CHEMISTRY LETTERS, pp. 1203-1206, 1994.

Regioselective Synthesis of Prenylphenols. Syntheses of Naturally Occurring 4'-Alkenyloxy-2',6'-dihydroxy-3'-(3-methyl-2-butenyl)acetophenones

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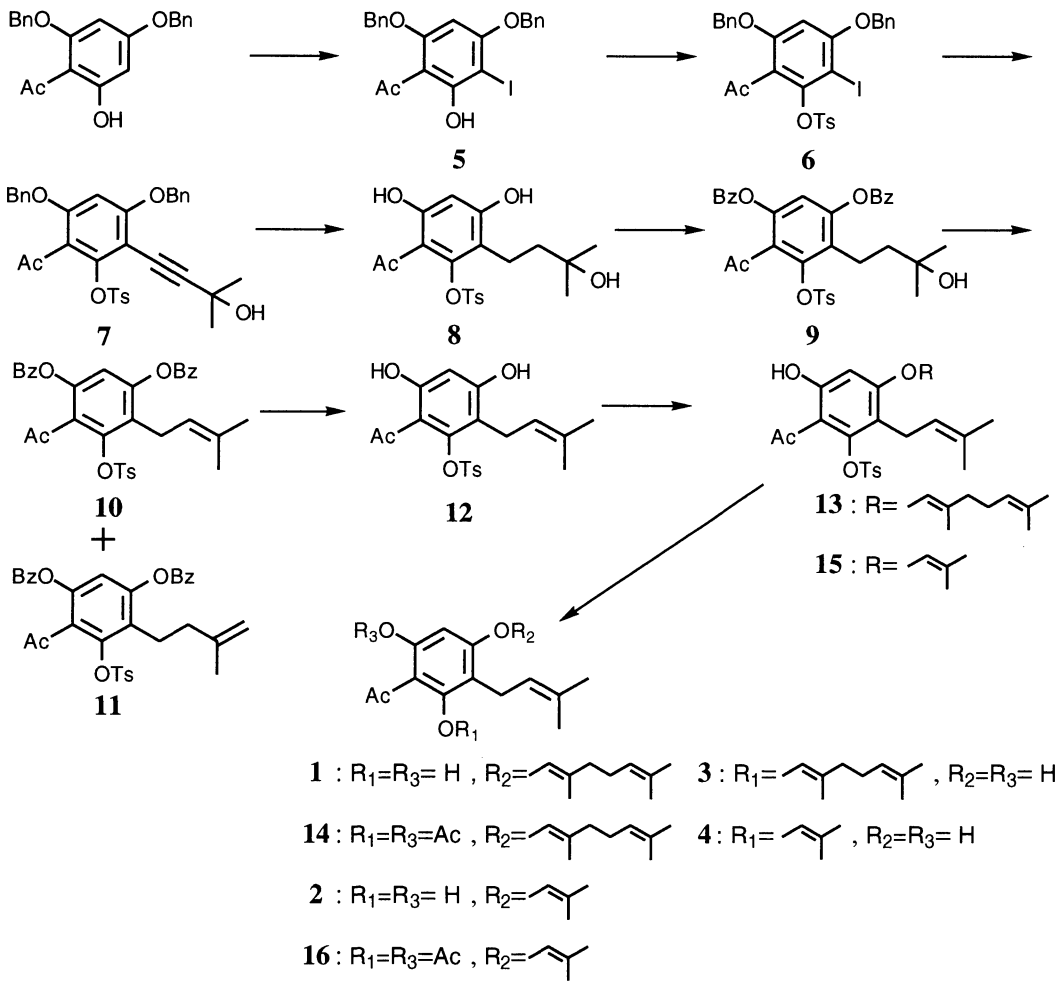
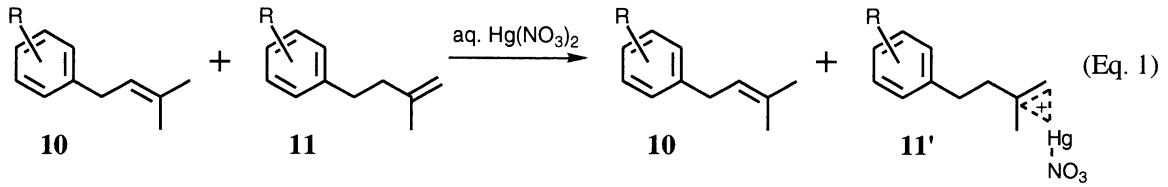
The palladium-catalyzed coupling reaction of 4',6'-bis(benzyloxy)-3'-iodo-2'-tosyloxyacetophenone with 2-methyl-3-butyn-2-ol gave 4',6'-bis(benzyloxy)-3'-(3-hydroxy-3-methylbutynyl)-2'-tosyloxyacetophenone (**7**). Dehydration of the benzoate obtained via two steps from **7** gave the 3'-prenylacetophenone, which was converted into 4',6'-dihydroxy-3'-prenyl-2'-tosyloxyacetophenone (**12**). Respective geranylation and prenylation of **12**, followed by hydrolysis gave 4'-geranyloxy- and 4'-prenyloxy-2',6'-dihydroxy-3'-prenylacetophenone (**1** and **2**). The structures of natural prenylacetophenones proposed as 2'-alkenyloxy isomers were revised as **1** and **2**, respectively.

A novel acetophenone was isolated from the fruit of *Evodia merrillii* along with other acetophenones.[1] Chemical evidence and spectroscopic studies have led to the assignment of 4'-geranyloxy-2',6'-dihydroxy-3'-(3-methyl-2-butenyl)acetophenone (**1**) to the novel acetophenone. Although C-alkenylation of phenols are traditionally carried out in acidic or basic media,[2] the majority of such reactions has resulted in relatively far from satisfactory yields. The Friedel-Crafts reactions of phenols bearing strongly electron-withdrawing substituents with allyl chloride have not proceeded at all.[3] The reaction of aryl halides with terminal alkynes in the presence of Pd(0) is very useful for the formation of carbon-carbon bonds,[4] and seems to be applicable to syntheses of prenylphenols. We wish to report here on the synthesis of 4'-geranyloxy-2',6'-dihydroxy-3'-(3-methyl-2-butenyl)acetophenone (**1**) and 4'-(3-methyl-2-butenyloxy)-2',6'-dihydroxy-3'-(3-methyl-2-butenyl)acetophenone (**2**) by using the palladium-catalyzed coupling reaction of the corresponding iodoacetophenone with propargyl alcohol. The present synthetic work has revealed that two natural prenylacetophenones isolated by Kumar et al.[5] are identical with the synthetic compounds **1** and **2**, respectively; their structural assignments as 2'-alkenyloxy-4',6'-dihydroxy-3'-prenylacetophenones (**3** and **4**) prove to be incorrect and have to be revised.

Tosylation of the iodoacetophenone[6] (**5**), which had been prepared from 4',6'-bis(benzyloxy)-2'-hydroxyacetophenone[7] by I_2-CF_3COOAg method, gave easily the tosylate (**6**). The coupling reaction of **6** (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 85 °C for 8.5 h gave the desired 3'-(3-hydroxy-3-methylbutynyl)acetophenone[8] (**7**) (paste) in a good yield. Catalytic hydrogenation of **7** in the presence of 5% Pd/C in MeOH at 30 °C gave easily 3'-(3-hydroxy-3-methylbutyl)-4',6'-dihydroxy-2'-tosyloxyacetophenone (**8**) (mp 181-183 °C), which was converted into the 4',6'-bis(benzoyloxy)acetophenone (**9**) (paste) with benzoyl chloride in the presence of K_2CO_3 in refluxing acetone. Compound **9** was dehydrated with $TsOH \cdot H_2O$ under



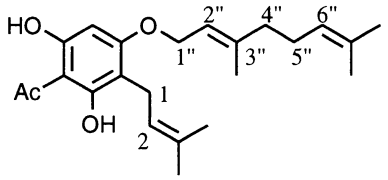
Scheme 1



(Eq. 1)

reflux in dry toluene for 1.5 h to give a mixture of the desired prenylacetophenone (**10**) and its isomer [3'-(3-methyl-3-butenyl)acetophenone] (**11**) in a high yield. ^{1}H NMR analysis indicated the ratio of **10** and **11** to be 87:13 [peaks due to C<u>H</u>$_2$-CH=CH(CH$_3$)$_2$ at δ 3.31 (2H, d) and CH$_2$CH$_2$C(CH$_3$)=C<u>H</u>$_2$ at δ 4.75 (2H, s)]. It was difficult to separate **10** from the mixture by column chromatography, recrystallization or distillation under reduced pressure. The mixture was treated with aq. Hg(NO3)2 (1.3 equiv. based on the above isomer ratio) in THF at room temperature for 40 min to give the terminal alkylmercurinium ion (**11'**) by the above equation 1,[9] and then the unchanged prenylacetophenone[10] (**10**) (paste) was quantitatively separated and purified in 72% yield (based on **9**) from the mixture by silica-gel column chromatography (CHCl3 as solvent). In the reaction of the alkene mixture with Hg(NO3)2, the internal alkylmercurinium ion of **10** was not obtained. The present separation procedure is the first successful attempt to separate the desired prenylphenol from the mixture of the internal and terminal alkenes. The selective reaction of Hg(NO3)2 to terminal alkenes may be used as a method

for the qualitative analysis of terminal alkenes, as well as a method for separation of a mixture of internal and terminal alkenes. Hydrolysis of **10** with a diluted solution of sodium hydroxide in MeOH under N_2 at 50 °C gave easily the dihydroxyprenylacetophenone (**12**) (paste). The reaction of **12** with geranyl bromide in the presence of K_2CO_3 in acetone at 20 °C for 2 h gave easily the 4'-geranyloxyprenylacetophenone (**13**) [δ 12.30 (1H, s, 6'-OH)]. The crude compound **13** was hydrolyzed with 30% potassium hydroxide in ethanol under reflux under N_2 for 1 h to give the desired 4'-geranyloxyprenylacetophenone[11] **1** (mp 98-100 °C), which was converted into the diacetate[12] (**14**). In a similar manner, prenylation of **12** with prenyl bromide, followed by hydrolysis of the resultant compound **15** [δ 12.50 (1H, s, 6'-OH)] gave easily the 4'-prenyloxyprenylacetophenone[13] **2** (mp 108-110 °C), which was converted into the diacetate[14] **16**.



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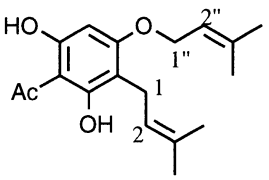

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Table 1. ^{1}H NMR (400MHz, $CDCl_3$) data for the prenylacetophenones **1** and **2**

Compd	*gem*-Me	Ac	CH_2	CH=C	Ar-H	OH
1	1.61(s), 1.68(s) 1.71(s), 1.77(s) 1.82(s)	2.66(s)	3.34(d, 1-H)[a] 4.53(d, 1"-H)[b] 2.06-2.13 (m, 4"-, 5"-H)	5.09(t, 6"-H)[b] 5.19(t, 2-H)[a] 5.44(t, 2"-H)[b]	6.02(s)	7.83(bs) 12.05(bs)
Natural product (**1**)	1.58(s), 1.66(s) 1.69(s), 1.73(s) 1.79(s)	2.64(s)	3.31(d, 1-H)[a] 4.51(d, 1"-H)[b] 2.09 (m, 4"-, 5"-H)	5.07(t, 6"-H) 5.17(t, 2-H)[a] 5.42(t, 2"-H)[b]	5.98(s)	8.41(bs) 11.64(bs)
2	1.72(s), 1.76(s) 1.78(s), 1.82(s)	2.66(s)	3.33(d, 1-H)[c] 4.51(d, 1"-H)[b]	5.19(t, 2-H)[c] 5.44(t, 2"-H)[b]	6.01(s)	8.14(bs) 11.90(bs)

a) J=7.3 Hz. b) J=6.4 Hz. c) J=6.8 Hz.

The ^{1}H NMR spectral data for the prenylacetophenones **1** and **2**, and the natural acetophenone are given in Table 1. The ^{1}H NMR spectra of **1** and the acetate **14** are shown to be identical with those of the natural prenylacetophenone **1** and the diacetate. The melting point (98-100 °C) of the synthetic 4'-geranyloxyprenylacetophenone **1** was not depressed by admixture with the natural product **1**. On the basis of these results, the structure of the natural acetophenone **1** was confirmed to be 4'-geranyloxy-2',6'-dihydroxy-3'-prenylacetophenone (**1**).

The ^{1}H NMR spectrum of the natural geranyloxyprenylacetophenone assigned as compound **3**[5] was identical with that of the synthetic 4'-geranyloxyprenylacetophenone **1**, but not identical with that of the synthetic 2'-geranyloxyprenylacetophenone **3**.[6] Therefore, the structure of this natural acetophenone isolated by Kumar et al. must be revised to be 4'-geranyloxy-2',6'-dihydroxy-3'-prenylacetophenone (**1**).

The ^{1}H NMR spectrum of another natural product, prenyloxyprenylacetophenone, assigned as compound **4**[5] was identical with that of the synthetic 4'-prenyloxyprenylacetophenone **2**, and not identical with that of the

synthetic 2'-prenyloxyprenylacetophenone **4**.[6] On the basis of these results, the structure of the second natural acetophenone described by Kumar et al. also must be revised to be 4'-prenyloxy-2',6'-dihydroxy-3'-prenylacetophenone (**2**).

The palladium-catalyzed coupling reaction of iodophenols with 2-methyl-3-butyn-2-ol has shown to be a useful method for regioselective syntheses of prenylphenols. The excellent chemoselectivity of $Hg(NO_3)_2$ to internal and terminal alkenes has been shown to be useful for the recognition and separation of terminal alkenes.

The authors are sincerely grateful to Dr. Chien-Fu Chen, National Research Institute of Chinese Medicine, Taiwan, Republic of China, for supplying natural 4'-geranyloxy-2',6'-dihydroxy-3'-prenylacetophenone.

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8) Compound **7**. ^1H NMR ($CDCl_3$) δ=1.52 (6H, s, CH_3 x 2), 2.28 (3H, s, $COCH_3$), 2.39 (3H, s, *p*-$C\underline{H}_3C_6H_4$), 4.93 and 5.00 (each 2H, s, CH_2Ph), 6.36 (1H, s, C5'-H), 7.80-8.10 (14H, m, Ar-H x 14). Found: C, 69.64; H, 5.61%. Calcd for $C_{34}H_{32}O_7S$: C, 69.85; H, 5.52%.
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10) Compound **10**: ^1H NMR ($CDCl_3$) δ=1.38 and 1.47 (each 3H, s, CH_3 x 2), 2.40 (3H, s, *p*-$C\underline{H}_3C_6H_4$), 2.45 (3H, s, $COCH_3$), 3.20 (2H, d, *J*=7 Hz, CH=C), 7.10 (1H, s, C5'-H), 7.15-8.15 (14H, m, Ar-H x 14).
11) Compound **1**: mp 98-100 °C; IR (KBr) 3115, 1640, 1590, 1525 cm^{-1}. Found: C, 74.13; H, 8.75%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%.
12) Diacetate **14**: An oil; ^1H NMR ($CDCl_3$) δ=1.61, 1.65 and 1.68 (each 3H, s, CH_3), 1.71 (6H, s, CH_3 x 2), 2.06-2.13 (4H, m, CH_2CH_2), 2.27 and 2.29 (each 3H, s, $OCOCH_3$), 2.42 (3H, s, $COCH_3$), 3.22 [2H, d, *J*=7.3 Hz, 1-H (CH_2)], 4.52 [2H, d, *J*=6.3 Hz, 1"-H (CH_2)], 5.06 [1H, t, *J*=7.3 Hz, 2-H (CH=C)], 5.09 [1H, t, *J*=6.3 Hz, 6"-H (CH=C)], 5.44 [1H, t, *J*=6.3 Hz, 1"-H (CH=C)], 6.54 (1H, s, C5'-H).
13) Compound **2**: mp 108-110 °C; IR (KBr) 3585, 3170, 1640, 1590, 1085 cm^{-1}. Found: C, 70.96; H, 7.66%. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95%.
14) Diacetate **16**: An oil; ^1H NMR ($CDCl_3$) δ=1.66, 1.71, 1.72 and 1.79 (each 3H, s, CH_3), 2.27 and 2.30 (each 3H, s, $OCOCH_3$), 2.42 (3H, s, $COCH_3$), 3.21 [2H, d, *J*=7.3 Hz, 1-H (CH_2)], 4.50 [2H, d, *J*=6.3 Hz, 1"-H (CH_2)], 5.06 [1H, t, *J*=7.3 Hz, 2-H (CH=C)], 5.44 [(1H, t, *J*=6.3 Hz, 2"-H (CH=C)], 6.54 (1H, s, C5'-H).

(Received March 11, 1994)