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Article

Preparation of Aromatic Geraniol Analogues *via* a Cu(I)-Mediated Grignard Coupling

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Terpenos alílicos difuncionais constituem-se em importantes blocos de construção sintéticos. A funcionalização de derivados geranílicos protegidos por SeO_2/*t*-BuO_2H adsorvido em SiO_2, propicia uma rota conveniente para tais compostos. Os grupos protetores escolhidos efetivamente influenciam o processo de oxidação. Também, desenvolveu-se uma eficiente síntese de derivados 2-geranilfenóis através de um acoplamento de Grignard mediado por Cu(I) entre derivados de 2-lítiofenóis e substratos geranílicos.

Difunctional allylic terpenes are important synthetic building blocks. Functionalization of protected geranyl derivatives by SeO_2/*t*-BuO_2H adsorbed on SiO_2 provides a convenient route to such compounds. The chosen protecting groups clearly influence the oxidation process. Also, an efficient synthesis of 2-geranylphenol derivatives *via* a Cu(I)-mediated Grignard coupling of 2-lithiophenols and geranyl substrates was developed.

Keywords: allylic oxidation, selenium dioxide, homoallylic alcohols, Grignard coupling, 2-geranylphenols

Introduction

A wide variety of phenolic natural products contain isoprenoid residues.[1] It has been suggested that the biosynthetic origin of phenolic isoprenoids involves initial *C*-alkylation of a preformed phenol or its poly-β-ketonic precursor by an active isoprenoid allylic alcohol derivative.[2] For example, *C*-geranyl compounds may arise by nucleophilic attack of a phenol on the resonance stabilized allylic cation or by an S_N2-type displacement of pyrophosphate from geranylpyrophosphate.

C-geranyl and *C*-farnesyl phenols have been prepared by reaction of geranyl or farnesyl bromide with the sodium salt of the phenol. Alkylation of sodium salts, however, invariably leads to complex mixtures containing both ring and oxygen substituted products.[3] *C*-alkylation has been obtained by acid-catalyzed condensation of geraniol or farnesol with phenols in aprotic solvents in the presence of Lewis acids,[4] mineral acids such as *p*-toluenesulfonic acid,[5] Friedel-Crafts alkylation,[6] copper-induced isomerization to 2-alkenyl 2-lithiophenyl ethers,[7] or Cu(I)-mediated Grignard coupling of THP ethers.[8] As part of our continuing interest in phenolic oxidative coupling mediated for iodine hypervalent reagents,[9] we describe the preparation of 2-geranylphenolic intermediates that will be necessary for future studies on synthesis of cyclic isoprenoids.

Results and Discussion

The Sharpless conditions for oxidation of geranyl acetate employs 0.5 equiv. of SeO_2 and 2 equiv. of *t*-BuO_2H, and the reaction was complete after 8 h[10] with formation of colloidal selenium by-products in small amounts that were difficult to eliminate after column chromatography or distillation. Using lower molar quantities of SeO_2 should reduce selenium by-products, facilitating the purification of selenium-free products. Our efforts with 1-2 mol% of SeO_2, reproducing literature conditions of these reactions, failed to proceed to completion.[11] Very recently, improvement of the oxidation procedure using 5 mol% of SeO_2 and 3.6 equiv. of *t*-BuO_2H led to complete consumption of the geranyl acetate, giving allylic alcohol (43%) and aldehyde (9%) in 52% yield.[12] We were able to improve those conditions and obtain complete conversion of geranyl acetate after 24 h at room temperature into alcohol **2** and aldehyde **3** in 70% and 30% yield, respectively (Table 1, entry 1). By making certain changes in above methods and employing SeO_2/*t*-BuO_2H adsorbed on silica gel, Chhabra *et al.* found this to be a highly selective reagent for the oxidation of allylic methyl

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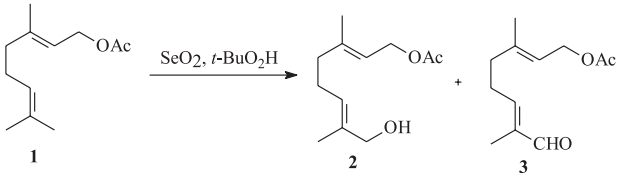
This paper is dedicated to Prof. Albert J. Kascheres on occasion of his 60th birthday

Table 1. Procedures used for oxidation of geranyl acetate

Entry	Reagents	**2** (%)[a]	**3** (%)[a]	Yield (%)[b]
1	SeO_2, *t*-BuO_2H, CH_2Cl_2, rt, 24 h	70	30	-
2	SeO_2 / SiO_2, *t*-BuO_2H, CH_2Cl_2, rt, 24 h	75	25	75 (**2**)
3	SeO_2 / SiO_2, *t*-BuO_2H, microwave, 10 min	-	-	75 (**3**)

[a] quantified by gas chromatography; [b] isolated yield.

groups.[13] In our hands, this methodology (SeO_2/SiO_2, 10% m/m, dichloromethane as solvent) gave after 24h at room temperature a 75% yield of **2** and a 25% yield of **3**, but the reaction was cleaner without by-products of organo-selenium and the work up was carried out easier (entry 2). The crude mixture was reduced with $NaBH_4$/EtOH to give the alcohol **2** in 75% after the two steps.

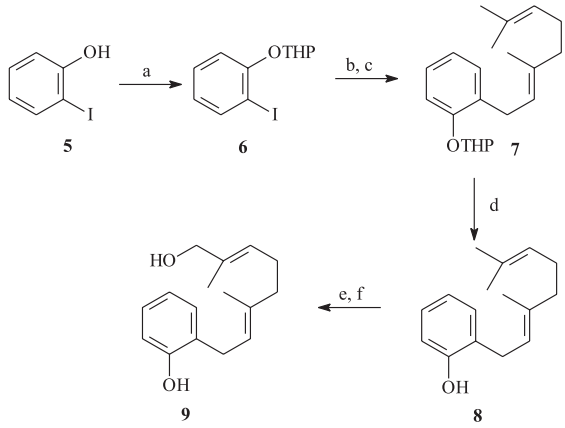


Scheme 1. Allylic methyl oxidation of geranyl acetate.

Singh *et al.* observed a faster reaction when SeO_2 and *t*-BuO_2H were adsorbed on silicagel without solvents and exposed to microwave irradiation for the oxidation of allylic methyl groups.[14] Using this condition for the oxidation of geranyl acetate, with 10 min of microwave irradiation (640 W), we obtained exclusively the aldehyde **3**. The reduction of crude mixture gave the alcohol **2** in 75% yield (Table 1, entry 3).

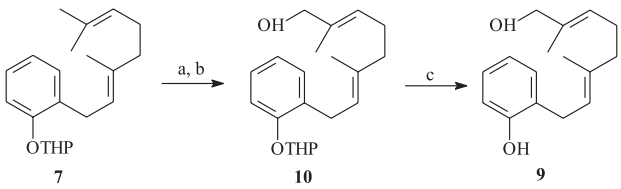
Geranyl bromide **4** was necessary in the next steps and its preparation (although it is commercially available) was achieved after some attempts in order to optimize the conditions for getting high yield. Bromination of geraniol[15] with phosphorus tribromide (0.5 equiv.) in hexane under argon at -30 °C followed by a slow increased of the temperature to -10 °C gave, after 45 min, pure geranyl bromide **4** in 98% yield.

Our target was to obtain 2-[(2*E*,6*E*)-3,7-dimethyl-8-hydroxy-2,6-octadienyl]phenol **9** by optimizing the coupling of geranyl acetate derivatives with more appropriate reagent *O*-protected 2-iodophenol. Scheme 2 shows the first attempt. Treating (2-iodophenyl)-2-tetrahydropyranyl ether **6** with butyllithium in THF-TMEDA at low temperature and then adding the geranyl bromide **4** gave the phenol derivative **7**, which was isolated after the usual work up in 95% yield. 2-Geranylphenol **8** was obtained in 93% yield after deprotection of precursor **7** with pyridinium *p*-toluenesulfonate (PPTS). This compound was identified by comparison of its NMR, IR and MS spectra with literature data.[16] Oxidation of the geranyl moiety with SeO_2/SiO_2, *t*-BuO_2H and then reduction with $NaBH_4$ of the intermediate aldehyde using the optimized protocol described above gave alcohol **9**, which was isolated in low yield (47%).



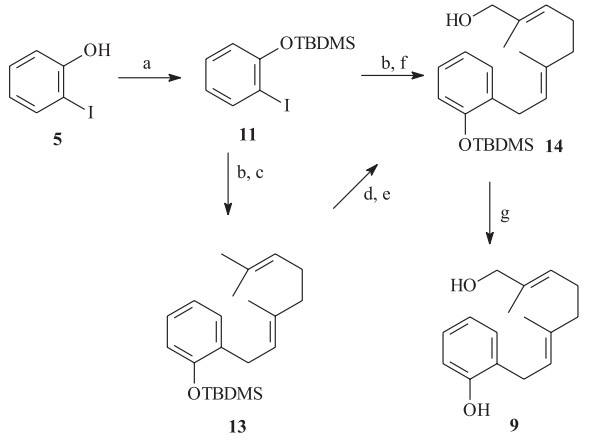
Scheme 2. (a) DHP (1.2 equiv.), PPTS (0.9 mmol%), CH_2Cl_2, Ar, 8 h, 95%. (b) *n*-BuLi, THF, TMEDA, -78 to -25 °C. (c) THF, -98 °C, geranyl bromide **4**, THF, -78 °C, two steps 95%. (d) MeOH, PPTS (0.9 mmol), 50 °C, 12h, 93%. (e) SeO_2/SiO_2 (10% m/m), *t*-BuO_2H (2 equiv.), CH_2Cl_2, 25 °C. (f) $NaBH_4$, THF (1/20 v/v), -10 °C, two steps 47%.

To improve the low yield that was obtained for the oxidation of **8**, we investigated a new route to reach **9**. Protected geranyl phenol **7** was oxidized under our optimized selenium oxide/silica gel and *t*-butylhydroperoxide methodology, and allylic alcohol **10** was obtained in 58% yield, a yield superior when compared with the sequence **8** to **9,** described earlier. After usual deprotection, phenol **9** was isolated in 92% yield (Scheme 3).



Scheme 3. (a) SeO_2/SiO_2 (10% m/m), *t*-BuO_2H (2 equiv.), CH_2Cl_2, 25 °C, 48 h. (b) $NaBH_4$, MeOH/THF (1/20, v/v), -10 °C, 20 min, two steps 58%. (c) MeOH, PPTS (0.9 mmol), 50 °C, 12 h, 92%.

A new sequence was investigated with another substrate in an attempt to improve the yield of the desired phenol-alcohol **9** (Scheme 4). Using a modified Mechelke-Wiemer protocol,[8] the transmetalation of the lithium derivative of the *O*-protected 2-iodophenol **11** with magnesium bromide was performed at low temperature to give the Grignard intermediate and then with CuI to afford the intermediate organocuprate which was alkylated with geranyl 2-tetrahydropyranyl ether **12** to give **13** in 88% yield. Oxidation of the geranyl moiety with SeO_2/SiO_2, *t*-BuO_2H and then with $NaBH_4$ reduction of the intermediate aldehyde using the optimized protocol described above gave the allylic alcohol **14** in 43% yield. This result was still not satisfactory so we tried a different approach. The *O*-protected 2-iodophenol **11** was treated with *n*-BuLi in THF at low temperature and then with $MgBr_2$. After allowing the reaction mixture to reach ambient temperature, CuI was added followed by the addition of allylic alcohol **2.** The reaction mixture was then heated to 50 °C and after usual work-up, monoterpenylphenol **9** was isolated with significative improvement of the overall yield (83% yield).



Scheme 4. (a) TBDMSCl (1.25 equiv.), Imidazole (1.5 equiv.), DMF, Ar, 0 °C then 25 °C, 12 h, 96%. (b) *n*-BuLi, THF, $MgBr_2$, -78 °C then 25 °C. (c) CuI, THF, (2*E*)-3,7-dimethyl-2,6-octadienyl tetrahydro-2*H*-2-pyranyl ether **12**, 25 °C then 50 °C, 88%. (d) SeO_2/SiO_2 (10% m/m), *t*-BuO_2H (2 equiv.), CH_2Cl_2, 25 °C, 48 h. (e) $NaBH_4$, MeOH/THF (1/20, v/v), -10 °C, 20 min, two steps 43%. (f) CuI, THF, (2*E*,6*E*)-8-hydroxy-3,7-dimethyl-2,6-octadienyl acetate **2**, 25 °C then 50 °C, 90%. (g) TBAF, THF, 30 °C, 1 h, 93%.

Conclusion

In brief, we optimized a selective oxidation of allylic methyl groups in geraniol derivatives over a solid support to the corresponding *trans*-α,β-unsaturated alcohols and aldehydes, using selenium dioxide and *t*-butylhydroperoxide adsorbed on silica gel as oxidants. The chosen protecting groups clearly influence the oxidation process. Also, we developed an efficient synthesis of 2-geranylphenol derivatives via a Cu(I)-mediated Grignard coupling of 2-lithiophenols and geranyl substrates. Further studies on phenolic oxidation of these synthetic intermediates to achieve the synthesis of cyclic isoprenoids will be reported in due course.

Experimental

The IR spectra were recorded on a Hartmann & Braun BOMEM MB SERIES spectrometer. The ^1H NMR and ^{13}C NMR were recorded on a VARIAN-INOVA spectrometer. Mass spectra were recorded on a SHIMADZU GC-MS QP 5000 gas chromatograph/mass spectrometer and with helium as carrier gas. A 30 m x 0.25 mm I.D. capillary column of fused silica, SUPELCO SIMPLICITY 1™, was used. An injector temperature of 230 °C and a detector temperature of 280 °C, with the column at 50 °C for 3 min; then using a rate of 20 °C min^{-1} up to 280 °C, with a pressure of 100 kPa and gas flow of 80 mL min^{-1}, was used. HMRS were obtained on a Fison VG Autospec. Preparative column chromatography was carried using silica gel 60 (Merck 7734, 70-230 mesh). Completion of the reactions was established by TLC analysis. Geraniol was purchased from Aldrich Chem. Co. (purity >98%), othres reagents were analytical (Aldrich or Acros) and we employed 230-400 mesh silica gel for flash chromatography.

*(2E,6E)-3,7-Dimethyl-8-hydroxy-2,6-octadienyl acetate (**2**)*

A suspension of selenium oxide (0.44 g, 5 mmol) and *t*-butylhydroperoxide (2.75 mL, 70% m/m, 20 mmol) in anhydrous dichloromethane (30 mL, ethanol free) was stirred for 20 min at room temperature and then silica gel (230-400 mesh, 5.55 g) was added. After 30 min the temperature was decreased to 0 °C and geranyl acetate (10 mmol) was slowly added. The mixture was stirred for 48 h. The solvent was stripped off until a yellow powder was obtained that was transferred to a fibrous glass frit Büchner funnel equipped with a layer of celite and neutral alumina, and washed with ethyl acetate/hexane (2/3, v/v, 3x50 mL). The extracts were washed with a saturated aqueous solution of $FeSO_4.2H_2O$ (3x30 mL), acidified with conc H_2SO_4, then washed with brine (2x30 mL) and dried with anhydrous $MgSO_4$. After the solvent was removed, the oily residue was dissolved in methanol/THF (1/20, v/v, 25 mL) while keeping the temperature at -10 °C (ice-water/NaCl bath 1:1, m/m) and then $NaBH_4$ was added (0.30 g, 80 mmol) in four portions. After 30 min, a cold saturated solution of NH_4Cl (30 mL)

was added, and the mixture was extracted with CH_2Cl_2 (3x30 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography eluting with AcOEt/hexane (3/7, v/v), to give pure **2** as an yellow oil (1.59 g, 75% yield); IR (film) ν_{max}/cm^{-1}: 3411, 2961, 2924, 2861, 1740, 1670, 1444, 1383, 1367, 1234, 1022, 954, 853, 608; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 5.30-5.40 (m, 2H), 4.58 (d, ^3J 7.0 Hz, 2H), 3.98 (s, 2H), 2.05-2.25 (m, 4H), 2.06 (s, 3H), 1.99 (s, 1H), 1.71 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 171.3, 141.8, 135.3, 125.2, 118.6, 68.6, 61.3, 38.9, 25.5, 20.8, 16.2, 13.4.

*(2E)-3,7-Dimethyl-2,6-octadienyl bromide (**4**)*

To stirred solution of 1.54 g of geraniol (10 mmol) in 10 mL of hexane at - 30 °C under argon, was added 0.49 mL of phosphorus tribromide (5 mmol, recently destilled) was added over a period of 20 min. The resulting solution was stirred at - 30 °C for 35 min. The mixture was treated drop wise with cold metanol (1 mL) and extracted with hexane. The organic extracts were washed with $NaHCO_3$ solution 5%, dried over $MgSO_4$ and concentrated to give a crude geranyl bromide (2.12 g, 98%). This was used without any purification; IR (film) ν_{max}/cm^{-1}: 2967, 2927, 2917, 2858, 1656, 1444, 1385, 1369, 1202, 1110, 840, 587.

*(2-iodophenyl)-2-tetrahydropyranyl ether (**6**)*

A solution of 2.2 g (10 mmol) of 2-iodophenol **5** in dichloromethane (10 mL) was stirred at room temperature under nitrogen and 23 mg (0.9 mmol%) of pyridinium *p*-toluenesulfonate was added, followed by drop wise addition of dihydropyran (1.13 mL, 12 mmol). The mixture was stirred at ambient temperature for 8 h and then diluted with 30 mL of ether. The organic layer was washed with two portions of brine then dried with anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash chromatography, eluting with AcOEt/hexane (1/19, v/v), to give 2.89 g (95%) of the tetrahydropyranyl ether **6** as an oil; IR (film) ν_{max}/cm^{-1}: 3060, 2943, 2872, 2851, 1582, 1471, 1439, 1356, 1275, 1240, 1202, 1123, 1036, 1018, 960, 920, 873, 749; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.76 (dd, ^3J 7,8 Hz, ^4J 1.5 Hz, 1H), 7.22-7.29 (m, 1H), 7.07 (dd, ^3J 8.2 Hz, ^4J 1.4 Hz, 1H); 6.68-6.75 (m, 1H), 5.53 (t, *J* 2,8 Hz, 1H), 3.87 (td, ^2J 11.3 Hz, ^3J 11.3 Hz, ^3J 2.8 Hz, 1H), 3.53-3.65 (m, 1H); 1.46-2.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 155.8, 139.5, 129.6, 123.5, 115.4, 96.6, 87.6, 61.8, 30.2, 25.3, 18.3; HRMS calcd. for $C_{11}H_{13}IO_2$, 303.99603; found. 304.00748.

*2-(2E)-3,7-Dimethyl-2,6-octadienyl]phenyl tetrahydro-2H-2-pyranyl ether (**7**)*

To a two-necked 250 mL round bottom flask with 2-iodophenyl tetrahydropyranyl ether **6** (3.04 g, 10 mmol) in THF (100mL) under argon at -78 °C *n*-BuLi (2.28 mol L^{-1}, 4.60 mL, 10.5 mmol) was added with a syringe to form a yellowish solution. After 30 min, geranyl bromide (2.28 g, 10.5 mmol) was added and the mixture was stirred until the disappearance of the yellowish color. When the temperature has increased to -20 °C, methanol (2 mL) was added and the temperature was allowed to increase to room temperature. The solvent was removed under vacuum and the residue was purified by flash chromatography, eluting with AcOEt/hexane (3/7, v/v) to give **7** as an oil (2.98 g, 95%); IR (film) ν_{max}/cm^{-1}: 3061, 3025, 2941, 2875, 2853, 1599, 1587, 1491, 1454, 1383, 1356, 1234, 1201, 1180, 1124, 1038, 1020, 970, 922, 818, 752; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.06-7.17 (m, 3H), 6.91 (td, ^3J 7.1 Hz, ^4J 1.8 Hz, 1H), 5.44 (t, ^3J 3.1 Hz, 1H), 5.34 (tq, ^3J 7.3 Hz, ^4J 1,3 Hz, 1H), 5.07-5.15 (m, 1H), 3.90 (ddd, ^2J 11.4 Hz, ^3J 9.7 Hz, ^4J 3.5 Hz, 1H), 3.60 (dtd, ^2J 11.4 Hz, ^3J 3.5 Hz, ^4J 1.5 Hz, 1H), 3.38 (d, *J* 7.3 Hz, 2H), 1.95-2.16 (m, 5H), 1.84-1.93 (m, 2H), 1.71 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H), 1.56-1.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 154.7, 135.8, 131.4, 130.6, 129.4, 126.8, 124.4, 122.7, 121.3, 114.1, 96.5, 61.9, 39.8, 30.6, 28.5, 26.6, 25.7, 25.3, 18.9, 17.6, 16.1 ppm; HRMS calcd. for $C_{21}H_{30}O_2$, 314.22458; found. 314.21539.

*2-[(2E)-3,7-Dimethyl-2,6-octadienyl]phenol (**8**)*

Tetrahydro-2*H*-2-pyranyl ether **7** (3.14 g, 10 mmol) in methanol (30 mL) and *p*-toluenesulfonate pyridinium (PPTS, 0.9 mmol%) were heated at 50 °C for 6 h. The solvent was removed under vacuum and the residue was diluted in ether (50 mL) and water (30 mL), then extracted with ether (2x30 mL), dried over $MgSO_4$ and filtered, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography, eluting with AcOEt/hexane (3/7, v/v), to give **8** (2.14 g, 93%) as an oil; IR (film) ν_{max}/cm^{-1}: 3451, 3067, 3032, 2966, 2925, 2916, 2856, 1591, 1489, 1454, 1376, 1330, 1219, 846, 752; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.08-7.15 (m, 2H), 6.86 (td, ^3J 7.5 Hz, ^4J 1.1 Hz, 1H), 6.81 (dd, ^3J 8.4 Hz, ^4J 1.1 Hz, 1H), 5.32 (td, ^3J 7.1 Hz, ^4J 1.1 Hz, 1H), 5.13 (sl, 1H), 5.03-5.20 (m, 1H), 3.37 (d, ^3J 7.1 Hz, 2H), 2.03-2.22 (m, 4H), 1.77 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 154.4, 138.5, 132.0, 129.9, 127.5, 126.8, 123.8, 121.6, 120.7, 115.8, 39.7, 29.8, 26.4, 25.7, 17.7, 16.1; HRMS calcd. for $C_{16}H_{22}O$, 230.16706; found 230.2832.

*(2E,6E)-2,6-Dimethyl-[2-(tetrahydro-2H-2-pyranyloxy)phenyl]-2,6-octadienyl-8-ol (**10**)*

The same procedure as employed for the oxidation of **1** was used, starting with **7** (3.15 g, 10 mmol), followed by oxidation with SeO_2 and reduction with $NaBH_4$. The residue was purified by flash chromatography, eluting with AcOEt/hexane (3/7, v/v), to give **10** (1.92 g, 58%) as a pale yellow oil; IR (film) ν_{max}/cm^{-1}: 3325, 2965, 2915, 2856, 1020, 758; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 6.93-6.97 (m, 2H), 6.81-6.85 (m, 1H), 6.73-6.76 (m, 1H), 5.46 (t, ^3J 3.3 Hz, 1H), 5.37 (m, 1H), 5.26 (t, ^3J 7.2 Hz, 1H), 4.02 (s, 2H), 3.83-3.94 (m, 1H), 3.55-3.63 (m, 1H), 3.25 (d, ^3J 7.2 Hz, 2H), 2.00-2.21 (m, 4H), 1.85 (sl, 1H), 1.69 (s, 3H), 1.58 (s, 3H), 1.54-2.12 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 154.9, 137.5, 135.2, 131.9, 128.0, 127.4, 122.4, 122.1, 121.0, 112.1, 98.1, 69.0, 61.9, 39.0, 30.8, 27.0, 26.3, 25.7, 19.3, 15.9, 13.7; GC/EIMS (*70 eV*) *m/z* 330 (M$^+$, 1%), 246 (35), 245 (20), 228 (22), 85 (100); HRMS calcd. for $C_{21}H_{30}O_3$, 330.21950; found 330.22005.

*tert-Butyldimethylsilyl 2-iodophenol ether (**11**)*

To a solution of 2-iodophenol (2.20 g, 10 mmol) in dry acetonitrile (20 mL) were added under an argon atmosphere, *tert*-butyldimethylsilyl chloride (TBDMSCl, 1.88 g, 12.5 mmol), imidazole (0.85 g, 12.5 mmol) and finally, tetrabutylammonium iodide (TBAI, 4.62 g, 12.5 mmol) were added. After stirring for 15 min at room temperature, cold pentane (25 mL) was added, and the organic layer was washed with cold water, extracted with pentane (2x25 mL) and then washed with brine. The organic layer was then dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude residue was purified by column chromatographic with silica gel using AcOEt/hexane as eluent to give **11** as a colorless oil (3.21 g, 96%); IR (film) ν_{max}/cm^{-1}: 3061, 2958, 2930, 2858, 1728, 1597, 1582, 1491, 1472, 1437, 1288, 1261, 917, 839, 781, 752; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.77 (dd, ^3J 7.9 Hz, ^4J 1.6 Hz, 1H), 7.18-7.25 (m, 1H), 6.85 (dd, ^3J 8.2 Hz, ^4J 1.3 Hz, 1H), 6.70 (td, ^3J 7.9 Hz, ^3J 7.9 Hz, ^4J 1.3 Hz, 1H), 1.06 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 155.2, 139.6, 129.2, 122.7, 118.5, 90.5, 25.8, 18.3, -4.0; HRMS calcd. for $C_{12}H_{19}IOSi$, 334.02500; found 334.02632.

*2-[(2E)-3,7-Dimethyl-2,6-octadienyl]phenyl tert-butyldimethylsilyl ether (**13**)*

In a three necked round bottom flask, *tert*-butyldimethylsilyl 2-iodophenol ether **11** (3.34 g, 10 mmol) and THF (20 mL) was added under an argon atmosphere at -78 °C. Then BuLi in hexane (2.28 mol L^{-1}, 10.5 mmol, 4.60 mL) and a solution of $MgBr_2$ (0.52 mol L^{-1}, 10.5 mmol) in THF (20 mL) were added. After the temperature reached room temperature, CuI (1.99 g, 10.5 mmol) was added in four portions with stirring. Then a solution of (2*E*)-3,7-dimethyl-2,6-octadienyl tetrahydro-2*H*-2-pyranyl ether **12** (10.5 mmol) in THF was added and the mixture was refluxed for 6 h. The reaction was cooled, a saturated solution of NH_4Cl was added, the solutions was extracted with ether (3x50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure by rotatory evaporation. The crude residue was purified by column chromatography with silica gel using AcOEt/hexane (1/8, v/v) as eluent to give **13** (3.03 g, 88%) as an oil; IR (film) ν_{max}/cm^{-1}: 3065, 3032, 2958, 2929, 2858, 1599, 1581, 1489, 1451, 1254, 928, 837, 779, 754; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.12 (d, ^3J 7.3 Hz, 1H), 7.05 (td, ^3J 7.7 Hz, ^4J 1.8 Hz, 1H), 6.87 (t, ^3J 7.3 Hz, 1H), 6.77 (d, ^3J 7.7 Hz, 1H), 5.33 (t, ^3J 7.0 Hz, 1H), 5.07-5.17 (m, 1H), 3.32 (d, ^3J 7.0 Hz, 2H), 1.96-2.18 (m, 4H), 1.68 (s, 6H), 1.60 (s, 3H), 1.02 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 153.4, 136.1, 132.2, 131.9, 129.6, 126.5, 124.4, 122.6, 121.0, 118.3, 39.7, 28.4, 26.6, 25.8, 25.7, 18.3, 17.7, 16.1, -4.1; GC/EIMS (*70 eV*) *m/z* 344 (M$^{+\bullet}$, 2%), 287 (3), 275 (7), 231 (2), 165 (17), 163 (50), 135 (9), 123 (19), 121 (2), 109 (2), 91 (6), 77 (3), 73 (75), 70 (6), 69 (100), 59 (13), 45 (8), 43 (8), 41 (85); HRMS calcd. for $C_{22}H_{36}OSi$, 344.25354; found 344.27659.

*(2E,6E)-2,6-Dimethyl-8-[2-(tert-butyldimethyl silyloxyphenyl]-2,6-octadienyl alcohol (**14**)*

Method A. From **13**. The same procedure as employed for allylic oxidation of **1** was used**;** compound **13** (3.45 g, 10 mmol) was oxidized with SeO_2 and then reduced with $NaBH_4$. The crude reaction product residue was purified by flash chromatography, eluting with AcOEt/hexane (1/3, v/v), to give **14** (2.99 g, 43%) as a pale yellow oil; IR (film) ν_{max}/cm^{-1}: 3342, 2956, 2865, 1669, 1747, 1235, 1025, 1009, 836, 753; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 6.92-6.96 (m, 2H), 6.81-6.84 (m, 1H), 6.72-6.76 (m, 1H), 5.36 (m, 1H), 5.26 (t, ^3J 7.2 Hz, 1H), 4.01 (s, 2H), 3.27 (d, ^3J 7.2 Hz, 2H), 2.02-2.21 (m, 4H), 1.98 (s, 1H), 1.71 (s, 3H), 1.58 (s, 3H), 0.95 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 157.0, 137.5, 135.2, 132.7, 132.0, 126.4, 122.4, 121.0, 120.5, 119.9, 69.0, 39.0, 27.2, 27.0, 23.5, 20.4, 15.9, 13.7, -4.9; GC/EIMS (*70 eV*) *m/z* 360 (2%), 75 (100); HRMS calcd. for $C_{22}H_{36}O_2Si$ 360.24846; found 360.24970.

Method B. From **11**. The same procedure as employed for the coupling of **11** and **12** was used**,** starting with *tert-*

butyldimethylsilyl 2-iodophenol ether **11** (3.34 g, 10 mmol) in THF (20 mL) under an argon atmosphere at -78 °C. Then BuLi in hexane (2.28 mol L^{-1}, 10.5 mmol, 4.60 mL) and a solution of $MgBr_2$ (0.52 mol L^{-1}, 10.5 mmol) in THF (20 mL) were added. After the temperature reached room temperature, CuI (1.99 g, 10.5 mmol) was added in four portions with stirring, followed by a solution of (2*E*,6*E*)-8-hydroxy-3,7-dimethyl-2,6-octadienyl acetate **2** (10.5 mmol) in THF and the mixture was refluxed for 6 h. The reaction was cooled, a saturated solution of NH_4Cl was added, the solutions was extracted with ether (3x50 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure by rotatory evaporation. The crude residue was purified by column chromatography with silica gel using AcOEt/hexane (1/3, v/v) as eluent to give **14** (3.25 g, 90%) as an oil.

*2-[(2E,6E)-3,7-Dimethyl-8-hydroxy-2,6-octadienyl]phenol (**9**)*

Method A. From **8**. The same procedure employed for the allylic oxidation of **1** was used; compound **8** (2.30 g, 10 mmol) was treated with SeO_2 (0.55 g, 5 mmol), *t*-butylhydroperoxide (2.75 mL, 20 mmol), SiO_2 (5.55 g) and then with $NaBH_4$ (0.30 g, 8 mmol). The crude reaction product residue was purified by flash chromatography, eluting with AcOEt/hexane (1/3, v/v), to give **9** as a pale yellow oil (1.16 g, 47%); IR (film) ν_{max}/cm^{-1}: 3641, 3355, 3067, 3036, 2958, 2921, 2871, 1593, 1483, 1456, 1431, 1363, 1232, 1156, 1097, 1041, 1002, 862, 752; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.06-7.16 (m, 2H), 6.86 (td, ^3J 7.3 Hz, ^4J 1.1 Hz, 1H), 6.81 (dd, ^3J 8.1 Hz, ^4J 1.1 Hz, 1H), 5.58 (s, 1H), 5.25-5.38 (m, 2H), 3.98 (s, 2H), 3.37 (d, *J* 7.0 Hz, 2H), 2.12-2.30 (m, 4H), 1.77 (s, 3H), 1.66 (s, 3H), 1.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 154.4, 138.4, 136.1, 130.1, 127.7, 126.5, 124.9, 122.6, 120.8, 116.0, 68.9, 39.1, 30.4, 25.1, 15.7, 13.7; GC/EIMS (*70 eV*) *m/z* 246 ($M^{+\bullet}$; 0.32), 228 (2), 213 (6), 185 (14), 161 (15), 146 (22), 145 (46), 133 (15), 131 (10), 128 (8), 121 (22), 119 (14), 115 (8), 108 (10), 107 (65), 105 (10), 93 (12), 91 (27), 81 (12), 79 (14), 77 (24), 69 (7), 67 (13), 65 (10), 55 (26), 53 (15), 51 (10), 43 (100), 41 (57); HRMS calcd. for $C_{21}H_{30}O_3$, 330.21950; found 330.22005.

Method B. From **10**. To a solution of **10** (3.30g, 10 mmol) in methanol (30 mL) pyridinium *p*-toluenesulfonate (PPTS, 0.025g, 0.1 mmol) was added and then heated to 50 °C for 6 h. The solvent was removed under reduced pressure and the residue was diluted with ether (50 mL) and water (30 mL) and extracted with ether (2x50 mL). The ether phase was washed with water (30 mL), then with brine (2x30 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure by rotatory evaporation. The residue was purified by flash chromatography, eluting with AcOEt/hexane (3/7 v/v) to give **9** (2.27 g, 92%).

Method C. From **14**. To a stirred solution of **14** (3.61 g, 10 mmol) in anhydrous THF (20 mL) under argon atmosphere, a solution of tetrabutylammonium fluoride (TBAF, 5.23 g, 20 mmol) in THF (20 mL) was added. After the disappearance of the starting material, water (30 mL) was added and the mixture was extracted with dichloromethane (2x30 mL). The extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure by rotatory evaporation. The crude residue was purified by column chromatography with silica gel using AcOEt/hexane to give pure **9** (2.29 g, 93%) as a yellow oil.

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