 10. ^1H NMR spectrum of the mixture compounds **21/22** and identification of the signals corresponding to the compound **22**.

The structure of compound **22** was unequivocally assigned from 2D HSQC and HMBC spectra data of the mixture of compounds **21/22**. Thus, for compound **22**, the signals at $d_{\text{H}} = 3.35$ ppm (d, $J = 7.1$ Hz, 2H, H-1') showed $^3J_{\text{H-C}}$ HMBC correlations with C-1 ($d_{\text{C}} = 151.9$ ppm), C-3 ($d_{\text{C}} = 126.3$ ppm) and C-3' ($d_{\text{C}} = 138.1$ ppm) and $^2J_{\text{H-C}}$ correlation with C-2 ($d_{\text{C}} = 123.8$ ppm) and C-2' ($d_{\text{C}} = 122.2$ ppm) also were observed. In addition other $^3J_{\text{H-C}}$ and $^2J_{\text{H-C}}$ HMBC correlations are shown in figure 11.

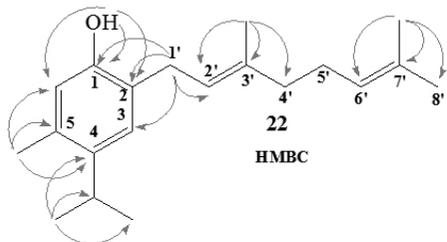


Figure 11. Major 2D ^1H - ^{13}C HMBC observed correlations in the NMR spectrum for the compound **22**.

On the other hand, from the 1D selective NOE NMR experiments was possible to determinate the long range interactions between the H-1' with aromatic H-3, olefinic H-2', OH and $\text{CH}_3\text{-C}3'$. In addition to this information, was possible to confirm the geometric orientation around the C2'-C3' double bond. These interactions are shown in Figure 12.

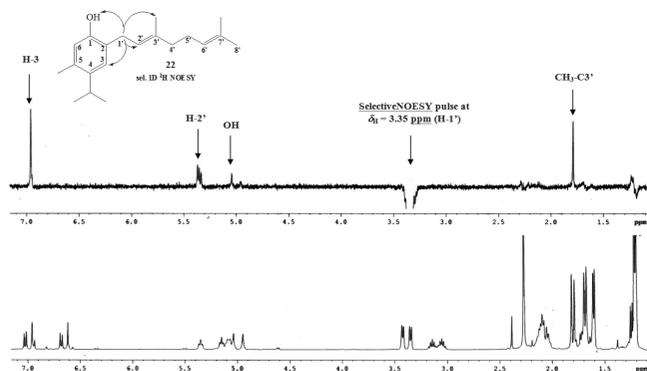


Figure 12. Bottom: normal ^1H -NMR spectrum of mixture **21/22**; Top: selective *gs* 1D NOESY irradiation at $\delta = 3.35$ ppm for compound **22** in the mixture, which long-range interactions can clearly be seen between H-1' with H-3, OH, H-2' and $\text{CH}_3\text{-C}3'$.

3.35 ppm (d, $J = 7.1$ Hz, 2H); 3.06 ppm (sept. $J = 6.8$ Hz, 1H); 2.27 ppm (s, 3H); 1.79 ppm (s, 3H); 1.70 ppm (s, 3H); 1.61 ppm (s, 3H) and 1.25 ppm (d, $J = 6.8$ Hz; 6H) were assigned to the OH, H-1', $\text{CH}(\text{CH}_3)_2$, $\text{CH}_3\text{-Ar}$, $\text{CH}_3\text{-C}3'$, $\text{CH}_3\text{-8}$, $\text{CH}_3\text{-C}7'$ and $(\text{CH}_3)_2\text{CH}$ respectively, as shown in Figure 10.

EXPERIMENTAL

General

Unless otherwise stated, all chemical reagents purchased (Merck or Aldrich) were of the highest commercially available purity and were used without previous purification. IR spectra were recorded as thin films in a FT-IR Nicolet 6700 spectrometer and frequencies are reported in cm^{-1} . Low resolution mass spectra were recorded on an Agilent 5973 spectrometer at 70eV ionising voltage in a DB-5 m, 30 m x 0.25 mm x 0.25 μm column, and dates are given as *m/z* (% rel. int.). ^1H , ^{13}C , ^{13}C DEPT-135, sel. *gs* 1D ^1H NOESY, *gs* 2D HSQC and *gs* 2D HMBC spectra were recorded in CDCl_3 solutions and are referenced to the residual peaks of CHCl_3 at $\delta = 7.26$ ppm and $\delta = 77.0$ ppm for ^1H and ^{13}C , respectively, on a Bruker Avance 400 Digital NMR spectrometer, operating at 400.1 MHz for ^1H and 100.6 MHz for ^{13}C . For selective 1D NOESY experiment the *selnpgp.3* with Z-PFG pulse program was used, obtained from Bruker Library and optimized parameter at *ns* = 32, *ds* = 4, *d1* = 2.0sec, *TD* = 16k, *sp2* = 73.0dB, *p12* = 80msec, *d8* = 600ms, and gradient ratios: *gpz3* = 40, *gpz4* = -40. For *gs* 2D HSQC experiment *invigpph* pulse program was used and optimized parameter at *ns* = 4, *ds* = 16, *d1* = 1.0sec, *TD* = 1k, *p16* = 1.0msec, *d16* = 500msec, gradient ratios: *gpz1* = 80, *gpz2* = 30 and *gpz3* = 20.1. For *gs* 2D HMBC experiment *invi4gplprndqf* with $^1J_{\text{H-C}}$ filter (low-pass J-filter) pulse program was used and optimized parameter at *ns* = 4, *ds* = 16, *d1* = 1.0sec, *TD* = 1k, *p16* = 1.0msec, *d16* = 500msec, gradient ratios: *gpz1* = 50, *gpz2* = 30 and *gpz3* = 40.1. Chemical shifts are reported in δ ppm and coupling constants (*J*) are given in Hz. Silica gel (Merck 200-300 mesh) was used for C.C. and silica gel plates HF-254 for TLC. TLC spots were detected by heating after spraying with 25% H_2SO_4 in H_2O .

(*E*)-2-(3,7-dimethylocta-2,6-dienyl)benzene-1,4-diol (1,4-geranylhydroquinone) **2**

To a solution of 1,4-hydroquinone (0,601 g, 5,5 mmol) and geraniol (0,8 g, 5,5 mmol) in 1,4-dioxane (30 mL) $\text{BF}_3\cdot\text{OEt}_2$ (0,23 g, 1,6 mmol) was slowly added dropwise with stirring at room temperature and under a N_2 atmosphere. After the addition was completed, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with diethyl ether (3 x 30 mL). Then the ethereal layer was washed with 5% NaHCO_3 (30 mL), water (2 x 15 mL), dried over Na_2SO_4 , filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH_2Cl_2 (5 mL) and chromatographed on silicagel with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2 \rightarrow 13.0:7.0) to obtain the title compound as a brownish oil 0.373 g, 28%). Spectroscopic data of compound **2** were consistent with those of literature.

(*E*)-2-(3,7-dimethylocta-2,6-dienyl)-5-methylbenzene-1,3-diol **4** and (*E*)-4-(3,7-dimethylocta-2,6-dienyl)-5-methylbenzene-1,3-diol **5**

To a solution of 5-methylbenzene-1,3-diol (1,21 g, 9,8 mmol) and $\text{BF}_3\cdot\text{OEt}_2$ (1,4 g, 9,8 mmol) in freshly distilled 1,4-dioxane (5 mL) was slowly added dropwise, with stirring at room temperature and under a N_2 atmosphere,

a solution of geraniol (1.5 g, 9.8 mmol) in 1,4-dioxane (5 mL). After the addition was complete, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with diethyl ether (3 x 30 mL). Then, the ethereal layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2→0.2:19.8) as the mobile phase. Two fractions were obtained. Fraction I: 0.320 g (12.6% yields) of viscous brownish oil compound **4**. ¹H NMR: 6.26 (s, 1H, H-6); 6.22 (s, 2H, H-2); 5.60 (brs, 2H, OH); 5.13 (t, *J* = 6.8 Hz, 1H, H-2'); 5.05 (t, *J* = 6.7 Hz, 1H, H-6'); 3.28 (d, *J* = 6.7 Hz, 2H, H-1'); 2.21 (s, 3H, CH₃-Ar); 2.09-2.06 (m, 2H, H-5'); 2.04-2.00 (m, 2H, H-4'); 1.78 (s, 3H, CH₃-C^{3'}); 1.67 (s, 3H, H-8'); 1.60 (s, 3H, CH₃-C^{7'}); ¹³C NMR: 155.2 (C-3); 154.1 (C-1); 138.6 (C-5); 137.2 (C-3'); 131.8 (C-7'); 123.9 (C-6'); 122.2 (C-2'); 118.1 (C-4); 109.7 (C-6); 101.0 (C-2); 39.6 (C-4'); 26.4 (C-5'); 25.6 (C-8'); 25.0 (C-1'); 20.0 (CH₃-Ar); 17.6 (CH₃-C^{7'}); 16.1 (CH₃-C^{3'}); IR (cm⁻¹): 3393, 2975, 2925, 2859, 1602; MS (*m/z*, %): M⁺ 260 (21.7), 191 (26.9), 177 (13.9), 137 (100), 123 (10.5). Fraction II: 0.704 g (27.6% yields) of viscous yellow oil, compound **5**. ¹H NMR: 6.26 (s, 1H, H-6); 6.22 (s, 2H, H-2); 5.60 (brs, 2H, OH); 5.13 (t, *J* = 6.8 Hz, 1H, H-2'); 5.05 (t, *J* = 6.7 Hz, 1H, H-6'); 3.28 (d, *J* = 6.7 Hz, 2H, H-1'); 2.21 (s, 3H, CH₃-Ar); 2.09-2.06 (m, 2H, H-5'); 2.04-2.00 (m, 2H, H-4'); 1.78 (s, 3H, CH₃-C^{3'}); 1.67 (s, 3H, H-8'); 1.60 (s, 3H, CH₃-C^{3'}); ¹³C NMR: 155.2 (C-3); 154.1 (C-1); 138.6 (C-5); 137.2 (C-3'); 131.8 (C-7'); 123.9 (C-6'); 122.2 (C-2'); 118.1 (C-4); 109.7 (C-6); 101.0 (C-2); 39.6 (C-4'); 26.4 (C-5'); 25.6 (C-8'); 25.0 (C-1'); 20.0 (CH₃-Ar); 17.6 (CH₃-C^{7'}); 16.1 (CH₃-C^{3'}); IR (cm⁻¹): 3393, 2975, 2925, 2859, 1602; MS (*m/z*, %): M⁺ 260 (21.7), 191 (26.9), 177 (13.9), 137 (100), 123 (10.5).

(E)-2-(3,7-dimethylocta-2,6-dienyl)benzene-1,3,5-triol (geranylphloroglucinol) 13

To a solution of phloroglucinol (1.21 g, 7.5 mmol) and BF₃OEt₂ (1.06 g, 7.5 mmol) in freshly distilled 1,4-dioxane (5 mL), a solution of geraniol (1.15 g, 7.5 mmol) in 1,4-dioxane (5 mL) was added dropwise, with stirring at room temperature and under a N₂ atmosphere. After the addition was complete, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with diethyl ether (3 x 30 mL). Then, the ethereal layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2→0.2:19.8) as the mobile phase to afford the compound **13** as a viscous brownish oil (0.832 g, 4.2% yield). ¹H NMR: 5.99 (brs, 2H, -OH); 5.93 (s, 2H, H-4 and H-6); 5.22 (t, *J* = 6.8 Hz, 1H, H-2'); 5.03 (t, *J* = 5.9 Hz, 1H, H-6'); 3.30 (d, *J* = 6.9 Hz, 2H, H-1'); 2.08-2.05 (m, 2H, H-5'); 2.03-2.02 (m, 2H, H-4'); 1.76 (s, 3H, CH₃-C^{7'}); 1.66 (s, 3H, H-8'); 1.57 (s, 3H, CH₃-C^{3'}); ¹³C NMR: 155.7 (C-1 and C-3), 154.7 (C-5), 138.7 (C-3'), 131.9 (C-7'), 123.7 (C-6'), 122.0 (C-2'), 106.3 (C-2), 96.1 (C-4 and C-6), 39.6 (C-4'), 26.3 (C-5'), 25.6 (C-8'), 21.9 (C-1'); 17.6 (CH₃-C^{7'}), 16.0 (CH₃-C^{3'}); IR (cm⁻¹): 3397, 2967, 2925, 1706, 1620, 1515, 1463, 1377; MS (*m/z*, %): M⁺ 262 (0.2%), 191 (100), 175 (52.7), 137 (49.8), 123 (47.8), 69 (22.1).

(E)-2-(3,7-dimethylocta-2,6-dienyl)-1,3,5-trimethoxybenzene 14

A solution of compound **13** (0.36 g, 1.4 mmol), dimethyl sulphate (0.58 g, 4.6 mmol) and potassium carbonate (0.58 g, 4.2 mmol) in dry acetone (50 mL) was refluxed for 6 h. in presence of. Later the mixture was filtered, and the inorganic salts washed with acetone (2 x 10 mL). The combined acetone solutions were evaporated under reduced pressure, the residue macerated with crushed ice, extracted with ethyl acetate (2 x 40 mL). Then, the organic layer was washed with sodium hydroxide solution (5%), water, dried under Na₂SO₄, filtered and the solvent was evaporated under reduced pressure to afford the compound **14** as a brownish oil (0.42 g, 98.5%). ¹H NMR: 6.14 (s, 2H, H-4 and H-6); 5.19 (t, *J* = 6.9 Hz, 1H, H-2'); 5.09 (t, *J* = 6.3 Hz, 1H, H-6'); 3.92 (s, 3H, OCH₃); 3.79 (s, 6H, 2xOCH₃); 3.29 (d, *J* = 7.0 Hz, 2H, H-1'); 2.08-2.05 (m, 2H, H-5'); 1.99-1.95 (m, 2H, H-4'); 1.78 (s, 3H, CH₃-C^{3'}); 1.66 (s, 3H, H-8'); 1.59 (s, 3H, CH₃-C^{7'}); ¹³C NMR: 159.0 (C-5); 158.4 (C-1 and C-3); 133.6 (C-3'); 130.6 (C-7'); 124.3 (C-6'); 123.2 (C-2'); 110.5 (C-2); 90.4 (C-4 and C-6); 55.3 (2xOCH₃); 54.9 (OCH₃); 39.6 (C-4'); 26.5 (C-5'); 25.3 (C-8'); 21.4 (C-1'); 17.3 (CH₃-C^{7'}); 15.6 (CH₃-C^{3'}); IR (cm⁻¹): 2935, 2836, 1726, 1608, 1596, 1496, 1455, 1437, 1417, 1377, 1322; MS (*m/z*, %): M⁺ 304 (10.9%), 235 (23.8), 181 (100), 167 (15.0), 69 (12.9)

(E)-2-(3,7-dimethylocta-2,6-dienyl)-6-methoxyphenol 15, (E)-3-(3,7-dimethylocta-2,6-dienyl)-2-methoxyphenol 16 and (E)-5-(3,7-dimethylocta-2,6-dienyl)-2-methoxyphenol 17.

To a solution of 2-methoxyphenol (1.50 g, 12.1 mmol) and BF₃OEt₂ (2.25 g, 15.8 mmol) in freshly distilled 1,4-dioxane (5 mL) was added dropwise, with stirring at room temperature and under a N₂ atmosphere, a solution of geraniol (2.44 g, 15.8 mmol) in 1,4-dioxane (5 mL). After the addition was complete, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with diethyl ether (3 x 30 mL). Then, the ethereal layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2→0.2:19.8) as the mobile phase. Three fractions were obtained. Fraction I: compound **15** as a yellow oil (0.09 g, 2.5%). ¹H NMR: 6.81-6.74 (m, 3H, H-3, H-4 and H-5); 5.72 (s, 1H, OH); 5.37 (t, *J* = 7.2 Hz, 1H, H-2'); 5.13 (t, *J* = 6.6 Hz, 1H, H-6'); 3.90 (s, 3H, OCH₃); 3.39 (d, *J* = 7.2 Hz, 2H, H-1'); 2.14-2.11 (m, 2H, H-5'); 2.09-2.05 (m, 2H, H-4'); 1.74 (s, 3H, CH₃-C^{3'}); 1.70 (s, 3H, H-8'); 1.62 (s, 3H, CH₃-C^{7'}); ¹³C NMR: 146.3 (C-6); 143.4 (C-1); 136.3 (C-3'); 131.4 (C-7'); 127.5 (C-2); 124.4 (C-6'); 122.1 (C-2'); 121.8 (C-3); 119.2 (C-4); 108.3 (C-5); 56.0 (OCH₃); 39.8 (C-4'); 27.8 (C-1'); 26.6 (C-5'); 25.7 (C-8'); 17.7 (CH₃-C^{7'}); 16.0 (CH₃-C^{3'}); IR (cm⁻¹): 3545, 2964, 2923, 2853, 1616, 1592, 1478, 1442, 1376, 1356, 1270, 1217; MS (*m/z*, %): M⁺ 260 (53.8%), 191 (29.4), 137 (100), 123 (78.7), 69 (36.7) Fraction II: compound **16** as aviscous yellow oil (0.12 g, 4.1%); ¹H NMR: 6.83 (d, *J* = 8.5 Hz, 1H, H-6); 6.68 (d, *J* = 6.8 Hz, 2H, H-4 and H-5); 5.47 (s, 1H, OH); 5.33 (t, *J* = 7.2 Hz, 1H, H-2'); 5.12 (t, *J* = 6.4 Hz, 1H, H-6'); 3.87 (s, 3H, OCH₃); 3.29 (d, *J* = 7.2 Hz, 2H, H-1'); 2.13-2.10 (m, 2H, H-5'); 2.07-2.06 (m, 2H, H-4'); 1.17 (s, 3H, CH₃-C^{3'}); 1.68 (s, 3H, H-8'); 1.60 (s, 3H, CH₃-C^{3'}); ¹³C NMR: 146.4 (C-2); 143.6 (C-1); 136.0 (C-3'); 133.7 (C-3); 131.4 (C-7'); 124.2 (C-6'); 123.4 (C-2'); 120.8 (C-5); 114.2 (C-6); 110.8 (C-4); 55.8 (OCH₃); 39.7 (C-4'); 33.8 (C-1'); 26.7 (C-5'); 25.7 (C-8'); 17.7 (C-10'); 16.1 (C-9'); IR (cm⁻¹): 3443, 2963, 2924, 2853, 1676, 1600, 1512, 1451, 1432, 1376, 1267, 1230; MS (*m/z*, %): M⁺ 260 (84.3%), 159 (100), 137 (89.9), 123 (42.0), 69 (40.4) Fraction III: compound **17** as aviscous yellow oil (0.01 g, 0.3%); ¹H NMR: 6.78 (d, *J* = 8.3 Hz, 1H, H-3); 6.76 (d, *J* = 1.7 Hz, 1H, H-6); 6.66 (dd, *J* = 8.3-1.7 Hz, 1H, H-4); 5.55 (s, 1H, OH); 5.31 (t, *J* = 7.2 Hz, 1H, H-2'); 5.10 (t, *J* = 6.7 Hz, 1H, H-6'); 3.86 (s, 3H, OCH₃); 3.26 (d, *J* = 7.2 Hz, 2H, H-1'); 2.12-2.08 (m, 2H, H-5'); 2.05-2.03 (m, 2H, H-4'); 1.69 (s, 6H, CH₃-C^{3'} and H-8'); 1.60 (s, 3H, CH₃-C^{7'}); ¹³C NMR: 145.5 (C-1); 144.7 (C-2); 136.0 (C-3'); 135.2 (C-5); 131.4 (C-7'); 124.3 (C-6'); 123.2 (C-2'); 119.5 (C-4); 114.6 (C-6); 110.6 (C-3); 56.0 (OCH₃); 39.7 (C-4'); 33.5 (C-1'); 26.6 (C-5'); 25.7 (C-8'); 17.7 (CH₃-C^{7'}); 16.1 (CH₃-C^{3'}); IR (cm⁻¹): 3443, 2923, 2853, 1591, 1509, 1442, 1377, 1270, 1212, 1128.

(E)-4-(3,7-dimethylocta-2,6-dienyl)benzene-1,3-diol 18

To a solution of resorcinol (1.00 g, 9.1 mmol) and BF₃OEt₂ (1.29 g, 9.1 mmol) in freshly distilled 1,4-dioxane (5 mL) was added dropwise, with stirring at room temperature and under a N₂ atmosphere, a solution of geraniol (2.80 g, 18.1 mmol) in 1,4-dioxane (5 mL). After the addition was complete, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with diethyl ether (3 x 30 mL). Then, the ethereal layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2→0.2:19.8) as the mobile phase to afford the compound **18** as a viscous yellow oil (0.268 g, 11.9%); ¹H NMR: 6.92 (d, *J* = 8.8 Hz, 1H, H-5); 6.37 (d, *J* = 2.4 Hz, 1H, H-2); 6.36 (dd, *J* = 2.4 and 8.8 Hz, 1H, H-6); 5.30 (t, *J* = 7.0 Hz, 1H, H-2'); 5.09 (t, *J* = 6.1 Hz, 1H, H-6'); 3.27 (d, *J* = 7.0 Hz, 2H, H-1'); 2.12-2.09 (m, 2H, H-5'); 2.08-2.06 (m, 2H, H-4'); 1.72 (s, 3H, CH₃-C^{3'}); 1.69 (s, 3H, H-8'); 1.60 (s, 3H, CH₃-C^{7'}); ¹³C NMR: 154.8 (*C-1); 154.7 (*C-3); 137.6 (C-3'); 131.7 (C-7'); 130.3 (C-5); 124.0 (C-6'); 122.1 (C-2'); 119.4 (C-4); 107.6 (C-6); 103.2 (C-2); 39.6 (C-4'); 28.3 (C-1'); 26.4 (C-5'); 25.6 (C-8'); 17.6 (CH₃-C^{7'}); 16.0 (CH₃-C^{3'}); IR (cm⁻¹): 3387, 2927, 1702, 1620, 1508, 1455, 1377, 1297, 1152; MS (*m/z*, %): M⁺ 246 (16.8%), 177 (43.5), 161 (28.5), 123 (100), 69 (29.0) * interchangeable signs.

(E)-3-(3,7-dimethylocta-2,6-dienyl)benzene-1,2-diol 19

To a solution of pyrocatechol (1.00 g, 9.1 mmol) and BF₃OEt₂ (1.3 g, 9.1 mmol) in freshly distilled 1,4-dioxane (5 mL) was added dropwise, with

stirring at room temperature and under a N₂ atmosphere, a solution of geraniol (1.4 g, 9.1 mmol) in 1,4-dioxane (5 mL). After the addition was complete, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with diethyl ether (3 x 30 mL). Then, the ethereal layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2→0.2:19.8) as the mobile phase to afford the compound **19** as a viscous brown oil (0.108 g, 4.8 %); ¹H NMR: 6.79-6.72 (m, 2H, H-5 and H-6); 6.66 (d, *J* = 7.0 Hz, 1H, H-4); 5.38 (s, 1H, OH); 5.33-5.31 (m, 2H, OH and H-2'); 5.05-5.04 (m, 1H, H-6'); 3.37 (d, *J* = 7.1 Hz, 2H, H-1'); 2.14-2.12 (m, 2H, H-5'); 2.11-2.09 (m, 2H, H-4'); 1.78 (s, 3H, CH₃-C3'); 1.69 (s, 3H, H-8'); 1.60 (s, 3H, CH₃-C7'); ¹³C NMR: 144.3 (C-1); 141.9 (C-2); 138.9 (C-3'); 132.2 (C-7'); 127.4 (C-3); 123.7 (C-6'); 121.7 (C-2'); 121.4 (C-4); 120.7 (C-5); 113.2 (C-6); 39.6 (C-4'); 29.9 (C-1'); 26.3 (C-5'); 25.7 (C-8'); 17.7 (CH₃-C7'); 16.1 (CH₃-C3'); IR (cm⁻¹): 3588, 3418, 2967, 2922, 2845, 1620, 1595, 1475, 1375, 1278.

(E)-4-(3,7-dimethylocta-2,6-dienyl)-5-isopropyl-2-methylphenol **20**

To a solution of carvacrol (0.25 g, 1.67 mmol) and BF₃·Et₂O (0.2 mL, 1.59 mmol) in freshly distilled ethyl ether (10 mL) a solution of geraniol (0.308 g, 2.00 mmol) in ethyl ether (5 mL) was added dropwise with stirring at room temperature and under a N₂ atmosphere. After the addition was complete, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with ethyl acetate (3 x 20 mL). Then, the organic layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/ethyl acetate mixtures of increasing polarity as the mobile phase to afford the compound **20** as a dark yellow viscous oil (86.6 mg, 21.7%); ¹H NMR: 6.88 (s, 1H, H-3); 6.69 (s, 1H, H-6); 5.20 (t, *J* = 6.9 Hz, 1H, H-2'); 5.10 (t, *J* = 6.7 Hz, 1H, H-6'); 4.49 (s, 1H, OH); 3.27 (d, *J* = 6.8 Hz, 2H, H-1'); 3.08 (sext. *J* = 6.8 Hz, 1H CH(CH₃)₂); 2.19 (s, 3H, CH₃-Ar); 2.19-2.08 (m, 2H, H-5'); 2.06-2.02 (m, 2H, H-4'); 1.71 (s, 3H, CH₃-C3'); 1.67 (s, 3H, H-8'); 1.59 (s, 3H, CH₃-C7'); 1.19 (d, *J* = 6.8 Hz, 6H, (CH₃)₂CH); ¹³C NMR: 152.4 (C-1); 146.1 (C-5); 135.3 (C-3'); 131.9 (C-3); 130.8 (C-4); 124.6 (C-7'); 124.3 (C-6'); 124.1 (C-2'); 111.8 (C-6); 39.7 (C-4'); 30.7 (C-1'); 28.6 (CH(CH₃)₂); 26.6 (C-5'); 25.7 (C-8'); 23.8 ((CH₃)₂CH); 17.7 (CH₃-C7'); 16.2 (CH₃-C3'); 15.2 (CH₃-Ar); IR (cm⁻¹): 3398, 3418, 2962, 2925, 2845, 1620, 1589, 1496, 1456, 1380, 1278, 1107, 889, 813; MS (*m/z*, %): M⁺ 285 (81%), 257 (14.9), 256 (22.3), 255 (14), 191 (13.5), 177 (100), 163 (40).

(E)-2-(3,7-dimethylocta-2,6-dienyl)-4-isopropyl-3-methylphenol **21** and (E)-2-(3,7-dimethylocta-2,6-dienyl)-4-isopropyl-5-methylphenol **22**

To a solution of 4-isopropyl-3-methylphenol (0.25 g, 1.67 mmol) and BF₃·Et₂O (0.2 mL, 1.59 mmol) in freshly distilled ethyl ether (10 mL) was added dropwise with stirring at room temperature and under a N₂ atmosphere, a solution of geraniol (0.308 g, 2.00 mmol) in ethyl ether (5 mL). After the addition was complete, the stirring was continued overnight. When the finish of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with ethyl acetate (3 x 20 mL). Then, the organic layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2→ 15.2:4.8) as the mobile phase to obtain two fractions: Fraction I: compound **21** as a yellow viscous oil (67.5 mg, 4.2%); ¹H NMR: 7.01 (d, *J* = 8.4 Hz, 1H, H-5); 6.67 (d, *J* = 8.4 Hz, 1H, H-6); 5.13 (t, *J* = 6.6 Hz, 1H, H-2'); 5.04 (t, *J* = 5.6 Hz, 1H, H-6'); 4.78 (s, 1H, OH); 3.41 (d, *J* = 6.6 Hz, 2H, H-1'); 3.13 (sext. *J* = 6.8 Hz, 1H CH(CH₃)₂); 2.26 (s, 3H, CH₃-Ar); 2.09-2.06 (m, 2H, H-5'); 2.04-2.02 (m, 2H, H-4'); 1.80 (s, 3H, CH₃-C3'); 1.66 (s, 3H, H-8'); 1.58 (s, 3H, CH₃-C7'); 1.20 (d, *J* = 6.8 Hz, 6H, (CH₃)₂CH); ¹³C NMR: 151.9 (C-1); 139.3 (C-4); 137.0 (C-3'); 131.7 (C-3); 129.7 (C-7'); 125.9 (C-2); 124.0 (C-5'); 123.3 (C-6'); 122.1 (C-2'); 114.6 (C-6); 39.7 (C-4'); 29.3 (CH(CH₃)₂); 26.5 (C-5'); 26.1 (C-1'); 25.7 (C-8'); 23.6 ((CH₃)₂CH); 17.7 (CH₃-C7'); 16.2 (CH₃-C3'); 14.7 (CH₃-Ar); IR (cm⁻¹): 3421, 2962, 2926, 1617, 1495, 1452, 1380, 1277, 1149, 1107, 1039, 888, 811; MS (*m/z*, %): M⁺ 285 (38%), 194 (68), 191 (13.5), 177 (100), 163 (40). Fraction II: isomers **21/22** mixture as dark yellow viscous oil (0.102 g, 21.6%) Compound **22**: ¹H NMR: 6.96 (s, 1H, H-3); 6.62 (s, 1H, H-6); 5.35 (t, *J* = 7.0 Hz, 1H, H-2');

5.17-5.07 (m, 1H, H-6'); 5.04 (s, 1H, OH); 3.35 (d, *J* = 7.0 Hz, 2H, H-1'); 3.06 (sext. *J* = 6.8 Hz, 1H CH(CH₃)₂); 2.27 (s, 3H, CH₃-Ar); 2.14-2.08 (m, 2H, H-5'); 2.05-2.04 (m, 2H, H-4'); 1.79 (s, 3H, CH₃-C3'); 1.70 (s, 3H, H-8'); 1.61 (s, 3H, CH₃-C7'); 1.25 (d, *J* = 6.8 Hz, 6H, (CH₃)₂CH); ¹³C NMR: 151.9 (C-1); 138.9 (C-4); 138.1 (C-3'); 131.6 (C-7'); 126.3 (C-3); 126.0 (C-5); 124.0 (C-6'); 123.8 (C-2); 122.2 (C-2'); 117.5 (C-6); 39.7 (C-4'); 29.9 (C-1'); 28.6 (CH(CH₃)₂); 26.5 (C-5'); 25.6 (C-8'); 23.5 ((CH₃)₂CH); 18.8 (CH₃-Ar); 17.6 (CH₃-C7'); 16.2 (CH₃-C3').

(E)-2-tert-butyl-4-(3,7-dimethylocta-2,6-dienyl)-5-methylphenol **23**

To a solution of 2-tert-butyl-5-methylphenol (0.25 g, 1.52 mmol) and BF₃·Et₂O (0.2 mL, 1.59 mmol) in freshly distilled ethyl ether (10 mL) a solution of geraniol (0.308 g, 2.00 mmol) in ethyl ether (5 mL) was added dropwise with stirring at room temperature and under a N₂ atmosphere. After the addition was complete, the stirring was continued overnight. When the end of the reaction was verified by TLC, the mixture was poured onto crushed ice (app. 30 g) and it was extracted with ethyl acetate (3 x 20 mL). Then, the organic layer was washed with 5% NaHCO₃ (30 mL), water (2 x 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude was redissolved in CH₂Cl₂ (5 mL) and the mixture was subjected to silica gel flash column chromatography with petroleum ether/ethyl acetate mixtures of increasing polarity as the mobile phase to afford the compound **23** as a brown viscous oil (123.4 mg, 17.7%); ¹H NMR: 7.03 (s, 1H, H-3); 6.48 (s, 1H, H-6); 5.23 (t, *J* = 7.0 Hz, 1H, H-2'); 5.10 (t, *J* = 6.3 Hz, 1H, H-6'); 4.59 (s, 1H, OH); 3.23 (d, *J* = 7.0 Hz, 2H, H-1'); 2.18 (s, 3H, CH₃-Ar); 2.11-2.08 (m, 2H, H-5'); 2.05-2.02 (m, 2H, H-4'); 1.71 (s, 3H, CH₃-C3'); 1.67 (s, 3H, H-8'); 1.60 (s, 3H, CH₃-C7'); 1.39 (s, 9H, (CH₃)₃C); ¹³C NMR: 152.0 (C-1); 135.5 (C-3'); 134.8 (C-4); 133.2 (C-2); 131.6 (C-7' + C-5); 127.5 (C-3); 124.3 (C-6'); 123.2 (C-2); 118.3 (C-6); 39.7 (C-4'); 34.2 (C(CH₃)₃); 31.6 (C-1'); 29.7 ((CH₃)₃C); 26.8 (C-5'); 25.7 (C-8'); 18.6 (CH₃-Ar); 17.7 (CH₃-C7'); 16.1 (CH₃-C3') IR (cm⁻¹): 3526, 2958, 2916, 2862, 1618, 1576, 1514, 1483, 1449, 1410, 1389, 1295, 1182, 1136, 1080, 949, 808; MS (*m/z*, %): M⁺ 300 (87.5%), 206 (41.6), 192 (100), 163 (75), 57 (25).

CONCLUSIONS

In summary we have prepared fourteen compounds, the known geranylhydroquinone **2**, geranylrocinol **4** and the derivative geranylrocinol **5** and the new geranylphenol derivatives **13-23**. All these compounds were obtained by direct geranylation reactions using BF₃·Et₂O as a catalyst between geraniol and commercially available activated phenols hydroquinone, rocinol, phloroglucinol, guaiacol, resorcinol, catechol, pyrocatechol, carvacrol, 4-isopropyl-3-methylphenol and 2-tert-butyl-5-methylphenol. Additionally, all the synthesized compounds were fully characterized by spectroscopic data, especially by NMR techniques.

On the other hand, the orientation in electrophilic aromatic substitution of geranyl chain was directed in *ortho* and/or *para* position according to the location the OH or OCH₃ groups in the aromatic system. Also, for the same reason, mixtures of regio-isomers were obtained in some cases. The low yields were observed due to that during the reaction time, part of geraniol was transformed into unidentified products and unreacted starting material (arenes nuclei) was recovered.

We are currently investigating the effect of a second catalyst in the geranylation reactions and we have found better results in yields for these reactions. These results, together with biological activity assay against plant pathogens will be informed soon.

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REFERENCES

- H. C. Lin, and W. L. Chang, *Chin. Pharm. J.* **43**, 11, (1991)
- G. D. Manners and L. Jurd, *J. Chem. Soc. Perkin. Tras.* **1**, 405, (1977)
- G. Reynolds and E. Rodriguez, *Phytochem.* **18**, 1567, (1979)
- G. Reynolds, W. L. Epstein, D. Terry, E. Rodriguez, *Contact Dermatitis* **6**, 272, (1980)

5. G. Reynolds and E. Rodríguez, *Planta Medica*, **43**, 187, (1981)
6. A. F. Benslimane, Y. F. Pouchus, J. Le Boterff, J. F. Verbist, *J. Nat. Prod.* **51**, 582, (1988)
7. A. Sato, T. Shindo, N. Kasanuki, K. Hasegawa, *J. Nat. Prod.* **52**, 975, (1989)
8. W. Fenical, "4th Proceeding of Food Drugs from the Sea." Marine Technological Society: Washington D.C., 1974.
9. S. De Rosa, A. De Giulio, C. Iodice, *J. Nat. Prod.* **57**, 1711, (1994)
10. G. Rudali, *Seances Soc. Biol. Ses Fil.* **160**, 1365 (1966)
11. G. Rudali, L. Menetrier, *Therapie*, **22**, 895, (1967)
12. L. K. Shubina, S. N. Fedorov, O. S. Radchenko, N. N. Balaneva, S. A. Kolesnikova, P. S. Dmitrenok, A. B. Zigang-Dong, V. A. Stonik, *Tetrahedron Lett.* **46**, 559, (2005)
13. S. N. Fedorov, O. S. Radchenko, L. K. Shubina, N. N. Balaneva, A.M. Bode, V. A. Stonik, Z. Dong, *Pharmaceutical Research*, **23**, 70, (2006)
14. H. N. Eisohly, C. E. Turner, C. A. M. Mahmoud, M. A. Eisohly, *Journal Pharmaceutical Science*, **71**, 1319, (1982)
15. G. Manners, L. Jurd, K. Stevenst, *Tetrahedron*, **28**, 2949, (1972)
16. L. F. Yamaguchi, J. H. G. Lago, T. M. Tanizaki, P. Di Mascio, M. J. Kato, *Phytochem.* **67**, 1838, (2006)
17. E. Rodriguez, P. Hedin; ACS Symposium Series Vol. 208; American Chemical Society: Washington, DC, 1983, Chapter 17, 291-303.
18. E. Baeza, K. Catalán, H. Peña-Cortés, L. Espinoza, J. Villena, H. Carrasco, *Quim. Nova*, **35**, 523, (2012)
19. E. Baeza, K. Catalán, J. Villena, H. Carrasco, M. Cuellar, and L. Espinoza, *J. Chil. Chem. Soc.* **57**, 1219, (2012)