JOC Article

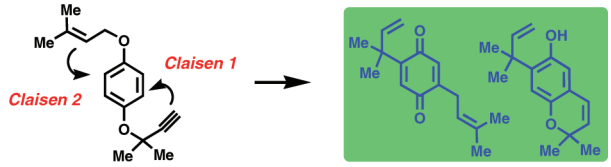
First Syntheses of 2,2-Dimethyl-7-(2′-methylbut-3′-en-2′-yl)-*2H*-chromen-6-ol and 2-(3′-Methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-benzoquinone, Novel Prenylated Quinone Derivatives from the New Zealand Brown Alga *Perithalia capillaris*

Catherine L. Coombes and Christopher J. Moody*

School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom

c.j.moody@nottingham.ac.uk

Received May 16, 2008



The first syntheses of 2,2-dimethyl-7-(2′-methylbut-3′-en-2′-yl)-*2H*-chromen-6-ol (**1**) and 2-(3′-methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-benzoquinone (**2**), novel prenylated quinone derivatives from the New Zealand brown alga *Perithalia capillaris*, are reported, in which the key steps are consecutive Claisen rearrangements that proceed with both high chemo- and regioselectivity.

Introduction

Quinones are ubiquitous in Nature and exhibit wide-ranging properties.[1−3] Not only do they constitute a large group of natural pigments, although surprisingly their contribution to natural coloring is relatively small, but they also participate in a range of important biological redox processes. One particular group of compounds is the isoprenoid benzoquinones, some of which such as the ubiquinones and the phyllaquinones have important roles in living organisms. Recently, two bis-prenylated derivatives, the chromenyl hydroquinone **1** and the related quinone **2** (Figure 1), were isolated from *Perithalia capillaris*, a seaweed found growing on the northern coasts of New Zealand by Perry and co-workers.[4] Despite their relative simplicity, these substances are novel structures, and both display antiproliferative activity in human leukemia cells. 2-(3′-Methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-benzoquinone (**2**) is only the second example of a naturally occurring bis-prenylated quinone,[5] and it is the first example containing an inverse prenyl group.

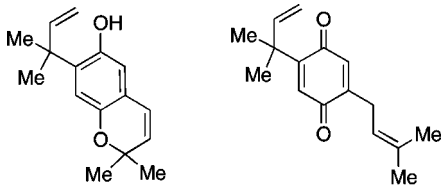
These novel structures were envisaged to be accessible via the Claisen rearrangement methodology previously used by us in the synthesis of other naturally occurring quinones.[6−8] Hence it was envisaged that both structures could be accessed from the same advanced intermediate **3** by divergent pathways involving two consecutive Claisen rearrangements (CR), exhibiting both chemoselectivity (CR 1 occurs before CR 2) and regioselectivity (CR 2 proceeds to C-5 rather than C-3) (Scheme 1).

Results and Discussion

The synthesis of the advanced intermediate **3** was relatively straightforward. The monoacetate **4** of hydroquinone[9] was alkylated with dimethylpropargyl chloride, using a copper-mediated coupling,[10] to form propargyl ether **5** (Scheme 2). Deprotection of the acetate and alkylation of the resulting phenol under standard conditions led to an efficient synthesis of the prenylated alkyne intermediate **3** (Scheme 2). The literature contains many examples of Claisen rearrangements involving both dimethylpropargyl and dimethylallyl (prenyl) groups;[11−13] however, to our knowledge, this is the first instance of rearrangement of both groups in the same

(1) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic Press: London, UK, 1971.
(2) Thomson, R. H. *Naturally Occurring Quinones III. Recent advances*, 3rd ed.; Chapman and Hall: London, UK, 1987.
(3) Thomson, R. H. *Naturally Occurring Quinones IV. Recent advances*, 4th ed.; Blackie: London, UK, 1997.
(4) Sansom, C. E.; Larsen, L.; Perry, N. B.; Berridge, M. V.; Chia, E. W.; Harper, J. L.; Webb, V. L. *J. Nat. Prod.* **2007**, *70*, 2042–2044.
(5) Permana, D.; Lajis, N. H.; Mackeen, M. M.; Ali, A. M.; Aimi, N.; Kitajima, M.; Takayama, H. *J. Nat. Prod.* **2001**, *64*, 976–979.
(6) Davis, C. J.; Hurst, T. E.; Jacob, A. M.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 4414–4422.
(7) Jacob, A. M.; Moody, C. J. *Tetrahedron Lett.* **2005**, *46*, 8823–8825.
(8) McErlean, C. S. P.; Moody, C. J. *J. Org. Chem.* **2007**, *72*, 10298–10301.
(9) Lee, Y.-S.; Kim, B.-T.; Min, Y.-K.; Park, N.-K.; Kim, K.-H.; Kim, K.-S. United States Patent 2204/0260114, 2004.
(10) Godfrey, J. D.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405–6408.
(11) Rhoads, S. H.; Raulins, N. R. *Org. React.* **1975**, *22*, 1–252.

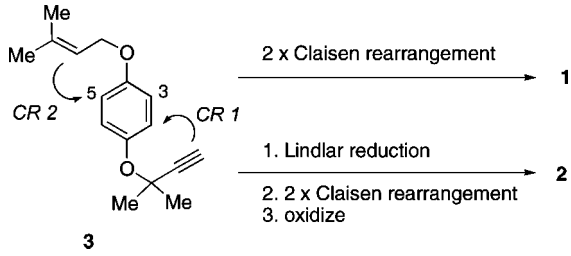
10.1021/jo801057x CCC: $40.75
Published on Web 08/06/2008



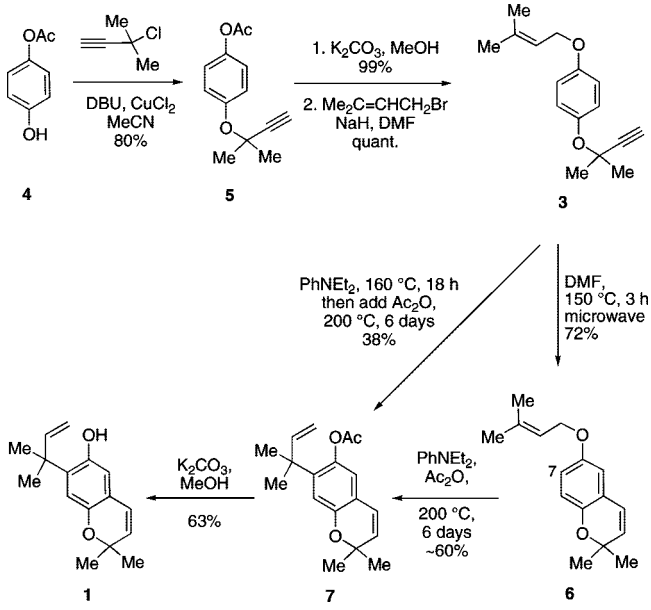
1 **2**

FIGURE 1. Structures of 2,2-dimethyl-7-(2′-methylbut-3′-en-2′-yl)-*2H*-chromen-6-ol (**1**) and 2-(3′-methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-benzoquinone (**2**), novel quinone derivatives from the New Zealand brown alga *Perithalia capillaris*.

SCHEME 1. Retrosynthetic Analysis of 1 and 2 Revealing Two Claisen Rearrangements



SCHEME 2. Synthesis of 2,2-Dimethyl-7-(2′-methylbut-3′-en-2′-yl)-*2H*-chromen-6-ol (1)

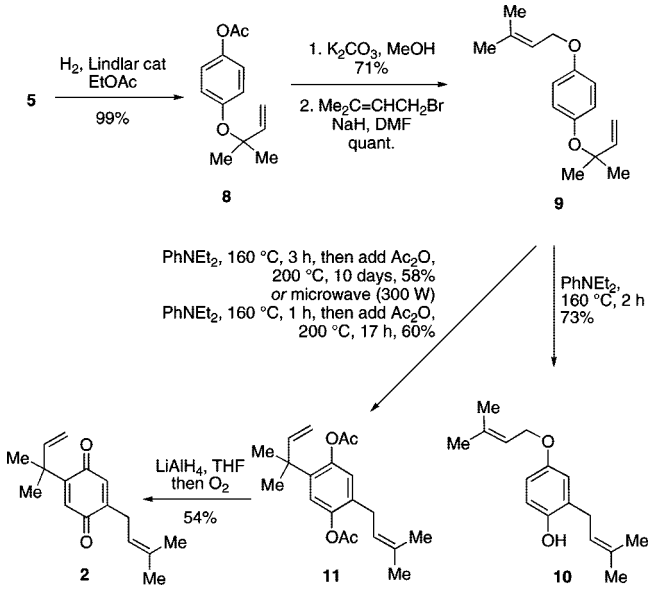


substrate. Notwithstanding the report that inverted prenyl ethers ($ArOCMe_2CH{=}CH_2$) undergo Claisen rearrangement in preference to their propargyl counterparts ($ArOCMe_2C{\equiv}CH$),[14] we reasoned that in our case the positioning of the two methyl groups on the terminus of the alkene would favor the Claisen rearrangement of the dimethylpropargyl group. Support for this view comes from detailed kinetic studies that show a significant rate enhancement in the rearrangement of aryl propargyl ethers due to the *gem*-dimethyl group,[15] and the fact there are examples of such rearrangements occurring at temperatures as low as 110 °C.[16,17] In the event, our predictions were well founded, and heating the Claisen substrate **3** to 150 °C in DMF for 3 h in a microwave reactor resulted in selective rearrangement of the propargyl ether to give the desired chromene **6** in good yield. As expected, the second Claisen rearrangement was less facile and required a higher temperature. Also, it is known that heating γ,γ-disubstituted allyl groups often results in formation of the so-called abnormal Claisen product, whereby the initial phenolic product undergoes further rearrangement.[11,18] The formation of the abnormal Claisen product can be prevented by trapping the initial phenol with an acylating agent under basic conditions,[16,19] and hence the rearrangement of the dimethylallyl ether **6** was carried out in *N*,*N*-diethylaniline in the presence of acetic anhydride at 200 °C, and allowed the isolation of the desired product as its acetate derivative **7** in modest yield. However, the reaction was complicated by competing cleavage of the prenyl group at the high temperature, a process observed previously,[20,21] to give 2,2-dimethyl-*2H*-chromen-6-yl acetate. Nevertheless, the desired rearrangement proceeded with complete regioselectivity to the less hindered 7-position, and none of the regioisomer was observed by ^{1}H NMR spectroscopy. More conveniently, the two sequential Claisen rearrangements can be effected in *N*,*N*-diethylaniline in the same reaction vessel simply by initial heating to 160 °C for 18 h, followed by addition of acetic anhydride and raising the temperature to 200 °C for a prolonged period. This gave the chromenyl acetate **7** in 38% yield (Scheme 2), which was again accompanied by the product from cleavage of the prenyl group (10% yield). Although the reaction times for the conversion of **3** into **7** could be shortened under microwave irradiation, the reaction was lower yielding and less clean. Finally, the synthesis was completed by deprotection of the acetate to give 2,2-dimethyl-7-(2′-methylbut-3′-en-2′-yl)-2*H*-chromen-6-ol (**1**), whose spectroscopic properties matched those of the natural product.[4]

It was originally planned to use the same intermediate **3** to access the second natural product, the quinone **2**, but attempts to hydrogenate the alkyne to the corresponding alkene over quinoline-poisoned Lindlar's catalyst resulted in recovery of the alkyne. However, the Lindlar hydrogenation of acetate **5** proceeded smoothly to give the allyl ether **8**. Deprotection of the acetate group and alkylation with dimethylallyl bromide gave the required precursor **9** for the 2-fold Claisen rearrangement (Scheme 3). As in the case of substrate **3** we required the two Claisen rearrangements to occur sequentially, with the second one proceeding regioselectively. In this case, there was some precedent to suggest that owing to the *gem*-dimethyl effect an inverted prenyl ether ($ArOCMe_2CH{=}CH_2$) would rearrange in preference to a prenyl ether ($ArOCH_2CH{=}CMe_2$), presumably due to relief of steric compression in the transition state.[22] This indeed proved to be the case, and heating the bis-allyl ether **9** to 160 °C resulted in a selective Claisen rearrangement to give

(12) Bennett, G. B. *Synthesis* **1977**, 589–606.
(13) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
(14) Tisdale, E. J.; Vong, B. G.; Li, H. M.; Kim, S. H.; Chowdhury, C.; Theodorakis, E. A. *Tetrahedron* **2003**, *59*, 6873–6887.
(15) Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841–848.
(16) Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1333–1337.
(17) Kolokythas, G.; Kostakis, I. K.; Pouli, N.; Marakos, P.; Kletsas, D.; Pratsinis, H. *Bioorg. Med. Chem.* **2003**, *11*, 4591–4598.
(18) Lauer, W. M.; Filbert, W. F. *J. Am. Chem. Soc.* **1936**, *58*, 1388–1392.
(19) Karanewsky, D. S.; Kishi, Y. *J. Org. Chem.* **1976**, *41*, 3026–3030.
(20) Daskiewicz, J. B.; Depeint, F.; Viornery, L.; Bayet, C.; Comte.Sarrazin, G.; Comte, G.; Gee, J. M.; Johnson, I. T.; Ndjoko, K.; Hostettmann, K.; Barron, D. *J. Med. Chem.* **2005**, *48*, 2790–2804.
(21) Ito, F.; Fusegi, K.; Kumamoto, T.; Ishikawa, T. *Synthesis* **2007**, 1785–1796.
(22) Murray, R. D. H.; Ballantyne, M. M.; Hogg, T. C.; McCabe, P. H. *Tetrahedron* **1975**, *31*, 2960–2965.

SCHEME 3. Synthesis of 2-(3′-Methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-benzoquinone (2)



phenol **10** in good yield. As before, the second Claisen rearrangement required a higher temperature, and was again conducted in the presence of acetic anhydride to avoid the formation of abnormal rearrangement products. Again this was conducted in a one-pot procedure by heating the bis-allyl ether in *N*,*N*-diethylaniline to 160 °C for 3 h, followed by addition of acetic anhydride and prolonged heating at 200 °C, although in this case no loss of the prenyl group was observed. This gave the hydroquinone diacetate **11** in 58% yield with no evidence for the formation of the regioisomeric Claisen rearrangement product (Scheme 3). The reaction time could be shortened considerably by conducting the reaction under microwave irradiation. Treatment of **11** with an excess of lithium aluminum hydride cleaved both acetates, and the resulting hydroquinone underwent oxidation to give 2-(3′-methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-benzoquinone (**2**), whose spectroscopic data matched those of the natural product.[4]

In summary, we have described the first syntheses of two unusual bis-prenylated marine natural products using routes that demonstrate both high chemoselectivity and regioselectivity in the key Claisen rearrangement steps.

Experimental Section

4-(2′-Methylbut-3′-yn-2′-yloxy)phenyl Acetate, 5. To a stirred solution of 4-acetoxyphenol (**4**) (5.0 g, 32.9 mmol), prepared by the literature method,[9] in anhydrous acetonitrile (165 mL) under argon at 0 °C was added copper(II) chloride dihydrate (5.6 mg, 0.032 mmol) followed by DBU (5.0 mL, 32.9 mmol) dropwise. To this mixture was added 3-chloro-3-methyl-1-butyne (3.32 mL, 29.6 mmol) dropwise, and the reaction mixture was stirred at 0 °C for 18 h. The reaction mixture was then concentrated under reduced pressure. The residue was partitioned between toluene (300 mL) and water (200 mL), and the water was extracted with toluene (3 × 100 mL). The combined organic extracts were washed with hydrochloric acid (2 M; 3 × 300 mL), aqueous sodium hydroxide (2 M; 2 × 300 mL), saturated sodium hydrogen carbonate (200 mL), and brine (200 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was subjected to flash chromatography with use of ether and light petroleum (5:95) to yield the title compound as a crystalline solid (4.51 g, 80%); mp 35.5−37.5 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3305, 3011, 2992, 1755, 1501, 1370, 1191, 1136, 1014; δ_H (400 MHz; $CDCl_3$) 7.21 (2H, d, J = 9.1 Hz), 7.00 (2H, d, J = 9.1 Hz), 2.57 (1H, s), 2.29 (3H, s), 1.64 (6H, s); δ_C (100 MHz; $CDCl_3$) 169.6 (C), 153.0 (C), 146.0 (C), 122.3 (CH), 121.7 (CH), 85.9 (C), 74.0 (CH), 72.7 (C), 29.5 (Me), 21.1 (Me). (Found: M + Na^+, 241.0847. $C_{13}H_{14}O_3$ + Na^+ requires 241.0835.) (Found: C, 71.7; H, 6.5. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5.)

4-(2′-Methylbut-3′-yn-2′-yloxy)phenol. To a stirred solution of 4-(2′-methylbut-3′-yn-2′-yloxy)phenyl acetate (**5**) (1.50 g, 6.87 mmol) in methanol (35 mL) at room temperature was added potassium carbonate (1.14 g, 8.25 mmol). The reaction mixture was stirred for 30 min, water was added (60 mL), and the reaction mixture was acidified to pH 3−4 with hydrochloric acid (2 M). The reaction mixture was concentrated under reduced pressure to 60 mL and extracted with ether (3 × 150 mL). The combined organic extracts were washed with water (3 × 200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield the title compound as an off-white powder (1.20 g, 99%); mp 125−127 °C (lit.[23] mp 132−134 °C); ν_{max} ($CHCl_3$)/cm^{-1} 3600, 3305, 2992, 2939, 1506, 1178, 1137; δ_H (400 MHz; $CDCl_3$) 7.08 (2H, d, J = 9.0 Hz), 6.75 (2H, d, J = 9.0 Hz), 4.74 (1H, s), 2.53 (1H, s), 1.60 (6H, s); δ_C (100 MHz; $CDCl_3$) 151.7 (C), 148.9 (C), 123.9 (CH), 115.3 (CH), 86.3 (C), 73.6 (CH), 73.1 (C), 29.5 (Me). (Found: M + H^+, 177.0899. $C_{11}H_{12}O_2$ + H^+ requires 177.0910.) (Found: C, 74.7; H, 6.8. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.9.)

1-(3′-Methylbut-2′-enyloxy)-4-(2′-methylbut-3′-yn-2′-yloxy)benzene, 3. To a stirred solution of 4-(2′-methylbut-3′-yn-2′-yloxy)phenol (1.10 g, 6.24 mmol) in DMF (31 mL) under argon at 0 °C was added sodium hydride (60% dispersion in mineral oils, 275 mg, 6.87 mmol) portionwise. After stirring for 5 min, light was excluded from the reaction and 3,3-dimethylallyl bromide (0.87 mL, 7.49 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 h. Saturated ammonium chloride solution (50 mL) was added and the mixture was extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (4 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield the title compound as a yellow oil (1.55 g, 100%), which was used without further purification; ν_{max} ($CHCl_3$)/cm^{-1} 3305, 3011, 2990, 2936, 2871, 1676 (w), 1504, 1466, 1448, 1383, 1364, 1287, 1138; δ_H (400 MHz; $CDCl_3$) 7.12 (2H, d, J = 9.1 Hz), 6.83 (2H, d, J = 9.1 Hz), 5.51 (1H, m), 4.48 (2H, d, J = 6.7 Hz), 2.53 (1H, s), 1.81 (3H, s), 1.75 (3H, s), 1.61 (6H, s); δ_C (100 MHz; $CDCl_3$) 155.1 (C), 148.8 (C), 138.0 (C), 123.6 (CH), 119.8 (CH), 114.6 (CH), 86.4 (C), 73.5 (CH), 72.9 (C), 65.0 (CH_2), 29.5 (Me), 25.8 (Me), 18.2 (Me); *m*/*z* (ESI) 267 ([M + Na]$^+$, 73%), 245/246 ([M + H]$^+$, 83/15), 234 (29), 200 (42), 189 (35), 177 (69). (Found: M + H^+, 245.1524. $C_{16}H_{20}O_2$ + H^+ requires 245.1536.) (Found: C, 78.8; H, 8.6. $C_{16}H_{20}O_2$ requires C, 78.7; H, 8.3.)

2,2-Dimethyl-6-(3′-methylbut-2′-enyloxy)-2*H*-chromene, 6. A stirred solution of 1-(3′-methylbut-2′-enyloxy)-4-(2′-methylbut-3′-yn-2′-yloxy)benzene (**3**) (50 mg, 0.20 mmol) in DMF (5 mL) in a sealed tube was subjected to microwave irradiation (300 W) at 150 °C for 3 h. Water (25 mL) was added and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were then washed with water (4 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure and the residue was subjected to flash chromatography with dichloromethane and light petroleum (1:9) to yield the title compound as a yellow oil (36 mg, 72%); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2979, 2928, 2858, 1576, 1491, 1439, 1384, 1362, 1305, 1258, 1167, 1120, 1105, 1010, 959; δ_H (400 MHz; $CDCl_3$) 6.73−6.67 (2H, m), 6.58 (1H, d, J = 2.1 Hz), 6.29 (1H, d, J = 9.8 Hz), 5.64 (1H, d, J = 9.8 Hz), 5.49 (1H, m), 4.45 (2H, d, J = 6.7 Hz), 1.80 (3H, s), 1.74 (3H, s), 1.42 (6H, s); δ_C (100 MHz; $CDCl_3$) 152.9 (C), 146.7 (C), 138.0 (C), 131.6 (CH), 122.4 (CH), 121.8 (C), 119.9 (CH), 116.7 (CH), 115.0 (CH), 112.3 (CH), 75.7

(23) Brown, P. E.; Lewis, R. A.; Waring, M. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2979–2988.

(C), 65.3 (CH_2), 27.6 (Me), 25.8 (Me), 18.2 (Me); *m/z* (ESI) 267/268 ($[M + Na]^+$, 100/19%), 245 ($[M + H]^+$, 38), 243 (18), 227 (24), 223 (15), 207 (11), 198 (47), 177 (72), 175 (51), 149 (15). (Found: $M + Na^+$, 267.1359. $C_{16}H_{20}O_2 + Na^+$ requires 267.1356.) (Found: C, 78.8; H, 8.3. $C_{16}H_{20}O_2$ requires C, 78.7; H, 8.3.)

2,2-Dimethyl-7-(2′-methylbut-3′-en-2′-yl)-2*H*-chromen-6-yl Acetate, 7. A stirred solution of 1-(3′-methylbut-2′-enyloxy)-4-(2′-methylbut-3′-yn-2′-yloxy)benzene (**3**) (500 mg, 2.05 mmol) in *N*,*N*-diethylaniline (15 mL) under argon was heated to 160 °C and stirred at this temperature for 18 h, after which complete disappearance of starting material was observed. Acetic anhydride (15 mL) was added and the temperature of the mixture was raised to 200 °C. The mixture was stirred at this higher temperature for 6 days, cooled to room temperature, and poured into ice−water. After being stirred for 15 min, the mixture was extracted with ether (3 × 150 mL) and the combined organic extracts were further washed with water (4 × 150 mL), hydrochloric acid (2 M; 4 × 150 mL), water (150 mL), saturated sodium hydrogen carbonate (4 × 150 mL), and brine (150 mL) and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography with ether and light petroleum (5:95) to give the title compound and a degradation product in a 4:1 ratio (429 mg). The products were then separated by using HPLC (gradient increase up to 55:45 acetonitrile and water) to yield the title compound as a colorless solid (225 mg, 38%); mp 73−75 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2976, 2935, 1750, 1640, 1621, 1495, 1465, 1421, 1361, 1188, 1157, 1112, 1050, 1010; δ_H (400 MHz; $CDCl_3$) 6.81 (1H, s), 6.61 (1H, s), 6.24 (1H, d, $J = 9.7$ Hz), 5.97 (1H, dd, $J = 17.4$, 10.6 Hz), 5.59 (1H, d, $J = 9.7$ Hz), 5.00 (1H, dd, $J = 17.4$, 1.5 Hz), 4.95 (1H, dd, $J = 10.6$, 1.5 Hz), 2.18 (3H, s), 1.44 (6H, s), 1.40 (6H, s); δ_C (100 MHz; $CDCl_3$) 169.8 (C), 150.1 (C), 147.0 (CH), 142.3 (C), 140.1 (C), 130.8 (CH), 121.3 (CH), 121.2 (CH), 119.6 (C), 114.9 (CH), 109.8 (CH_2), 76.4 (C), 40.2 (C), 28.2 (Me), 27.5 (Me), 21.7 (Me); *m/z* (ESI) 309/310 ($[M + Na]^+$, 100/18), 304 ($M + NH_4^+$, 11), 287/288 ($[M + H^+]$, 34/7), 251 (10), 250 (13), 245 (11), 227 (6), 223 (6), 219 (7), 177 (7). (Found: $M + Na^+$, 309.1447. $C_{18}H_{22}O_3 + Na^+$ requires 309.1461.) (Found: C, 75.6; H, 7.7. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.7.)

The degradation product was identified as 2,2-dimethyl-2*H*-chromen-6-yl acetate (43 mg, 10%); δ_H (400 MHz; $CDCl_3$) 6.83−6.77 (1H, m), 6.77−6.71 (2H, m), 6.27 (1H, d, $J = 9.7$ Hz), 5.64 (1H, d, $J = 9.7$ Hz), 2.27 (3H, s), 1.43 (6H, s).

2,2-Dimethyl-7-(2′-methylbut-3′-en-2′-yl)-2*H*-chromen-6-ol, 1. To a stirred solution of 2,2-dimethyl-7-(2′-methylbut-3′-en-2′-yl)-2*H*-chromen-6-yl acetate (**7**) (30 mg, 0.11 mmol) in methanol (1 mL) at room temperature was added potassium carbonate (18 mg, 0.13 mmol). After the reaction mixture had been stirred for 1 h, saturated ammonium chloride was added (20 mL), the reaction mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with water (4 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a green solid (37 mg). Trituration with light petroleum gave the title compound as a colorless crystalline solid (16 mg, 63%); mp 89−91 °C (lit.[4] yellow oil); ν_{max} ($CHCl_3$)/cm^{-1} 3485 (br), 2976, 2934, 1640, 1494, 1437, 1363, 1322, 1264, 1253, 1163, 1112, 949, 929, 909, 881; δ_H (400 MHz; $CDCl_3$) 6.72 (1H, s), 6.51 (1H, s), 6.26 (1H, d, $J = 9.8$ Hz), 6.17 (1H, dd, $J = 17.8$, 10.5 Hz), 5.60 (1H, d, $J = 9.8$ Hz), 5.42 (1H, s), 5.33 (1H, d, $J = 17.8$ Hz), 5.29 (1H, dd, $J = 10.5$, 0.9 Hz), 1.43 (6H, s), 1.42 (6H, s); δ_C (100 MHz; $CDCl_3$) 148.4 (C), 147.6 (CH), 146.4 (C), 132.9 (C), 131.1 (CH), 121.8 (CH), 120.6 (C), 115.0 (CH), 113.9 (CH), 113.4 (CH_2), 75.8 (C), 40.4 (C), 27.8 (Me), 26.9 (Me); *m/z* (ESI) 267/268 ($[M + Na]^+$, 100/24), 251 (45), 250 (21), 245/246 (55/10), 242 (15), 227 (29), 223 (26), 217 (9), 178 (10), 177 (12), 164 (23). (Found: $M + Na^+$, 267.1360. $C_{16}H_{20}O_2 + Na^+$ requires 267.1356.)

4-(2′-Methylbut-3′-en-2′-yloxy)phenyl Acetate, 8. To a solution of 4-(2′-methylbut-3′-yn-2′-yloxy)phenyl acetate (**5**) (600 mg, 2.75 mmol) in ethyl acetate (43 mL) was added Lindlar catalyst (99 mg) and quinoline (2.8 mL). The reaction mixture was then evacuated and stirred under a hydrogen atmosphere for 3.7 h. The mixture was then filtered through Celite, washed with ethyl acetate (3 × 100 mL), and concentrated under reduced pressure. The residue was then subjected to flash chromatography with ether and light petroleum (1:9) to yield the title compound as a pale yellow oil (602 mg, 99%); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2985, 2933, 1749, 1501, 1415, 1370, 1192, 1129, 1013; δ_H (400 MHz; $CDCl_3$) 7.00−6.92 (4H, m), 6.12 (1H, dd, $J = 17.7$, 10.8 Hz), 5.17 (1H, dd, $J = 17.7$, 1.0 Hz), 5.14 (1H, dd, $J = 10.8$, 1.0 Hz), 2.28 (3H, s), 1.44 (6H, s); δ_C (100 MHz; $CDCl_3$) 169.7 (C), 153.5 (C), 145.4 (C), 144.1 (CH), 122.4 (CH), 121.6 (CH), 113.6 (CH_2), 79.7 (C), 26.9 (Me), 21.1 (Me); *m/z* (ESI) 243/244 ($[M + Na]^+$, 100/14), 153 ($C_8H_9O_3$, 21). (Found: $M + Na^+$, 243.0998. $C_{13}H_{16}O_3 + Na^+$ requires 243.0992.) (Found: C, 71.1; H, 7.4. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3.)

4-(2′-Methylbut-3′-en-2′-yloxy)phenol. To a stirred solution of 4-(2′-methylbut-3′-en-2′-yloxy)phenyl acetate (**8**) (400 mg, 1.8 mmol) in methanol (9 mL) under argon at 0 °C was added potassium carbonate (301 mg, 2.2 mmol). After the solution was stirred for 10 min, water was added (20 mL) and the reaction mixture was acidified to pH 3−4 with hydrochloric acid (2 M). The reaction mixture was then concentrated under reduced pressure to 20 mL and extracted with ether (3 × 50 mL). The combined organic extracts were then washed with water (3 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure and the residue was subjected to flash chromatography with ether and light petroleum (2:8) to yield the title compound as a yellow crystalline solid (230 mg, 71%); mp 72−75 °C (lit.[24] mp 34−37 °C); ν_{max} ($CHCl_3$)/cm^{-1} 3600, 3011, 2984, 1506, 1177, 1129; δ_H (400 MHz; $CDCl_3$) 6.86 (2H, d, $J = 9.0$ Hz), 6.68 (2H, d, $J = 9.0$ Hz), 6.11 (1H, dd, $J = 17.5$, 10.8 Hz), 5.30 (1H, br s), 5.15−5.09 (2H, m), 1.40 (6H, s); δ_C (100 MHz; $CDCl_3$) 151.4 (C), 148.7 (C), 144.0 (CH), 124.2 (CH), 115.3 (CH), 113.6 (CH_2), 79.7 (C), 26.6 (Me); *m/z* (ESI) 201 (27), 171 (11), 159 (14), 157 (8), 149 (17). (Found: $M + Na^+$, 201.0897. $C_{11}H_{14}O_2 + Na^+$ requires 201.0886.) (Found: C, 74.4; H, 8.0. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9.)

1-(3′-Methylbut-2′-enyloxy)-4-(2′-methylbut-3′-en-2′-yloxy)benzene, 9. To a stirred solution of 4-(2′-methylbut-3′-en-2′-yloxy)phenol (200 mg, 1.12 mmol) in DMF (6 mL) under argon at 0 °C was added sodium hydride (60% dispersion in mineral oils, 49 mg, 1.23 mmol) portionwise. After 5 min of stirring, light was excluded from the reaction and 3,3-dimethylallyl bromide (0.16 mL, 1.35 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 1 h. Saturated ammonium chloride solution (50 mL) was added and the mixture was extracted with ether (3 × 50 mL). The combined organic extracts were further washed with water (4 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to yield the title compound as a yellow oil (280 mg, 100%) that was used without further purification; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2983, 2931, 2859, 1503, 1468, 1380, 1240, 1129, 1002; δ_H (400 MHz; $CDCl_3$) 6.91 (2H, d, $J = 9.1$ Hz), 6.78 (2H, d, $J = 9.1$ Hz), 6.12 (1H, dd, $J = 17.5$, 10.8 Hz), 5.50 (1H, m), 5.13 (1H, dd, $J = 17.5$, 0.9 Hz), 5.11 (1H, dd, $J = 10.8$, 0.9 Hz), 4.46 (2H, d, $J = 6.7$ Hz), 1.80 (3H, s), 1.74 (3H, s), 1.40 (6H, s); δ_C (100 MHz; $CDCl_3$) 154.6 (C), 149.1 (C), 144.3 (CH), 138.0 (C), 123.8 (CH), 119.9 (CH), 114.6 (CH), 113.4 (CH_2), 79.3 (C), 65.1 (CH_2), 26.7 (Me), 25.8 (Me), 18.2 (Me); *m/z* (ESI) 269/270 ($[M + Na]^+$, 100/17), 251 (23), 250 (21), 247/248 ($[M + H]^+$, 39/7), 242 (9), 227 (16), 223 (13), 200/201 (48/7), 191 (16), 177 (7). (Found: $M + Na^+$, 269.1502, $C_{16}H_{22}O_2 + Na^+$ requires 269.1512.)

2-(3′-Methylbut-2′-enyl)-4-(3′-methylbut-2′-enyloxy)phenol, 10. A solution of 1-(3′-methylbut-2′-enyloxy)-4-(2′-methylbut-3′-en-2′-yloxy)benzene (**9**) (60 mg, 0.24 mmol) in *N*,*N*-diethylaniline (2 mL) was stirred under argon at 160 °C for 2 h. After this time, the reaction mixture was cooled, poured into ice−water, and stirred

(24) Lantero, D. R.; Welker, M. E. *J. Organomet. Chem.* **2002**, *656*, 217–227.

for 15 min. The aqueous was extracted with ether (3 × 50 mL) and the combined organic extracts were further washed with water (4 × 50 mL), hydrochloric acid (2 M; 3 × 50 mL), water (50 mL), saturated sodium hydrogen carbonate (50 mL), and brine (50 mL) and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography with ether and light petroleum (1:9) to yield the title compound as a yellow oil (44 mg, 73%), ν_{max} ($CHCl_3$)/cm^{-1} 3603, 3469 (br), 3011, 2976, 2917, 1496, 1440, 1383, 1174; δ_H (400 MHz; $CDCl_3$) 6.75−6.65 (3H, m), 5.50 (1H, m), 5.32 (1H, m), 4.83 (1H, br s), 4.45 (2H, d, J = 6.8 Hz), 3.33 (2H, d, J = 7.3 Hz), 1.80 (3H, s), 1.78 (6H, s), 1.74 (3H, s); δ_C (100 MHz; $CDCl_3$) 152.9 (C), 148.1 (C), 137.9 (C), 134.7 (C), 128.0 (C), 121.6 (CH), 120.0 (CH), 116.6 (CH), 116.1 (CH), 112.8 (CH), 65.3 (CH_2), 29.8 (CH_2), 25.79 (Me), 25.76 (Me), 18.1 (Me), 17.8 (Me); *m/z* (ESI) 269/270 ([M + Na]$^+$, 100/17), 251 (9), 250 (8), 247/248 (19/3), 200 (11), 191 (9), 177 (4). (Found: M + Na$^+$, 269.1501. $C_{16}H_{22}O_2$ + Na$^+$ requires 269.1512.)

2-(3′-Methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-hydroquinone Diacetate, 11. (a) A stirred solution of 1-(3′-methylbut-2′-enyloxy)-4-(2′-methylbut-3′-en-2′-yloxy)benzene (**9**) (100 mg, 0.41 mmol) in *N*,*N*-diethylaniline (4 mL) under argon was heated to 160 °C and stirred at this temperature for 3 h, when complete disappearance of starting material was observed. Acetic anhydride (4 mL) was added and the temperature of the reaction was raised to 200 °C. The reaction was then stirred at this higher temperature for 10 days, after which time the reaction mixture was cooled to room temperature and poured into ice−water. After being stirred for 15 min, the mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were further washed with water (4 × 50 mL), hydrochloric acid (2 M; 8 × 50 mL), water (50 mL), sodium hydrogen carbonate (50 mL), and brine (50 mL) and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography with ether and light petroleum (1:9) to yield the title compound as a yellow solid (78 mg, 58%); mp 57−58 °C, ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2973, 2933, 1758, 1496, 1370, 1160; δ_H (400 MHz; $CDCl_3$) 7.02 (1H, s), 6.83 (1H, s), 5.97 (1H, dd, J = 17.5, 10.6 Hz), 5.21 (1H, m), 5.01 (1H, dd, J = 17.5, 1.2 Hz), 4.97 (1H, dd, J = 10.6, 1.2 Hz), 3.19 (2H, d, J = 7.2 Hz), 2.31 (3H, s), 2.20 (3H, s), 1.74 (3H, d, J = 1.0 Hz), 1.68 (3H, s), 1.41 (6H, s); δ_C (100 MHz; $CDCl_3$) 169.4 (C), 169.3 (C), 146.8 (CH), 146.5 (C), 146.1 (C), 138.2 (C), 133.6 (C), 132.5 (C), 125.1 (CH), 121.1 (CH), 121.0 (CH), 110.1 (CH_2), 40.0 (C), 28.3 (CH_2), 27.4 (Me), 25.7 (Me), 21.7 (Me), 20.9 (Me), 17.8 (Me); *m/z* (ESI) 353/354 ([M + Na]$^+$, 100/20), 348/349 ([M + NH_4]$^+$, 90/18), 331 ([M + H]$^+$, 3), 289 ($C_{18}H_{24}O_3$ + H]$^+$, 5). (Found: M + Na$^+$, 353.1715. $C_{20}H_{26}O_4$ + Na$^+$ requires 353.1723.) (Found: C, 72.5; H, 7.9. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9.)

(b) A stirred solution of 1-(3′-methylbut-2′-enyloxy)-4-(2′-methylbut-3′-en-2′-yloxy)benzene (**9**) (36 mg, 0.15 mmol) in *N*,*N*-diethylaniline (1 mL) in a sealed tube was subjected to microwave irradiation (300 W) at 160 °C for 1 h. Acetic anhydride was added (1 mL) and the reaction mixture was again stirred and subjected to microwave irradiation at 200 °C for 17 h. The reaction mixture was cooled, poured into ice−water, and stirred for 15 min. The aqueous mixture was extracted with ether (3 × 50 mL) and the combined organic extracts were washed with water (4 × 50 mL), hydrochloric acid (2 M; 3 × 100 mL), water (100 mL), saturated sodium hydrogen carbonate (100 mL), and brine (100 mL) and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography with ether and light petroleum (1:9) to yield the title compound as a yellow solid (28 mg, 60%), identical with the material from the previous experiment.

2-(3′-Methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-benzoquinone, 2. To a stirred solution of lithium aluminum hydride (5 mg, 0.12 mmol) in anhydrous THF (1 mL) under argon at 0 °C was added 2-(3′-methylbut-2′-enyl)-5-(2′-methylbut-3′-en-2′-yl)-1,4-hydroquinone diacetate (**11**) (20 mg, 0.06 mmol) dissolved in anhydrous THF (1 mL). After 3 h only the monoacetate was observed by TLC and mass spectrometry, more $LiAlH_4$ was added (20 mg), and the reaction mixture was warmed to room temperature and stirred under an oxygen atmosphere overnight. Ethyl acetate (10 mL) was added to destroy the unreacted $LiAlH_4$, the mixture was diluted with distilled water (15 mL), and the organic solvents were removed in vacuo. The aqueous residue was extracted with dichloromethane (4 × 10 mL), and the combined organic extracts were further washed with water (20 mL) and brine (2 × 20 mL) and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography with ether and light petroleum (1:9) to yield the title compound as a yellow crystalline solid (8 mg, 54%); mp 27.5−29 °C (lit.,[4] yellow oil); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2971, 2930, 1652, 1599, 1379, 1339, 1240, 916; δ_H (400 MHz; $CDCl_3$) 6.61 (1H, s), 6.43 (1H, t, J = 1.8 Hz), 6.08 (1H, dd, J = 17.5, 10.7 Hz), 5.14 (1H, m), 5.05 (1H, dd, J = 10.7, 0.8 Hz), 5.00 (1H, dd, J = 17.5, 0.8 Hz), 3.09 (2H, d, J = 7.4 Hz), 1.76 (3H, d, J = 0.9 Hz), 1.64 (3H, s), 1.38 (6H, s); δ_C (100 MHz; $CDCl_3$) 188.6 (C), 187.6 (C), 154.2 (C), 146.9 (C), 145.3 (CH), 136.2 (C), 134.2 (CH), 132.3 (CH), 118.0 (CH), 112.7 (CH_2), 40.4 (C), 26.8 (Me and CH_2), 25.7 (Me), 17.8 (Me); *m/z* (ESI) 267/268 ([M + Na]$^+$, 100/18), 251 (82), 245 ([M + H]$^+$, 41), 227 (98), 223 (46), 217 (15), 185 (18), 171 (47), 158 (26), 157 (31), 149 (23), 141 (14). (Found: M + Na$^+$, 267.1363. $C_{16}H_{20}O_2$ + Na$^+$ requires 267.1356.)

Supporting Information Available: General experimental details and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801057X