

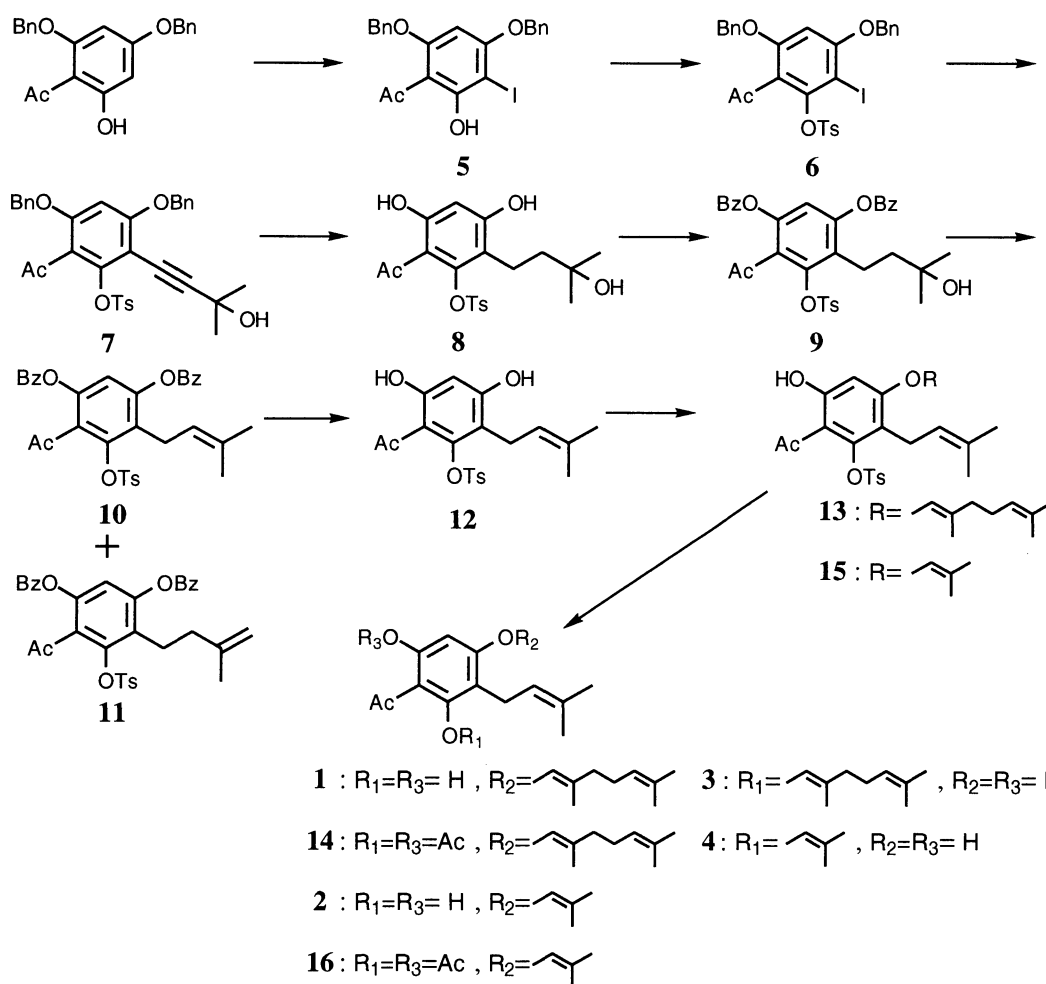
Regioselective Synthesis of Prenylphenols. Syntheses of Naturally Occurring 4'-Alkenyloxy-2',6'-dihydroxy-3'-(3-methyl-2-butenyl)acetophenones

Masao TSUKAYAMA,* Makoto KIKUCHI, and Yasuhiko KAWAMURA
Department of Chemical Science and Technology, Faculty of Engineering,
The University of Tokushima, Minamijosanjima-cho, Tokushima 770

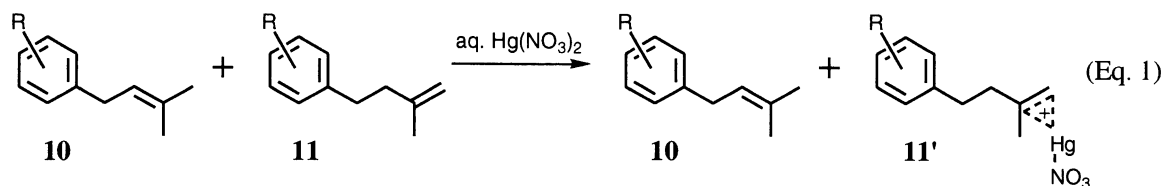
The palladium-catalyzed coupling reaction of 4',6'-bis(benzyloxy)-3'-iodo-2'-tosyloxyacetophenone with 2-methyl-3-butyn-2-ol gave 4',6'-bis(benzyloxy)-3'-(3-hydroxy-3-methylbutynyl)-2'-tosyloxyacetophenone (**7**). Dehydration of the benzoate obtained via two steps from **7** gave the 3'-prenylacetophenone, 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 iodoacetophenone⁶⁾ (**5**), which had been prepared from 4',6'-bis(benzyloxy)-2'-hydroxyacetophenone⁷⁾ by I₂-CF₃COOAg 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 PdCl₂ (0.03 mmol), CuI (0.03 mmol), PPh₃ (0.06 mmol) in Et₃N-DMF under N₂ at 85 °C for 8.5 h gave the desired 3'-(3-hydroxy-3-methylbutynyl)acetophenone⁸⁾ (**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 K₂CO₃ in refluxing acetone. Compound **9** was dehydrated with TsOH-H₂O under



Scheme 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. ^1H NMR analysis indicated the ratio of **10** and **11** to be 87:13 [peaks due to $\text{CH}_2\text{-CH=CH(CH}_3)_2$ at δ 3.31 (2H, d) and $\text{CH}_2\text{CH}_2\text{C(CH}_3)_2=\text{CH}_2$ 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. $\text{Hg}(\text{NO}_3)_2$ (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 prenylacetophenone¹⁰⁾ (**10**) (paste) was quantitatively separated and purified in 72% yield (based on **9**) from the mixture by silica-gel column chromatography (CHCl_3 as solvent). In the reaction of the alkene mixture with $\text{Hg}(\text{NO}_3)_2$, 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 $\text{Hg}(\text{NO}_3)_2$ 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 N₂ at 50 °C gave easily the dihydroxyprenylacetophenone (**12**) (paste). The reaction of **12** with geranyl bromide in the presence of K₂CO₃ 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 N₂ for 1 h to give the desired 4'-geranyloxyprenylacetophenone¹¹⁾ **1** (mp 98-100 °C), which was converted into the diacetate¹²⁾ (**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'-prenyloxyprenylacetophenone¹³⁾ **2** (mp 108-110 °C), which was converted into the diacetate¹⁴⁾ **16**.

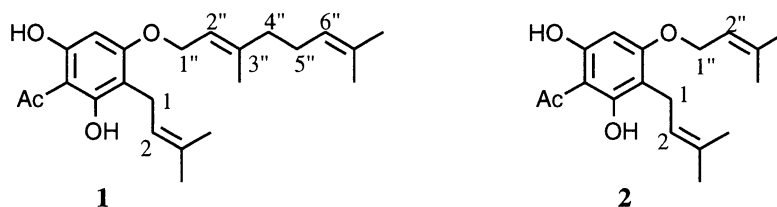


Table 1. ¹H NMR (400MHz, CDCl₃) data for the prenylacetophenones **1** and **2**

Compd	<i>gem</i> -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 ¹H NMR spectral data for the prenylacetophenones **1** and **2**, and the natural acetophenone are given in Table 1. The ¹H 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 ¹H 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 ¹H 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'-prenyloxyphenylacetophenone **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 $\text{Hg}(\text{NO}_3)_2$ 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.

References

- 1) L.-C. Lin, C.-J. Chou, K.-T. Chen, and C.-F. Chen, *J. Natural Products*, **56**, 926 (1993). Natural 4'-geranyloxy-2',6'-dihydroxy-3'-prenylacetophenone (**1**): mp 98-101 °C; IR (KBr) 3220, 1635, 1585, 1515 cm^{-1} .
- 2) A. C. Jain, P. Lal, and T. R. Seshadri, *Tetrahedron*, **26**, 2631 (1970); W. Steck, *Can. J. Chem.*, **49**, 1197 (1971); G. Manners, L. Jurd, and K. Stevens, *Tetrahedron*, **28**, 2949 (1972); P. Piccardi, S. Marcaletti, E. Bianchini, and L. Abis, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 624; A. C. Jain, A. Kumar, and R. C. Gupta, *ibid.*, **1979**, 279.
- 3) F. Bigi, G. Casiraghi, G. Casnati, and G. Sartori, *Synthesis*, **1981**, 310.
- 4) K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, **1975**, 4467.
- 5) V. Kumar, V. Karunaratne, M. R. Sanath, K. Meegalle, and J. K. MacLeod, *Phytochemistry*, **29**, 243 (1990). Natural geranyloxydihydroxy-3'-prenylacetophenone: mp 88-90 °C; ^1H NMR (CDCl_3) δ =1.59 (3H, s, CH_3), 1.65-1.68 (12H, s, CH_3), 2.08 (4H, m, $\text{W}_{1/2}$ =6 Hz, allylic H), 2.64 (3H, s, COCH_3), 3.31 and 4.52 (each 2H, d, J =7 Hz, 1- and 1''-H), 4.98-5.25 (2H, m, $\text{W}_{1/2}$ =14 Hz, vinyl H), 5.42 (1H, t, J =7 Hz, vinyl H), 5.98 (1H, s, C_5' -H), 8.76 and 11.50 (each 1H, s, OH). Natural prenyloxydihydroxy-3'-prenylacetophenone: mp 73-75 °C; ^1H NMR (CDCl_3) δ =1.73 and 1.80 (each 6H, s, CH_3), 2.66 (3H, s, COCH_3), 3.31 and 4.51 (each 2H, d, J =7 Hz, 1- and 1''-H), 5.21 and 5.44 (each 1H, t, J =7 Hz, 2- and 2''-H), 6.00 (1H, s, C_5' -H), 8.33 and 14.26 (each 1H, s, OH).
- 6) M. Tsukayama, M. Kikuchi, and S. Yoshioka, *Chem. Lett.*, **1993**, 1895.
- 7) M. Tsukayama, Y. Kawamura, H. Tamaki, T. Kubo, and T. Horie, *Bull. Chem. Soc. Jpn.*, **62**, 826 (1989).
- 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 - $\text{CH}_3\text{C}_6\text{H}_4$), 4.93 and 5.00 (each 2H, s, CH_2Ph), 6.36 (1H, s, C_5' -H), 7.80-8.10 (14H, m, Ar-H x 14). Found: C, 69.64; H, 5.61%. Calcd for $\text{C}_{34}\text{H}_{32}\text{O}_7\text{S}$: C, 69.85; H, 5.52%.
- 9) J. L. Wardell, "Mercury," in "Comprehensive Organometallic Chemistry," ed by G. Wilkinson, F. G. A. Stone, and E. W. Abel, Pergamon Press, New York (1982), Vol. 2, Chap. 17, pp. 867-873.
- 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 - $\text{CH}_3\text{C}_6\text{H}_4$), 2.45 (3H, s, COCH_3), 3.20 (2H, d, J =7 Hz, $\text{CH}=\text{C}$), 7.10 (1H, s, C_5' -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 $\text{C}_{23}\text{H}_{32}\text{O}_4$: 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 ($\text{CH}=\text{C}$)], 5.09 [1H, t, J =6.3 Hz, 6''-H ($\text{CH}=\text{C}$)], 5.44 [1H, t, J =6.3 Hz, 1''-H ($\text{CH}=\text{C}$)], 6.54 (1H, s, C_5' -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 $\text{C}_{18}\text{H}_{24}\text{O}_4$: 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 ($\text{CH}=\text{C}$)], 5.44 [(1H, t, J =6.3 Hz, 2''-H ($\text{CH}=\text{C}$)), 6.54 (1H, s, C_5' -H)].

(Received March 11, 1994)