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Synthesis of fluorine-containing prenylated benzophenones

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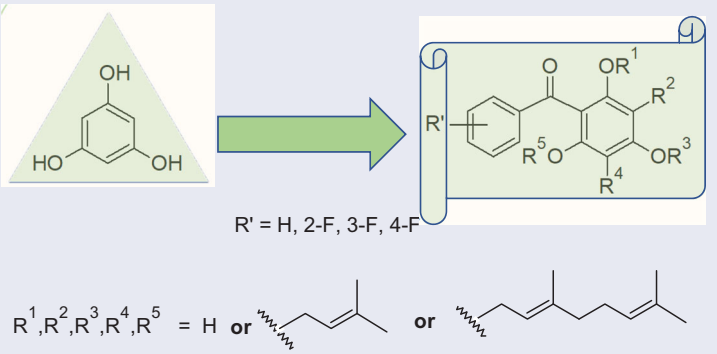
ABSTRACT

In this study, an effective route to synthesize fluorine-containing prenylated benzophenones was developed. Friedel–Crafts acylation and electrophilic aromatic substitution reactions were the key reactions of this synthesis to achieve these fluorinated prenylated benzophenones. The use of DBU in the prenylation step achieved only the *C*-prenylated benzophenones, whereas K_2CO_3 produced the *C*- and *O*-prenylated benzophenones.

GRAPHICAL ABSTRACT



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Benzophenone; fluorine; Friedel–Crafts acylation; prenylation

Introduction

Prenylated benzophenones and geranylated benzophenones have shown interesting biological activities such as anti-inflammation,[1] anticancer,[2] anti-HIV,[3–5] cholesterol regulatory,[6] cytotoxic,[7] and antimicrobial activity.[8] These compounds belong to a well-known class of natural compounds, benzophenones,[9,10] and are characterized by two benzene rings linked by a carbonyl carbon. Vismiaphenone D (**A**), garciniaphenone (**B**) and 4-geranyloxy-2,6-dihydroxybenzophenone (**C**) are examples of natural prenylated benzophenones and exhibit anti-HIV,[4] anti-cancer and antimicrobial[7] activities.

Over 150 types of fluorine-containing drugs have come onto the market, accounting for about 20% of all pharmaceuticals.[11] The increasing prevalence and success of fluorine-containing pharmaceuticals has stimulated further interest into the synthesis of such compounds.

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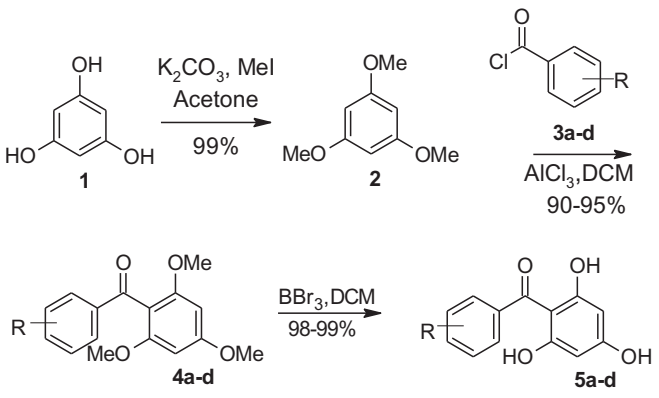


a R=H; **b** R=2-F; **c** R=3-F; **d** R=4-F

Scheme 1. Synthesis of arcylphloroglucinols **5a–d** from phloroglucinol **1**.

Despite the biological importance of prenylated benzophenones found in the literature, there has been a limited synthetic methods found in the literature to synthesize them. Some prenylated benzophenones have been synthesized *via* the Friedel–Crafts reaction but none of them contains fluorine.[12,13] In this paper, we report a convenient way to synthesize prenylated benzophenones which involves the usage of mild conditions and give good yields of the products.

Results and discussion

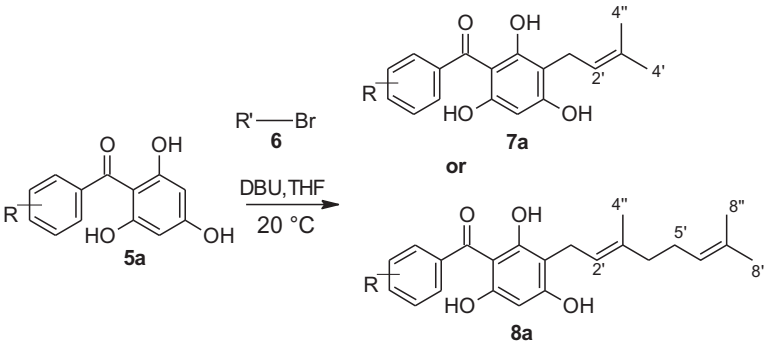
The aim of this study was to synthesize fluorine-containing prenylated benzophenones, but no effective synthetic route could be found in the literature. However, we managed to adopt the synthetic route we published in 2017,[14] to develop an effective synthetic method to synthesize fluorine-containing prenylated benzophenones. The first step of this synthesis was the methylation of phloroglucinol (**1**) to form 1,3,5-trimethoxybenzene (**2**).[15] This reaction was run under acetone reflux in the presence of potassium carbonate. Compound **2** was found to react better than phlorogucinol in the subsequent step.

The second step of the reaction was the Friedel–Crafts acylation reaction.[13,14] This reaction was carried out in dichloromethane and promoted by aluminum trichloride ($AlCl_3$) for an optimum yield of **4a–d** (yield: $90-95\%$) as colorless crystals. Iron trichloride ($FeCl_3$) was also used in these reactions but yields were relatively low (yield: $48-61\%$) (Scheme 1).

The third step was the demethylation of the methoxy groups using a strong Lewis acid (boron tribromide, BBr_3).[14,16–18] The use of BBr_3 for demethylation in this step was preferred because the reactions proceeded under mild conditions. The reactions were stirred at room temperature for 24 h for a complete demethylation.

The last step of the synthesis was the prenylation of benzophenones (**5a** was used as a model reaction, Table 1, entry 1).[12,14] An aromatic proton is replaced by a prenyl group under the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). These reactions took place in THF at room temperature. Having successfully synthesized **7a**, derivatives were

Table 1. Synthesis of mono-*C*-prenylated benzophenones[a].



Entry	5	6	Product	Yield[b] (%)
1	**5a**	Prenyl-Br	**7a** (R = H)	62
2	**5a**	Geranyl-Br	**8a** (R = H)	42
3	**5b**	Prenyl-Br	–	0
4	**5b**	Geranyl-Br	–	0
5	**5c**	Prenyl-Br	**7c** (R= 3-F)	61
6	**5c**	Geranyl-Br	**8c** (R= 3-F)	40
7	**5d**	Prenyl-Br	**7d** (R= 4-F)	62
8	**5d**	Geranyl-Br	**8d** (R= 4-F)	44

[a]All reactions were run in THF (15 mL), 24 h.
[b]Isolated yields.

also synthesized in the same manner (Table 1) except the 2-fluoro derivative (**7b**). The product that the 2-fluoro-benzophenone (**5b**) formed did not have characteristics of a prenylated benzophenone, for example, the NMR data detected no fluorine in the structure. We tried the reaction in different conditions, such as low to high temperature (0–60 °C) and different solvents (DMF, ethyl acetate), but still it did not form a desired product. After elucidating the structure of this product (**7b**), it was determined that a prenylated xanthone is being formed instead and the fluorine gets eliminated in the process. The mechanism and the structure of the prenylated xanthones that were formed are not included in this paper.

NMR, IR and mass spectra were used to elucidate the structure to prove the success of the prenylation reaction. ^{1}H spectrum of **7a** revealed two methyl peaks at 1.76 (doublet, $J = 1.1$ Hz) and 1.80 ppm (singlet) corresponding to *cis*-allylic methyl-protons (**H**-4″) and *trans*-allylic protons (**H**-4′), respectively.[19] A doublet peak, integrating for two hydrogens, appears at δ_H 3.36 ($J = 7.0$ Hz) and was assigned to H-1′. A vinylic proton peak (**H**-2′) appeared as a multiplet at 5.26 ppm. The aromatic protons of the monosubstituted ring appeared at δ_H 7.64 (H-9,13), δ_H 7.51 (H-10,12) and δ_H 7.58 (H-11). DEPT-135, HSQC and HMBC spectra were used for the assignment of 13C NMR peaks. In the 13C NMR spectrum of **7a** the prenyl carbons resonate upfield. The terminal allylic carbons, C-4′ and C-4′' resonate at δ_C 17.9 and δ_C 25.8, respectively,[20] whereas the olefinic carbons (C-2′ and C-3′) resonate at δ_C 121.6 and δ_C 135.4, respectively. The peak appearing downfield at δ_C 197.7 was assigned for the carbonyl carbon (C-7). The quaternary carbon (C-8) and hydroxy carbons (C-2, C-4 and C-6) were deshielded and appeared downfield at δ_C 140.0, δ_C 160.8, δ_C 162.6 and δ_C 159.4, respectively.

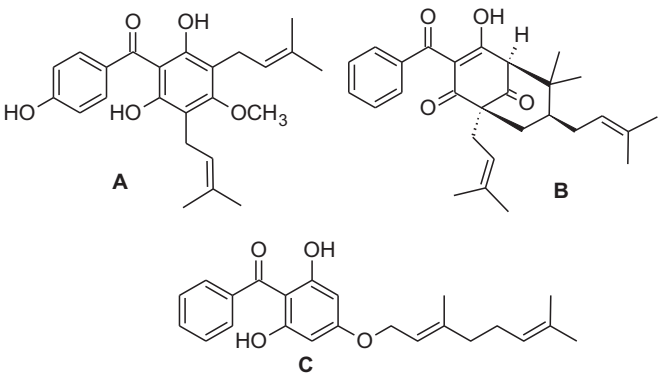


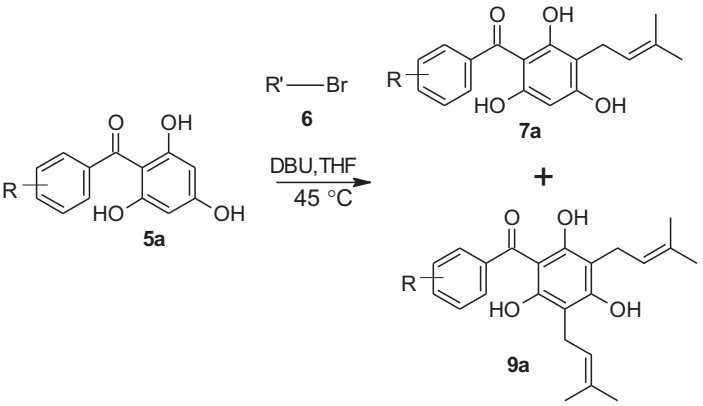
Figure 1. Structures of some bioactive benzophenones.

The 1H NMR spectrum of **8a** showed the appearance of the geranyl protons confirms the incorporation of a geranyl group. Geranyl protons including the terminal allylic protons (H-4″, H-8″ and H-8″), non-terminal allylic protons (H-1′, H-4′ and H-5′) and olefinic protons (H-2′ and H-6′) are shown in the experimental section as well as in the ^{1}H NMR spectrum (supplementary data).[21,22] The DEPT-135, HSQC and HMBC spectra were used to assign the signals in the ^{13}C NMR spectrum.

Derivatives of Vismiaphenone D (Fig. 1), characterized by two prenyl groups bonded to the aromatic ring, were also synthesized in this study. This was achieved by increasing the temperature of the prenylation reaction to 45 °C as well as double the equivalence of the prenyl bromide and DBU (Table 2). At this temperature, both mono-prenylated and di-prenylated benzophenones were isolated. The further increase in the temperature of the reaction had no effect on the relative yields of the mono- and di-prenylated benzophenone. Fluorinated derivatives of di-prenylated benzophenones were also synthesized in the same conditions as shown in Table 2. The isolation of mono-prenylated and di-prenylated benzophenones was achieved using rotatory thin-layer chromatotron with high ratio of non-polar-to-polar solvent as eluent (e.g., hexane:ethylacetate, 4:1). The results above clearly show that DBU is a good base to be used for *C*-prenylation and *C*-geranylation reactions of trihydroxybenzophenones as there were no *O*-prenylated benzophenone isolated. DBU can selectively mono-prenylate or di-prenylate benzophenones depending on the reaction conditions.

Since the use of DBU restrict the reaction to *C*-prenylation only, we chose to use a harder base to achieve an *O*-prenylation.[23,24] For *O*-prenylation reactions, a mono-prenylated benzophenone **7c** was reacted with 1.2 equivalence of prenyl bromide (**6**) in the presence of K_2CO_3 under acetone-reflux (Table 3, entry 1). This reaction resulted in the formation of two products (**11c** and **12c**). The structure elucidation of compound **12c** clearly indicated that both *C*- and *O*-prenylation had taken place during the reaction. A geranylation reaction of **8d** under the same conditions formed a similar type of products (**11d′** and **12d′**) (Table 3, entry 3). These geranylated benzophenones were isolated by rotatory thin-layer chromatotron using solvent system that is dominated by non-polar solvent as eluent (e.g.,

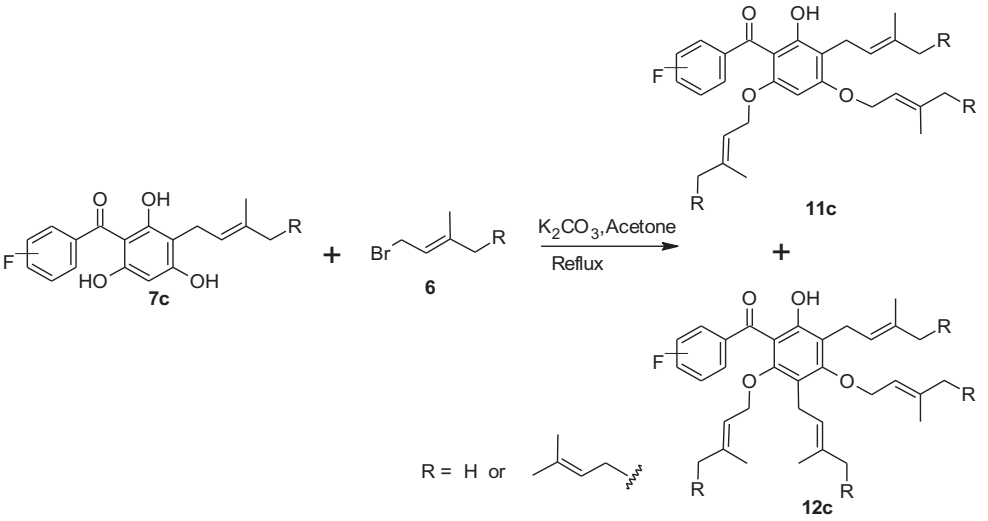
Table 2. Synthesis of di-*C*-prenylated benzophenones[a].



Entry	5	6	Product	Yield[b] (%)
1	**5a**	Prenyl-Br	**7a** (R = H)	13
			9a (R = H)	48
2	**5c**	Prenyl-Br	**7c** (R= 3-F)	16
			9c (R= 3-F)	46
3	**5c**	Geranyl-Br	**8c** (R= 3-F)	5
			10c (R= 3-F)	16
4	**5d**	Prenyl-Br	**7d** (R= 4-F)	18
			9d (R= 4-F)	47
5	**5d**	Geranyl-Br	**8d** (R= 4-F)	7
			10d (R= 4-F)	16

[a]All reactions were run in THF (10 mL), 24 h.
[b]Isolated yields.

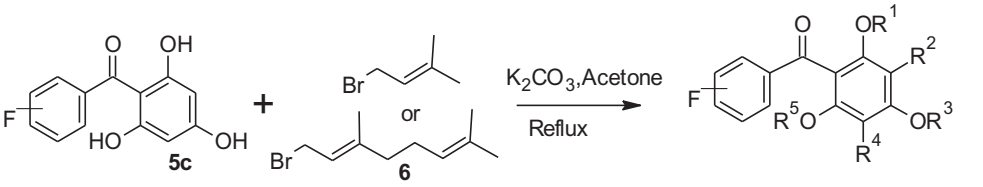
Table 3. *O*-prenylation reactions of mono-prenylated benzophenones[a].



Entry	7/8	6	R	Products (Yield[b])
1	**7c** (3-F)	Prenyl-Br	H	**11c** (82%) + **12c** (18%)
2	**7d** (4-F)	Prenyl-Br	H	**11d** (81%) + **12d** (19%)
3	**8d** (4-F)	Geranyl-Br	Prenyl	**11d′** (83%) + **12d′** (13%)

[a]All reactions were run at 1:1.2 ratio of **7**:**6**, acetone (10 mL), 2 h.
[b]Relative yields at 100% conversion of the starting material.

Table 4. Prenylation of benzophenones under K_2CO_3[a].



Entry	5	6	Products (Yield[b])
1	**5c** (3-F)	Prenyl-Br	**13c** (R^1=R^2=R^4=H, R^3=R^5=prenyl) + **14c** (R^2=R^4=H, R^1=R^3=R^5=prenyl) + **11c** + **12c**
2	**5d** (4-F)	Prenyl-Br	**13d** (R^1=R^2=R^4=H, R^3=R^5=prenyl) + **14d** (R^1=R^2=H, R^3=R^4=R^5=prenyl) + **11d** + **12d**
3	**5d** (4-F)	Geranyl-Br	**13d′** (R^1=R^2=R^4=H, R^3=R^5=geranyl) + **14d′** (R^2=R^4=H, R^1=R^3=R^5=geranyl) + **11d′** + **12d′**

[a]All reactions were run at 1:1.5 ratio of 5:6, acetone (10 mL), 2 h.
[b]Relative yields at 100% conversion of the starting material.

hexane:ethylacetate, 5:1). NMR and mass spectra were used to elucidate the structure of the *O*-prenylated benzophenones (spectral data found in the supplementary file).

When a non-prenylated benzophenone **5c** was subjected to a prenylation reaction under K_2CO_3, four products (**11c**, **12c**, **13c** and **14c**) were isolated (Table 4, entry 1). The structure of these compounds were elucidated and the findings showed that the reaction underwent both *O*-prenylation and *C*-prenylation. A 4-fluoro benzophenone derivative (**5d**) was also prenylated under similar conditions and four products were isolated (Table 4, entry 2). Geranylation of **5d** under similar conditions resulted in the isolation of four compounds (Table 4, entry 3).

Conclusion

In conclusion, we have developed an effective route to synthesize fluorine-containing prenylated benzophenones. This method does not involve harsh conditions and gives the products in moderate yields and is expected to be a useful synthetic method for a wide range of novel compounds. The key reaction steps of this synthesis were the Friedel–Crafts acylation and prenylation steps. In general, *C*-prenylation of the benzophenones was obtained when DBU was used as a base, whereas the use of K_2CO_3 as a base resulted in *O*-prenylation.

Experimental

General

Qualitative thin-layer chromatography (TLC) was used to monitor reactions. TLC plates (Merck Kieselgel 60_{254} aluminum backed) were bought ready for use. Visualization of

the TLC plates was achieved using an iodine tank and/or fluorescence on exposure to short wavelength ultraviolet light (254 nm). For purification, centrifugal chromatography was conducted on a Harrison Research Chromatotron model 7924 T on glass plates coated with Merck silica gel (particle size 0.040–0.063 mm), 1–4 mm thick.

Melting points (mp) were determined using a Stuart melting point apparatus with open-ended capillary tubes and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz UltraShield spectrometer at frequencies of 399.995 MHz and 100.4296 MHz for proton (^{1}H) and carbon (^{13}C), respectively. Infrared (IR) spectra were recorded on a Perkin Elmer spectrometer (FTIR Spectrum 100) as neat solid or liquid samples. High-resolution mass spectrometry (HRMS) was performed on a Waters LCT Premier time-of-flight mass spectrometer.

Synthesis

Phenyl(2,4,6-trimethoxyphenyl)methanone (4a)

Benzoyl chloride (1.1 g, 7.8 mmol) was added dropwise to an ice-cooled stirred mixture of $AlCl_3$ (1.0 g, 7.8 mmol) in DCM (20 mL). After being stirred at 0 °C for 1 h, the reaction mixture was added slowly to a solution of 1,3,5-trimethoxybenzene (0.5 g, 7.8 mmol) in DCM (15 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for further 12 h. An ice-cooled 6 mol/L HCl (20 mL) was poured slowly into the reaction mixture and DCM (20 mL) was also added into the mixture. The organic layer was separated and washed with saturated $NaHCO_3$ solution (15 mL), water (20 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The resulting product was purified by silica gel column chromatography (hexanes:EtOAc, 7:3) to give **4a** as a white solid (1.9 g, 7.0 mmol, 90%). After recrystallization (Hexanes:EtOAc, 9:1), **4a** was obtained as colorless crystals, mp 113–115 °C (lit.[15] 113–114 °C); TLC R_f 0.35 (Hexanes:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (6H, s), 3.84 (3H, s), 6.16 (2H, s), 7.39 (2H, t, $J = 7.9$ Hz), 7.50 (1H, tt, $J = 7.9$, 1.3 Hz), 7.82 (2H, dd, $J = 7.9$, 1.3 Hz). 13C NMR (100 MHz, $CDCl_3$): δ 55.7, 56.1 (2×), 91.0 (2×), 111.3, 128.5 (2×), 129.6 (2×), 133.1, 138.5, 159.0 (2×), 162.7, 195.2; HRMS (ESI$^+$): Found $[M + Na]^+$ 295.0945, Calc. for $C_{16}H_{16}NaO_4$ 295.0946; IR (neat) ν_{max} (cm^{-1}) 3053, 2949, 1660, 1599, 1583, 1453, 1123.

Phenyl(2,4,6-trihydroxyphenyl)methanone (5a)

To a stirring solution of phenyl(2,4,6-trimethoxyphenyl)methanone (1.6 g, 6.0 mmol) in DCM (30 ml) at –78 °C was added boron tribromide (3 ml). The temperature of the reaction mixture was allowed to reach the room temperature slowly. After being stirred for 24 h at room temperature, the reaction mixture was cooled to 0 °C and quenched with water. DCM (15 ml) was added into a stirring mixture. A clear liquid was decanted off the mixture and the residue was washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 40% EtOAc in hexanes as eluent and **5a** was obtained a light yellow crystalline solid (1.4 g, 5.9 mmol, 99%), mp 168–170 °C (lit.[12] 168–170 °C); TLC R_f 0.52 (Hexanes:EtOAc, 3:2); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.84 (2H, s), 7.43 (2H, t, $J = 7.9$), 7.53 (1H, tt, $J = 7.9$, 1.3), 7.62 (2H, dd,

$J = 7.9$, 1.3), 9.82 (1H, bs), 10.08 (2H, bs). 13C NMR (100 MHz, DMSO-d_6): δ 94.8 (2×), 106.0, 128.6 (2×), 128.9 (2×), 132.1, 140.2, 159.8 (2×), 162.3, 196.9; HRMS (ESI^-): Found $[M - H]^-$ 229.0497, Calc. for $C_{13}H_9O_4$ 229.0501; IR (neat) ν_{max} (cm^{-1}): 3621, 1625, 1598, 1543, 1319.

Phenyl[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl] methanone (7a)

To a mixture of phenyl(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 ml) was added a prenyl bromide (0.179 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 24 h. After addition of 2 M HCl (30 ml), the mixture was stirred for a further 15 min and extracted with EtOAc (4 × 20 ml), washed with brine (30 ml) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vavuo* resulted in a light orange product. After purification by the silica gel column chromatography (Hexanes:EtOAc, 4:1), **7a** was obtained as a light orange semisolid (0.222 g, 0.744 mmol, 62%); TLC R_f 0.54 (Hexanes:EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76 (3H, d, $J = 1.1$), 1.80 (3H, s), 3.36 (2H, d, $J = 7.0$), 5.26 (1H, m), 5.93 (2H, s), 6.15 (1H, bs), 7.51 (2H, dd, $J = 8.1$, 7.5), 7.58 (1H, tt, $J = 7.5$, 1.5), 7.64 (2H, dd, $J = 8.1$,1.5), 10.29 (1H, bs). 13C NMR (100 MHz, $CDCl_3$): δ 17.9, 21.7, 25.8, 96.2, 104.6, 106.6, 121.6, 127.8 (2×), 129.2 (2×), 132.2, 135.4, 140.0, 159.4, 160.8, 162.6, 197.7; HRMS (ESI^-): Found $[M - H]^-$ 297.1130, Calc. for $C_{18}H_{17}O_4$ 297.1127; IR (neat) ν_{max} (cm^{-1}): 3523, 3023, 2953, 1652, 1594, 1577, 1420, 1111.

Phenyl[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (9a)

To a mixture of phenyl(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.366 g, 2.4 mmol) in dry THF (15 ml) was added a prenyl bromide (0.358 g, 2.4 mmol) in small increments. The temperature of the reaction mixture was increased to 45 °C and stirred for 24 h. After the temperature of the mixture was reduced to room temperature, a 2 M HCl (20 mL) was added to the mixture, it was stirred for a further 15 min and extracted with EtOAc (4 × 20 mL), washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes:EtOAc, 4:1), **9a** was obtained as a light orange semisolid (48%); TLC R_f 0.85 (Hexanes:EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (6H, d, $J = 1.1$), 1.79 (6H, s), 3.34 (4H, d, $J = 7.1$), 5.22 (2H, m), 6.35 (1H, bs), 7.50 (2H, dd, $J = 8.0$, 7.7), 7.57 (1H, tt, $J = 7.7$, 1.5), 7.64 (2H, dd, $J = 8.0$, 1.5), 8.91 (2H, bs). 13C NMR (100 MHz, $CDCl_3$): δ 17.6 (2×), 21.8 (2×), 26.0 (2×), 104.6, 106.3 (2×), 121.9 (2×),127.8 (2×), 129.2 (2×), 132.2, 135.4 (2×), 140.0, 157.5 (2×), 161.0, 198.0; HRMS (ESI^+): Found $[M + Na]^+$ 389.1723, Calc. for $C_{23}H_{26}NaO_4$ 389.1729; IR (neat) ν_{max} (cm^{-1}): 3512, 3023, 2942, 1632, 1586, 1566, 1443, 1121.

Full experimental detail, characterization data for all compounds and 1H and ^{13}C NMR spectra. This material can be found via the "Supplementary materail" section of this article's webpage.

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