Synthesis of triprenylated toluquinone and toluhydroquinone metabolites from a marine-derived *Penicillium* fungus

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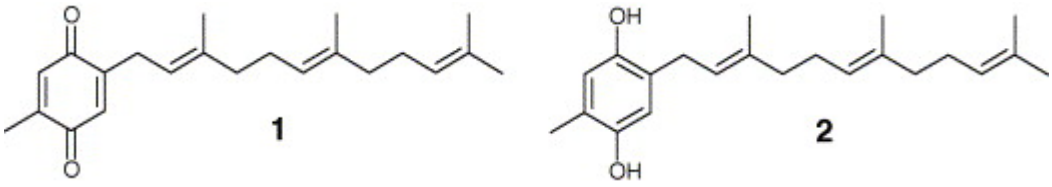
Abstract

Two triprenylated toluquinone and toluhydroquinone marine fungal metabolites, 5-methyl-2-[(2′*E*,6′*E*)-3′,7′,11′-trimethyl-2′,6′,10′-dodecatrienyl]-2,5-cyclohexadiene-1,4-dione and 5-methyl-2-[(2′*E*,6′*E*)-3,7,11-trimethyl-2′,6′,10′-dodecatrienyl]-1,4-benzenediol, were synthesized in four and five steps, respectively, from 2-methyl-1,4-benzoquinone. The synthesis extends the applicability of the oxidative ether cleavage of hydroquinone dimethyl ethers with argentic oxide under acidic conditions to include the oxidative demethylation of polyprenylated-1,4-dimethoxy-toluhydroquinones with a quantitative survival of the oxidation- and acid-sensitive polyprenyl side chain.

Graphical abstract

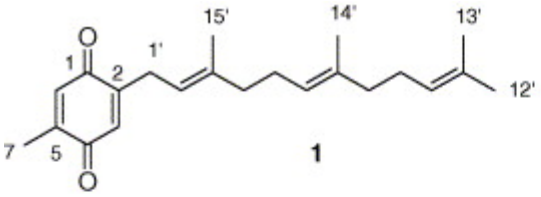
Marine fungal metabolites **1** and **2** were synthesized from 2-methyl-1,4-benzoquinone in four and five steps, respectively.



Keywords: *Penicillium*; Marine fungus; Triprenyl; Toluhydroquinone; Toluquinone

Triprenylated toluquinone and toluhydroquinone secondary metabolites have been isolated from both marine and terrestrial fungi. A marine derived *Penicillium* species afforded 5-methyl-2-[(2′*E*,6′*E*)-3′,7′,11′-trimethyl-2′,6′,10′-dodecatrienyl]-2,5-cyclohexadiene-1,4-dione **1** and 5-methyl-2-[(2′*E*,6′*E*)-3,7,11-trimethyl-2′,6′,10′-dodecatrienyl]-1,4-benzenediol **2**,[1 and 2] while grifolin **3** and neogrifilin **4**, isomeric with **2**, were obtained from the inedible mushroom *Albatrellus caeruleoporus*.[3] Compound **1** is

not confined to the marine environment and has also been isolated from *Phellinus pini*, a terrestrial fungus pathogenic to conifer trees,[4] and from three species of the terrestrial plant genus *Seseli*.[5] Oxygenation within the triprenyl side chain is a common structural feature in naturally occurring prenylated quinones and hydroquinones, for example, *A. caeuuleoporus* is also the source of grifolinone **5**,[3] while the South African marine nudibranch *Leminda millecra* has yielded **6** and several other metabolites related to **1** and **2**.[6] The diverse biological activities associated with this cohort of compounds, including radical scavenging,[1] cytotoxicity,[2] and potential anti-inflammatory properties,[3] prompted us to explore the use of metal halogen exchange (MHE) methodology for the syntheses of **1** and **2**.



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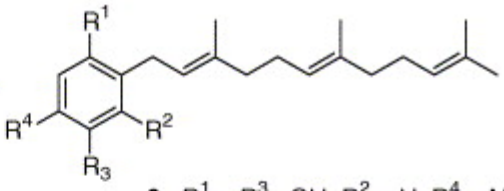
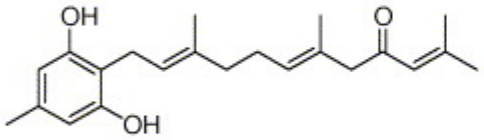


2 $R^1 = R^3 = OH$, $R^2 = H$, $R^4 = Me$
3 $R^1 = R^2 = OH$, $R^3 = H$, $R^4 = Me$
4 $R^1 = Me$, $R^2 = R^4 = OH$, $R^3 = H$



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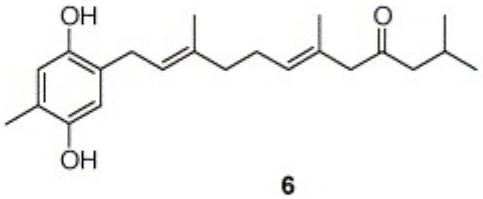

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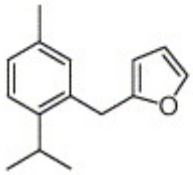

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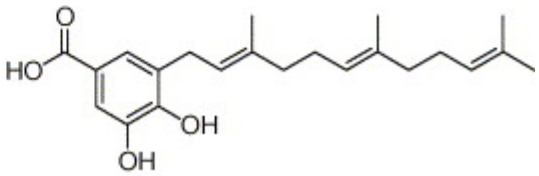

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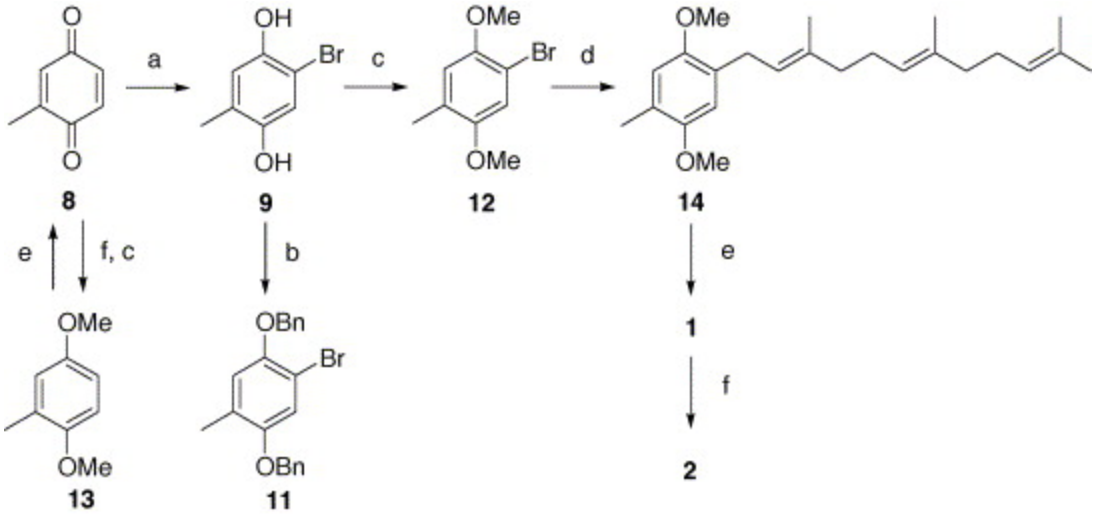
Bohlmann et al. briefly reported the isolation of **1** via distillation following the MnO_2 oxidation of the product mixture obtained from the reaction of farnesol with 1,4-dihydroxytoluene, in the presence of a BF_3-etherate Lewis acid catalyst.[5] No discussion was presented of either the regioselectivity, if any, of this reaction or, in the absence of this discussion a quantification of the yields of the plethora of different regioisomers and polyprenylation products, which could reasonably be expected from this Friedel–Crafts type alkylation reaction involving such a highly activated aromatic precursor. We therefore opted for a different approach as our primary goal was to find a regiospecific route to **1** and **2**, which we could readily exploit for the synthesis of other prenylated quinones and hydroquinones. Several strategies are available for the regioselective

synthesis of *ortho*-prenylated phenols including Claisen rearrangements, directed *ortho*-metallation (D*o*M), metal mediated coupling, and MHE.[7] The latter approach attracted us given our previous successful use of MHE methodology to synthesize the marine natural product tsitsikammafuran **7**.[8] The success of the MHE approach initially requires the availability of a suitably halogenated, aryl precursor.[7] Accordingly, the regiospecific reductive bromination of 2-methyl-1,4-benzoquinone **8**, originally reported by Miller and Stewart,[9] proceeded smoothly in our hands to give 2-bromo-5-methyl-1,4-benzenediol **9**. The appropriate protection of the phenolic functionalities in **9** and subsequent coupling of the organolithium reagent derived from protected **9** to a prenyl electrophile, for example, farnesyl bromide followed by deprotection appeared to be a feasible regiospecific route to **2** (Scheme 1).



Scheme 1. Synthesis of triprenyl toluquinone **1** and triprenyl toluhydroquinone **2** from 2-methyl-1,4-benzoquinone **8**. Reagents and conditions: (a) Me_3SiBr, Et_4NBF_4, MeCN, RT (61%); (b) $PhCH_2Br$, K_2CO_3, NaI, Ac_2O, reflux (80%); (c) NaOH, Me_2SO_4, reflux (70%); (d) TMEDA, *n*-BuLi, farnesyl bromide, Et_2O 0 °C (27%); (e) AgO, dioxane, HNO_3, rt (98%); (f) $Na_2S_2O_4$, 1:3 DCM/Et_2O, rt (98%).

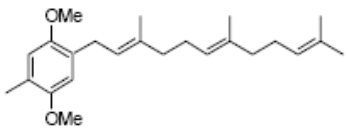
Our choice of a convenient phenol protection/deprotection strategy was guided by the need to ensure that first, the protecting group was unaffected by the initial strongly basic environment necessary for MHE, and that second, the reaction conditions required for deprotection were compatible with the unsaturated triprenylated side chain. Thus esters, which can be deprotonated by *n*-BuLi, and silyl ethers, which may undergo a retro-Brook rearrangement,[10 and 11] were rejected in favor of aryloxy ether protection. Recently, Odejinmi and Wiemer drew attention to the suitability of benzyl protection in their synthesis of the *E*,*E*-isomer of piperoic acid **10** also via an MHE strategy.[11] Odejinmi and Wiemer's benzyl protection was particularly attractive because the olefins of the farnesyl side chain were immune to the mild deprotection conditions used (heating with sodium metal). Regrettably, our attempts to couple the organolithium reagent derived from the benzylated precursor **11** to prenyl bromides, using the same MHE protocol reported by Odejinmi and Wiemer for the preparation of **10**, were unsuccessful.

Following this initial setback we turned to the possibility of protecting **9** as dimethyl ether **12** prior to the MHE step. Although we recognized at the outset that the prenyl side chain in **2** would possibly not survive the harsh Lewis acid-mediated conditions commonly used for the efficient O-demethylation of phenyl methyl ethers, we were encouraged by several reports in which milder conditions had been used successfully to accomplish this transformation in selected examples, for example, deprotection with L-Selectride,[12] trimethylsilyl iodide,[13] and an intriguing 'phase vanishing' reaction using perfluorohexane as a phase screen and boron tribromide as the dealkylating agent.[14] In addition, an alternative approach to direct demethylation is the oxidative demethylation of 1,4-dimethoxyhydroquinones to yield 1,4-benzoquinones.[15 and 16] After preliminary deprotection studies on the simple toluhydroquinone dimethyl ether **13**, we opted for the simple oxidative cleavage approach of Snyder and Rapoport,[15] in which 1,4-hydroquinone dimethyl ethers are efficiently cleaved with argentic oxide[17] to afford 1,4-benzoquinones. Despite the strongly acidic conditions required for this transformation, we surmised that given the short length of time (<2 min) that a 1,4-dioxane solution of the prenylated toluhydroquinone would be stirred with a 6 N nitric acid solution of argentic oxide, it would be unlikely that the prenyl side chain would be adversely affected. We accordingly methylated **9** with dimethyl sulfate in the usual manner to give **12** and were subsequently able to successfully couple the organolithium reagent derived from this compound with farnesyl bromide to afford **14** in a moderate yield.[18] It is important to note that the coupling could only be achieved in dry diethyl ether solutions at 0 °C in the presence of TMEDA (1.5 equiv) and all attempts to carry out this reaction in dry THF at various temperatures and different concentrations of either CuBr·DMS or TMEDA were unsuccessful. Interestingly, Odejinmi and Wiemer also found THF to be an unsuitable solvent for MHE and subsequent prenylation during their synthesis of **10**.[11]

As hoped, the oxidative demethylation of **14** proceeded quantitatively to afford **1**.[19] The absence of any cyclization, oxidation or acid-induced degradation of the triprenyl side chain during the argentic oxide mediated oxidative demethylation of **14** suggests that Snyder and Rapoport's[15] methyl ether protection/oxidative deprotection strategy might find wide applicability to the synthesis of other prenylated 1,4-toluquinones. The reduction of **1** with sodium dithionite[20] gave **2** in a quantitative yield and the spectroscopic data of both compounds were consistent with literature values reported for these two compounds.[1, 2, 4 and 5]

SUPPLEMENTARY DATA

The ^{1}H NMR spectrum of compound **14** ($CDCl_3$, 400 MHz)



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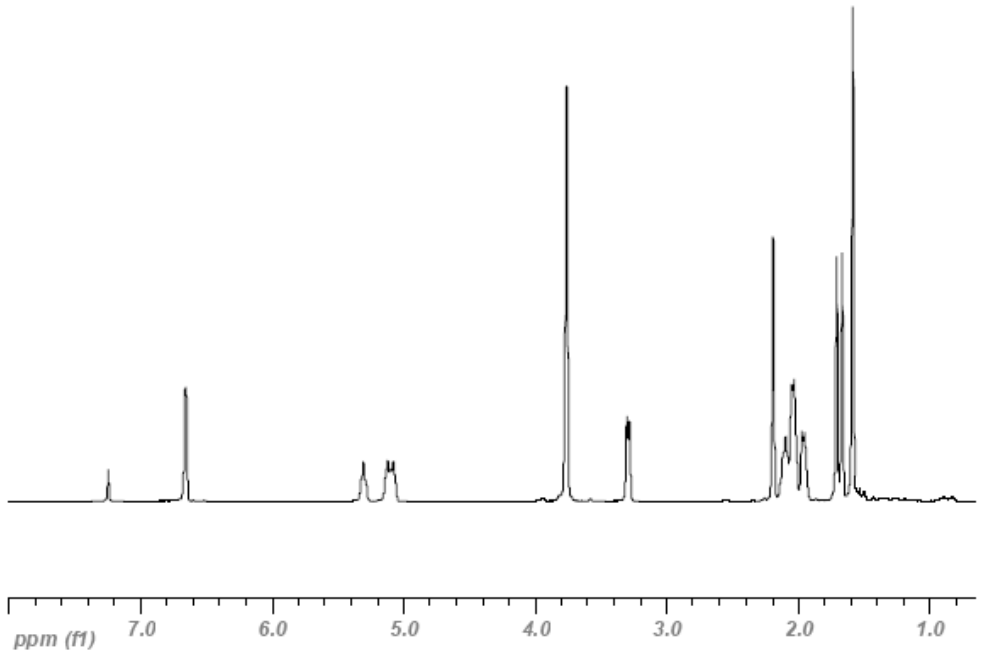
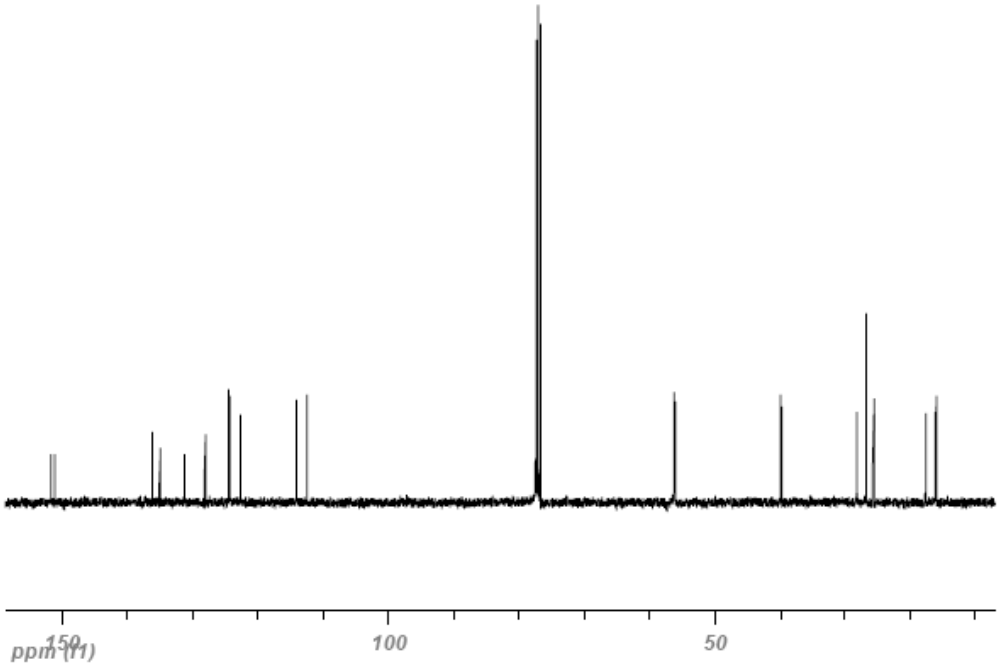
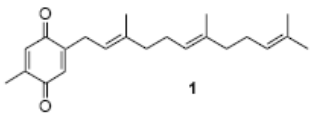


The ^{13}C NMR spectrum of compound **14** ($CDCl_3$, 100 MHz)



The ^{1}H NMR spectrum of compound **1** ($CDCl_3$, 400 MHz)



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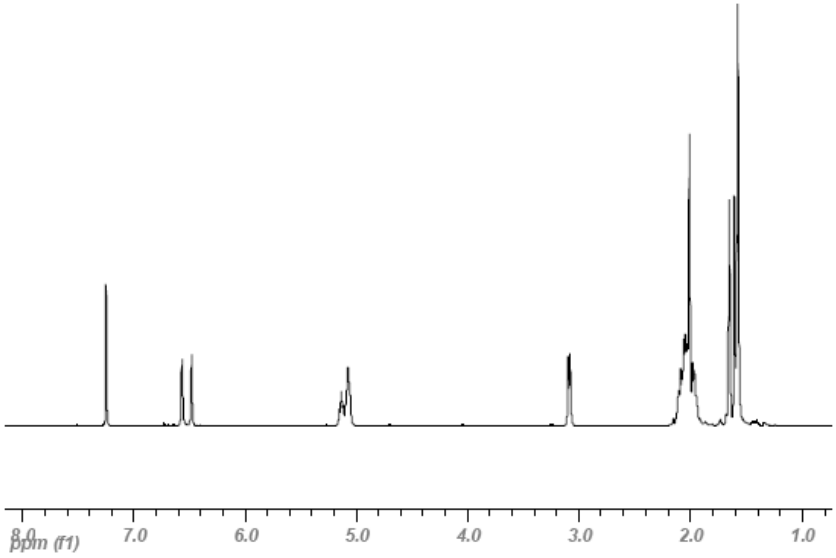
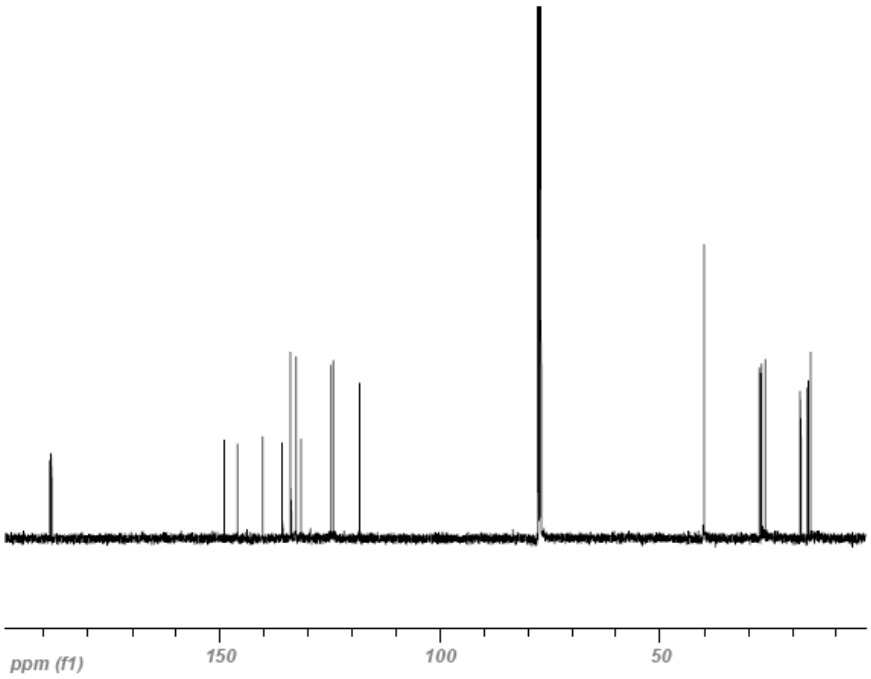
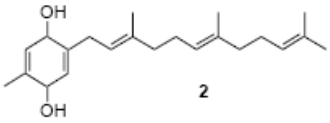


The ^{13}C NMR spectrum of compound **1** ($CDCl_3$, 100 MHz)



The ^{1}H NMR spectrum of compound **2** ($CDCl_3$, 400 MHz) Note: There is some residual diethylether evident in the spectrum.



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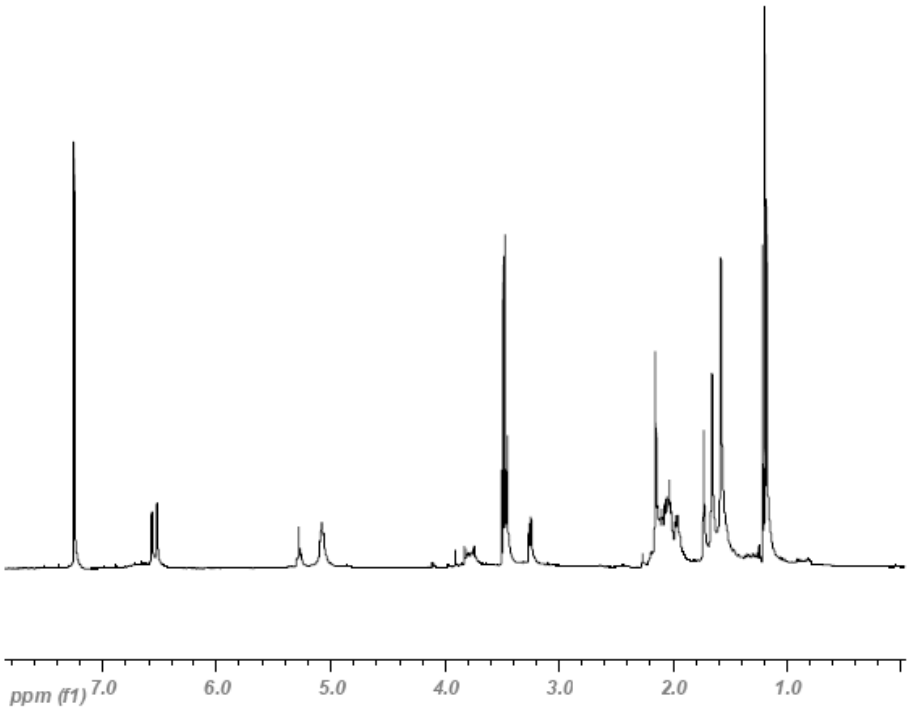
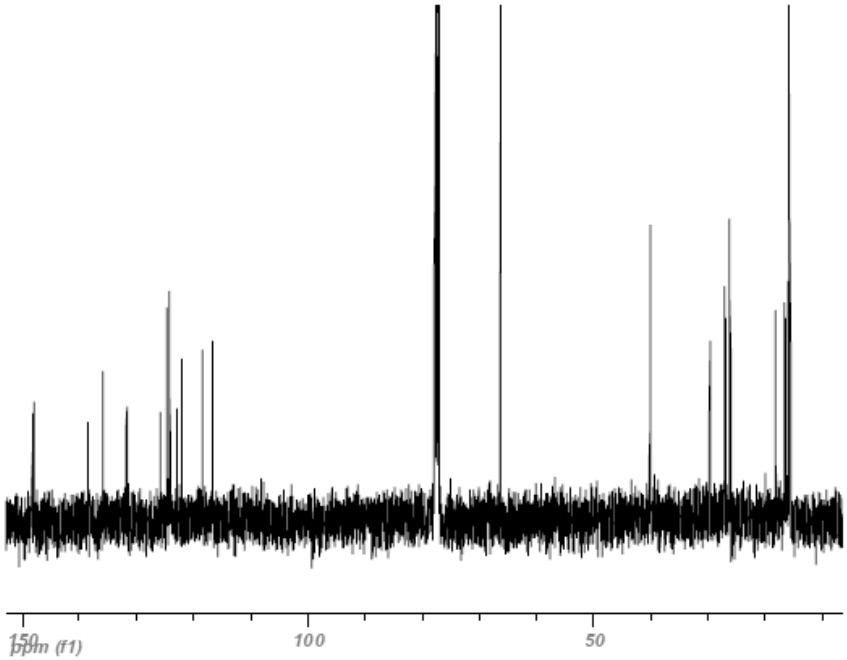


The ^{13}C NMR spectrum of compound **2** ($CDCl_3$, 100 MHz) Note: There is some residual diethylether evident in the spectrum.



Acknowledgments

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18

Preparation of **14**. A solution of **12** (309 mg, 1.34 mmol), TMEDA (0.30 mL, 2 mmol) and *n*-BuLi (2 mmol) in dry Et_2O (2 mL) was stirred (15 min) at 0 °C before the addition of farnesyl bromide (0.36 mL, 1.34 mmol). The solution was allowed to stir overnight and the reaction was finally quenched with satd NH_4Cl (5 mL) and extracted with ether (2 × 5 mL). The Et_2O fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Normal phase HPLC (10 hexane:1 EtOAc) purification of the product mixture afforded **14** (0.129 g) as a yellow oil. UV (MeOH) λ_{max} 290 (ε 2487), 230 (ε 3305) nm; ^{13}C NMR (100 MHz, $CDCl_3$) 151.6 (C-4), 151.0 (C-1), 136.1 (C-3′), 135.0 (C-7′), 131.2 (C-11′), 128.0 (C-2), 124.4 (C-6′ and C-10′), 124.2 (C-5), 122.7 (C-2′), 114.1 (C-6), 112.4 (C-3), 56.3 (OMe), 56.1 (OMe), 39.8 (C-4′), 39.7 (C-8′), 28.2 (C-1′), 26.8 (C-5′ and C-9′), 25.7 (C-12′), 17.7 (C-13′), 16.1 (C-15′ and C-14′), 16.0 (C-7); ^{1}H NMR (400 MHz, $CDCl_3$) 6.67 (s, 1H, H-6), 6.66 (s, 1H, H-3), 5.31 (t, *J* 7.23, 1H, H-2′), 5.13 (t, *J* 6.51, 1H, H-6′) 5.09 (t, *J* 6.51, 1H, H-10′), 3.77 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.30 (d, *J* 7.21, 1H, H-1′), 2.20 (s, 3H, 3H-7), 2.05 (m, 8H, 2H-4′, 2H-8′, 2H-5′ and 2H-9′), 1.71 (s, 3H, 3H-15′), 1.67 (s, 3H, 3H-12′), 1.60 (s, 3H, 3H-13′), 1.59 (s, 3H, 3H-14′); HRFABMS [M^+] 356.2714 (calcd for $C_{24}H_{36}O_2$ 356.2715).

19

Oxidative demethylation of **14**. A solution of **14** (190 mg, 0.53 mmol), freshly prepared AgO[17] (71 mg, 0.58 mmol) and dry 1,4-dioxane (2 mL) was briefly sonicated to obtain a uniform distribution of the oxidant. 6 N HNO_3 (0.2 mL) was added with stirring and the reaction mixture allowed to proceed until most of the AgO had been consumed (<2 min). The reaction was quenched by the addition of $CHCl_3$–H_2O (10 mL, 4:1). The $CHCl_3$ fraction was separated, washed with H_2O (3 × 4 mL) to remove excess acid, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give **1** as a bright yellow oil (170 mg). UV, ^{1}H and ^{13}C NMR data was consistent with published values.[5, 6, 7 and 8] HRFABMS [M+H]$^+$ 327.2323 (calcd for $C_{22}H_{31}O_2$ 327.2324).

20

Reduction of **1**. A solution of **1** (87 mg, 0.27 mmol) in a mixture (1:3) of DCM–Et_2O (4 mL) was shaken (5 min) with a freshly prepared solution of sodium dithionite (330 mg, 1.89 mmol) in H_2O (4 mL). The organic layer was separated, washed with brine (2 × 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give **2** as a brown oil (80 mg). UV, ^{1}H and ^{13}C NMR data was consistent with published values.[5, 6, 7 and 8] HRFABMS [M^+] 328.2403 (calcd for $C_{22}H_{32}O_2$ 328.2402).