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# A New Synthetic Route to Prenylphenols. Synthesis of 4',6'-Dihydroxy-2'-alkenyloxy-3'-(3-methyl-2-butenyl)acetophenones

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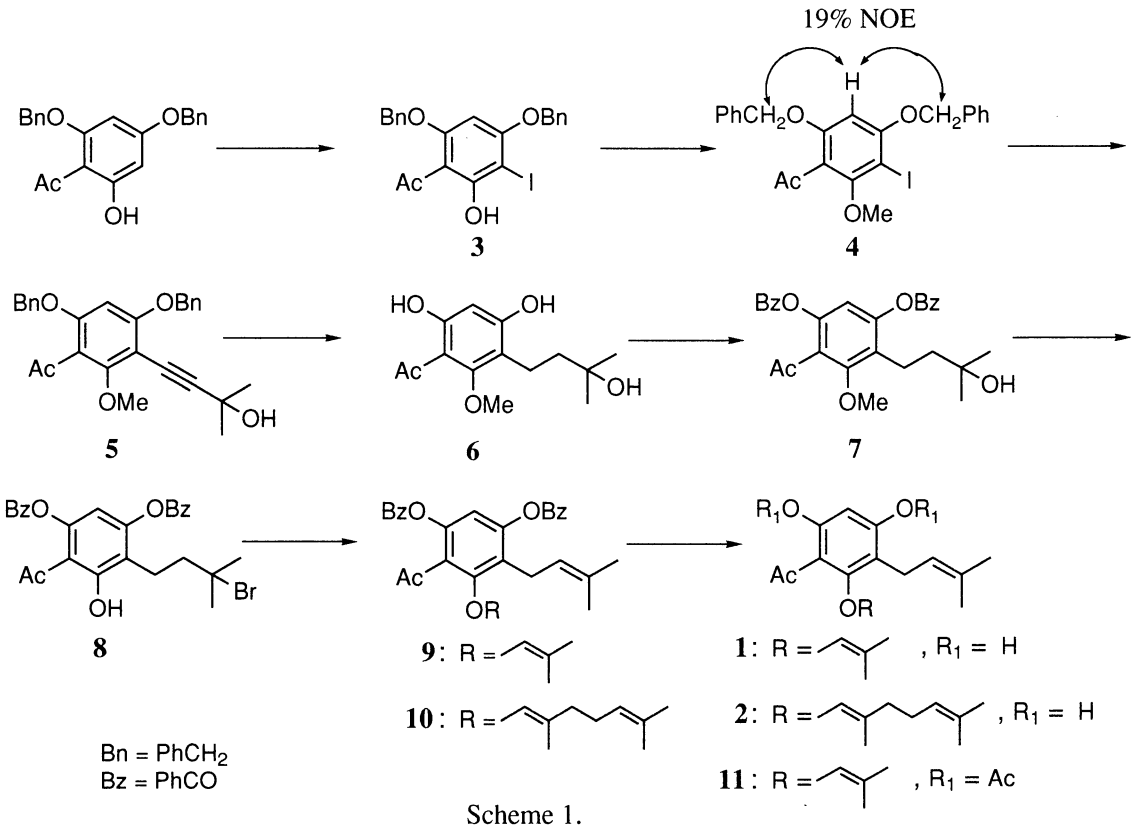
The palladium-catalyzed coupling reaction of 4',6'-bis(benzyloxy)-3'-iodo-2'-methoxyacetophenone with 2-methyl-3-butyn-2-ol gave 4',6'-bis(benzyloxy)-3'-(3-hydroxy-3-methylbutynyl)-2'-methoxyacetophenone (**5**). Demethylation and bromination of the benzoate obtained from **5** with $BBr_3$ gave 4',6'-bis(benzoyloxy)-3'-(3-bromo-3-methylbutyl)-2'-hydroxyacetophenone (**8**). *O*-Prenylation of **8** with prenyl bromide, followed by hydrolysis of the resultant compound gave 4',6'-dihydroxy-2'-prenyloxy-3'-prenylacetophenone. In a similar manner, 4',6'-dihydroxy-2'-geranyloxy-3'-prenylacetophenone also was prepared from **8** and geranyl bromide.

Prenylphenols are potentially valuable intermediates in the synthesis of chromenes, chromans, and natural products.[1] Many modifications of these structures are observed in nature[2] and it has been reported that these compounds have antifungal activity.[3] Although these compounds are synthesized from suitable phenols by direct acid- or base-catalyzed alkylation, or by Claisen rearrangement,[4] the majority of such reactions reported resulted in relatively low yields; *O*-and di-alkylation and lack of regioselectivity are common problems.

The reaction of aryl halides with terminal alkynes in the presence of Pd(0) is very useful for the formation of carbon-carbon bonds,[5] and seems to be applicable to syntheses of prenylphenols. We report here on the first synthesis of 4',6'-dihydroxy-2'-(3-methyl-2-butenyloxy)-3'-(3-methyl-2-butenyl)acetophenone (**1**) and 4',6'-dihydroxy-2'-(3,7-dimethyl-2,6-octadienyloxy)-3'-(3-methyl-2-butenyl)acetophenone (**2**) by using the palladium-catalyzed coupling reaction. These synthetic works have suggested that the prenylphenol types of natural products isolated by Kumar et al.[6] were assigned structures incorrectly as **1** and **2**.

The reaction of 2'-hydroxy-4',6'-bis(benzyloxy)acetophenone[7] with iodine in the presence of silver trifluoroacetate in $CHCl_3$ at room temperature gave 3'-iodoacetophenone (**3**) [mp 204-206 °C; 83%; $^1$H NMR($CDCl_3$) $\delta$=6.08 (1H, s, Ar-H)], which was converted into 2'-methoxy-3'-iodoacetophenone (**4**) (mp 108-109 °C) with dimethyl sulfate in the presence of $K_2CO_3$ in acetone. The structures of **3** and **4** were confirmed by the NOE of **4** observed by $^1$H NMR spectroscopy; irradiation of benzyl methylene protons ($CH_2$) of **4** led to a 19% NOE of the proton at the $C_{5'}$ position, and irradiation of methoxy protons did not cause any appreciable enhancement for the proton ($C_{5'}$-H) (Scheme 1). From these results, the structure of **3** was confirmed to be 4',6'-bis(benzyloxy)-2'-dihydroxy-3'-iodoacetophenone. The structure of **3** was also supported by a 17% NOE in the $C_8$-H of 6-acetyl-7-benzyloxy-5-methoxychroman[8] obtained from compound **6**.

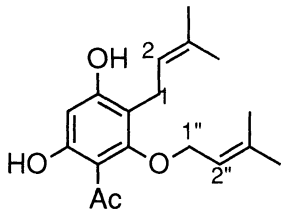



Scheme 1.

The coupling reaction of the acetophenone **4** (1 mmol) with 2-methyl-3-butyn-2-ol (3 mmol) in the presence of $PdCl_2$ (0.03 mmol), CuI (0.03 mmol), $PPh_3$ (0.06 mmol) in $Et_3N$-DMF under $N_2$ at 80-85 °C for 15 h afforded the desired 3'-(3-hydroxy-3-methylbutynyl)acetophenone[9] (**5**) (mp 97-98 °C; 95%). Catalytic hydrogenation of **5** in the presence of Pd/C in MeOH at 20 °C gave easily 3'-(3-hydroxy-3-methylbutyl)-4',6'-dihydroxyacetopheanone (**6**) [mp 156-158 °C; $^1$H NMR($CDCl_3$) δ=1.30-1.73 and 2.40-2.75 (each 2H, m, $CH_2$)], which was converted into 4',6'-bis(benzoyloxy)acetophenone (**7**) (mp 107-108 °C) with benzoyl chloride in the presence of $K_2CO_3$ in acetone. The treatment of **7** with $BBr_3$ in $CH_2Cl_2$ at -70 °C for 30 min brought about simultaneous demethylation and bromination to give 2'-hydroxy-3'-(3-bromo-3-methylbutyl)acetophenone[10] (**8**) (mp 145-147 °C; 79% based on **7**). The reaction of **8** with prenyl bromide in the presence of $K_2CO_3$ in DMF at room temperature for 1 h and the subsequent heating of the mixture at 70 °C for 1 h gave 2'-(3-methyl-2-butenyloxy)-3'-(3-methyl-2-butenyl)acetophenone (**9**) (73%). The $^1$H NMR spectrum of **9** showed two prenyl-group signals [δ=3.32 and 4.32 (each 2H, d, *J*=7 Hz, $CH_2$), 5.08 and 5.40 (each 1H, t, *J*=7 Hz, CH=)]. Hydrolysis of **9** with diluted sodium hydroxide under $N_2$ at 50 °C gave easily the desired compound **1**[11] (mp 71-72 °C), which was converted into the diacetate **11**.[12]

In a similar manner, the reaction of **8** with geranyl bromide gave 2'-geranyloxy-3'-(3-methyl-2-butenyl)acetophenone (**10**) [$^1$H NMR($CDCl_3$) δ=1.92-2.25 (4H, m, $CH_2CH_2$), 4.36 (2H, d, *J*=7 Hz, CH2), 4.89-5.22 (1H, m, CH=), 5.40 (1H, t, *J*=7 Hz, CH=)], which was converted into the desired compound **2**[13] (mp 71-73 °C) in good yield.

The $^1$H NMR spectral data for the synthetic prenylphenols **1** and **2** are given in Table 1. The $^1$H NMR spectra of **1** and the diacetate **11** were not superimposable on those of the natural products to which the

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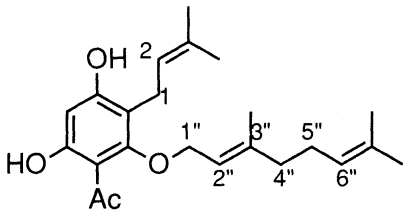


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Table 1. $^1$H NMR (400MHz, $CDCl_3$) data for the prenylacetophenones **1** and **2**

| Compd | *gem*-Me | Ac | $CH_2$ ($J$ =7Hz) | CH=C ($J$ =7Hz) | Ar-H | OH |
|---|---|---|---|---|---|---|
| **1** | 1.63 (s), 1.76 (s)<br>1.79 (s), 1.82 (s) | 2.67 (s) | 3.36 (d, 1-H)<br>4.29 (d, 1"-H) | 5.21 (t, 2-H)<br>5.50 (t, 2"-H) | 6.22 (s) | 6.04 (s)<br>13.02 (s) |
| **2** | 1.61 (s), 1.62 (s)<br>1.69 (s), 1.77 (s)<br>1.82 (s) | 2.67 (s) | 3.37 (d, 1-H)<br>4.32 (d, 1"-H)<br>2.05-2.15<br>(m, 4"-, 5"-H) | 5.08 (t, 6"-H)<br>5.21 (t, 2-H)<br>5.50 (t, 2"-H) | 6.22 (s) | 5.98 (s)<br>13.04 (s) |

same structures as **1** and **11** were assigned[6]; the aromatic proton ($C_5$'-H) and methylene protons (1"-H) of **1** were 6.22 and 4.29 ppm, respectively, whereas those reported for the natural product were 6.00 and 4.51 ppm, respectively. On the basis of the above results, the structure of the natural product is presumed to be an isomer of the synthetic prenylphenol **1**.

Similarly, the melting point and the spectral data of the synthetic prenylphenol **2** were not consistent with those of the natural product assigned as **2**.[6] Therefore, the structure of the natural product is also considered to be an isomer of the synthetic prenylphenol **2**.

The synthesis described above seems to be a useful method for the regioselective introduction of prenyl groups to the desired positions of aromatic rings.

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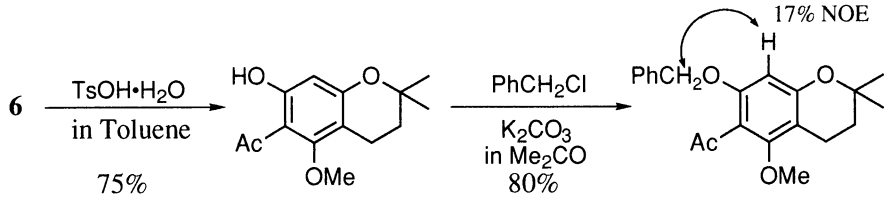
8) 6-Acetyl-7-benzyloxy-5-methoxy-2,2-dimethylchroman was synthesized as follows:




9) Compound **5**: $^1H$ NMR($CDCl_3$) δ=1.60 (6H, s, $CH_3$ x 2), 2.15 (1H, s, OH), 2.43 (3H, s, $COCH_3$), 3.92 (3H, s, $OCH_3$), 5.01 and 5.05 (each 2H, s, $PhCH_2$), 6.28 (1H, s, Ar-H), 7.31 and 7.37 (each 5H, s, $C_6H_5$). Found: C, 75.45; H, 6.60%. Calcd for $C_{28}H_{28}O_5$: C, 75.65; H, 6.35%.

10) Compound **8**: $^1H$ NMR($CDCl_3$) δ=1.72 (6H, s, $CH_3$ x 2), 1.73-2.21 (2H, m, $CH_2$), 2.72-3.14 (2H, m, $CH_2$), 2.55 (3H, s, $COCH_3$), 6.65 (1H, s, Ar-H), 7.40-8.30 (10H, m, $C_6H_5CO$). Found: C, 61.75; H, 4.85%. Calcd for $C_{27}H_{25}O_6Br$: C, 61.72; H, 4.80%.

11) Compound **1**: IR(KBr) 3455, 2930, 1625, 1270, 835 $cm^{-1}$. Found: C, 70.86; H, 7.89%. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95%.

12) Diacetate **11**: An oil; $^1H$ NMR ($CDCl_3$) δ=1.58 (3H, s, $CH_3$), 1.72 (9H, s, $CH_3$ x 3), 2.18, 2.22 and 2.48 (each 3H, s, $COCH_3$), 3.26 and 4.26 (each 2H, d, *J*=7 Hz, $CH_2$), 5.01 and 5.36 (each 1H, t, *J*=7 Hz, CH=), 6.62 (1H, s, $C_5$'-H).

13) Compound **2:** IR(KBr) 3310, 2910, 1630, 1275, 840 $cm^{-1}$. Found: C, 73.97; H, 8.52%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%.

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