Synthesis of Geranyl Phenyl Ethers Based on the Cytotoxic Monoterpenoids from the Liverwort Genus *Trichocolea*

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The synthesis of three geranyl ethers, methyl 4-[{(2*E*)-3,7-dimethyl-5-oxo-2,6-octadienyl}oxy]-3-methoxybenzoate **(1)**, methyl 4-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-3-methoxybenzoate (**2**), and methyl 4-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-3-hydroxybenzoate (**3**), previously isolated from New Zealand *Trichocolea* liverworts, is described. Differing reactivity of the hydroxy groups of methyl protocatachuate toward alkylation and the ability of alkyl groups to migrate from oxygen to an *ortho*-oxygen in these benzene derivatives are noted.

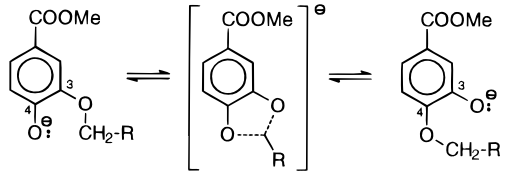
Liverworts of the genus *Trichocolea* (family Trichocolaceae) are a treasury of isoprenyl phenyl ethers. We have reported[1] that the main cytotoxic component of *T. mollissima* (Hook. F. and Tayl.) Gott. is the 5-oxogeranyl ether **1**. This compound has shown cytotoxic activity in the U.S. National Cancer Institute's AIDS-related lymphoma screens.[2]

Here we describe the preparation of **1**, along with syntheses of two less-oxidized geranyl ethers, **2** and **3**, which we have isolated from *T. tomentella* (Ehrh.) Dum.[1] and *T. hatcheri* Hodgs.,[3] respectively. These compounds have not been synthesized previously.

The key intermediate in the synthesis of **1** is a geranyl halide that has appropriate functionality at C-5 and is suitable for alkylating methyl vanillate. The inexpensive and commercially available 3-methyl-2-butenoic acid is readily converted into its acid chloride by reaction with excess thionyl chloride.[4] This compound has been converted previously into 8-chloro-2,6-dimethyl-2,6-octadien-4-one (**4**) by treatment with isoprene in the presence of tin (IV) chloride.[5] Both **4** and the corresponding bromide were able to be stored for short periods at low temperature, but decomposed rapidly and spontaneously, presumably when concentrations of HBr or HCl had built up to a critical level. When freshly prepared **4** or the bromide was used in an attempted alkylation of methyl vanillate, the only products identified were ocimenones (**5**). To avoid loss of halide from the alkylating agent, via either enolic or enolate species, **4** was reduced to alcohol **6**. This compound could be reacted satisfactorily with methyl vanillate to yield the 5-hydroxygeranyl ether (**7**), which, upon oxidation by pyridinium chlorochromate−alumina,[6] formed the desired natural product **1** in about 30% yield. Synthetic **1** proved to be identical (TLC, IR, ^{1}H and ^{13}C NMR) to the natural product isolated from *T. mollissima*.[1]

Geranyl phenyl ether **2**, identical to that isolated from *T. tomentella*,[1] was readily obtained in good yield by reaction of methyl vanillate with geranyl bromide. The synthesis of the corresponding phenolic compound **3**, however, uncovered some interesting chemistry. Reaction of methyl 3,4-dihydroxybenzoate (methyl protocatechuate) with geranyl bromide and sodium hydride in DMF at 0° gave a monogeranyl ether, which proved to be identical to the natural product **3** from *T. hatcheri*.[3] Also obtained was the double alkylation product **8**. When the reaction was conducted at room temperature, however, compound **8** and a new monogeranyl ether **9** were obtained. Compound **9** had very similar ^{1}H and ^{13}C NMR spectra to those of **3** but differed significantly in the pattern of the two overlapping signals for the protons ortho to the carboxymethyl group (δ 7.5−7.7) in the ^{1}H NMR spectrum. The phenolic OH signals also differed considerably (δ 5.7 in **3** and δ 6.1 in **9**). As **3** had already been established as having the 4-geranyloxy-3-hydroxy substitution pattern by NOE studies,[3] the new compound was deemed to be the 3-geranyloxy-3-hydroxy isomer **9**. It appears that **3** is the kinetically favored product, corresponding to alkylation of the more acidic 4-hydroxyl group. Compound **9** might arise through the intermediacy of the dialkyl compound **8** or through an alkyl migration. Equilibrium should favor formation of the more stabilized 4-oxyanion (Scheme 1), and this would lead to the 3-geranyloxy compound. This latter proposal was supported by the surprising observation that methylation of either **3** or **9** (with methyl iodide and potassium carbonate in DMF) led to the same 4-geranyl-3-methoxy product, **2**. It appears that, under these reaction conditions, migration of the geranyl group does indeed occur, with the reaction being completed by preferential alkylation of the less stabilized and more nucleophilic 3-oxyanion. In a similar fashion, alkylation of methyl 3-hydroxy-4-methoxybenzoate with geranyl bromide gave a mixture consisting of mainly the 3-geranyloxy-4-methoxy compound **10**, along with a small percentage of its isomer **2**, the result of methyl migra-

Scheme 1. Proposed Alkyl Migrations



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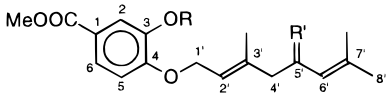
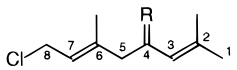
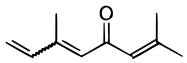
tion. Such migrations of alkyl groupings between *ortho*-positioned oxygens on a benzene ring are unusual and are probably facilitated by the electron-withdrawing carboxymethyl grouping.



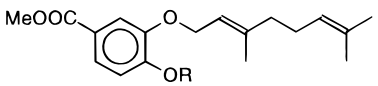
1 R = Me; R' = O
2 R = Me; R' = H,H
3 R = H; R' = H,H
7 R = Me; R' = H,OH



4 R = O
6 R = H,OH



5



8 R = geranyl
9 R = H
10 R = Me

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler hot stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using Varian Gemini-200 and Varian VXR-300 spectrometers for $CDCl_3$ solutions referenced to either $CHCl_3$ (^{1}H, δ_H, 7.27) or $CDCl_3$ (^{13}C, δ_c 77.08). Multiplicities of the ^{13}C NMR signals were determined from the DEPT spectra, and spectral assignments were based on those for compounds already reported in this series.[1,3] Elemental analyses were performed by the Campbell Microanalytical Laboratory, Otago University. IR spectra were recorded on a Perkin−Elmer 1600 FTIR spectrophotometer. TLC was carried out on Si gel 60 F_{254} precoated 0.2-mm aluminum sheet (Merck 5562). Developed plates were visualized by UV light and by staining with solution of either 1% anisaldehyde + 2% H_2SO_4 in AcOH or 1% vanillin + 1% H_2SO_4 in EtOH. Flash chromatography was carried out with Si gel 230−400 mesh.

8-Chloro-2,6-dimethyl-2,6-octadien-4-ol (6). A solution of 8-chloro-2,6-dimethyl-2,6-octadien-4-one (**4**)[5] (140 mg, 0.75 mmol) in dry THF (0.25 mL) was added to absolute EtOH (2.5 mL). The mixture was cooled to −40 °C and $NaBH_4$ (56.5 mg, 1.5 mmol) was added. The reaction mixture was stirred for 15 min at −40 °C, allowed to warm to −10 °C, and quenched by the addition of H_2O (50 mL). Et_2O (25 mL) was added, the layers were separated, and the organic layer was evaporated to dryness. Separation by flash chromatography (elution with EtOAc−hexane 25:75) yielded **6** (45 mg, 32%): colorless oil; TLC R_f 0.22 (blue with anisaldehyde−H_2SO_4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70/1.73/1.79 (each 3H, s, H-1, 2-Me, 6-Me), 2.23 (2H, m, H-5), 4.10 (2H, d, 8 Hz, H-8), 4.50 (1H, m, H-4), 5.17 (1H, br d, 8 Hz, H-3), 5.55 (1H, br t, 8 Hz, H-7); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.2/22.6 (each q, 2-Me, 6-Me), 25.7 (q, C-1), 40.6 (t, C-8), 47.6 (t, C-5), 66.5 (d, C-4), 123.5/127.3 (each d, C-3, 7), 127.3 (C-2), 135.3/139.2 (each s, C-2,6).

General Procedure for Preparation of Geranyl Phenyl Ethers. A solution of the alkyl halide in dry DMF was added dropwise with stirring to a flame-dried flask containing the phenolic esters and NaH under N_2. The mixture was stirred at the specified temperature for the specified time, following which the reaction mixture was partitioned between H_2O and CH_2Cl_2. The H_2O fraction was re-extracted with CH_2Cl_2, the organic fractions combined, dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. Flash chromatography afforded the geranyl phenyl ethers. Conditions are summarized as: product, phenolic ester (mass, mmol); alkyl halide (mass, mmol); NaH (mass, mmol); DMF (vol); reaction temperature; reaction time; data.

Methyl 4-[{(2*E*)-3,7-dimethyl-5-hydroxy-2,6-octadienyl}oxy]-3-methoxybenzoate (7): methyl vanillate (88 mg, 0.48 mmol); 8-chloro-2,6-dimethyl-2,6-octadien-4-ol (110 mg, 0.58 mmol); NaH (60%, 19.2 mg, 0.48 mmol) in dry DMF (0.5 mL); 20 °C; 26 h. Flash chromatography (5% EtOAc−hexane) gave **7** (125 mg, 78%); colorless oil; TLC R_f 0.13 (blue with anisaldehyde−H_2SO_4); *anal.* C 68.26%, H 7.64%, calcd for $C_{19}H_{26}O_5$, C 68.26%, H 7.78%; IR (film) 3426, 2924, 1714, 1599, 1513, 1435, 1271, 1219, 1135, 990, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69 (3H, d, J = 2 Hz, 7′-Me), 1.71 (3H, d, J = 1 Hz, H-8′), 1.80 (3H, d, J = 1 Hz, 3′-Me), 2.23 (2H, m, H-4′), 3.89 (3H, s, 1-COOMe), 3.92 (3H, s, 3-OMe), 4.51 (1H, dt, J = 5, 8 Hz, H-5′), 4.70 (2H, d, J = 6 Hz, H-1′), 5.16 (1H, br d, J = 8 Hz, H-6′), 5.60 (1H, br d, J = 7 Hz, H-2′), 6.87 (1H, d, J = 8 Hz, H-5), 7.55 (1H, d, J = 2 Hz, H-2), 7.65 (1H, dd, J = 2, 8 Hz, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.1 (q, 3′-Me), 18.2 (q, 7′-Me), 25.7 (q, C-8′), 47.8 (t, C-4′), 51.9 (q, 1-COO*Me*), 56.0 (q, 3-OMe), 65.6 (t, C-1′), 66.4 (d, C-5′), 111.8 (d, C-5), 112.2 (d, C-2), 122.4 (d, C-2′), 122.6 (s, C-1), 123.4 (d, C-6), 127.4 (d, C-6′), 135.2 (s, C-7′), 138.0 (s, C-3′), 149.0 (s, C-3), 152.1 (s, C-4), 166.8 (s, 1-*C*OOMe).

Methyl 4-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-3-methoxybenzoate (2): methyl vanillate (300 mg, 1.65 mmol); geranyl bromide (295 mg, 1.36 mmol); NaH (60%, 66 mg, 1.65 mmol) in dry DMF (2 mL); 20 °C; 26 h; flash chromatography (5% EtOAc−hexane) gave **2** (380 mg, 60%); mp 39−40 °C; TLC (25% EtOAc−hexane) R_f 0.31 (grey with vanillin−H_2SO_4); *anal.* C 71.79%, H 8.31%, calcd for $C_{19}H_{26}O_4$, C 71.70%, H 8.18%; identical to the natural product (TLC, IR ^{1}H and ^{13}C NMR).[1]

Methyl 4-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-3-hydroxybenzoate (3): methyl 3,4-dihydroxybenzoate (278 mg, 1.65 mmol); geranyl bromide (434 mg, 2.00 mmol); NaH (60%, 66 mg, 1.65 mmol) in dry DMF (2 mL); 0 °C; 17 h; flash chromatography (5% EtOAc−hexane) gave **3** (220 mg, 44%): mp 32−34 °C; TLC (40% EtOAc−hexane) R_f 0.58 (dark green with vanillin−H_2SO_4); *anal.* C 71.92%, H 8.61%, calcd for $C_{18}H_{24}O_4$, C 71.05%, H 7.89%; identical to the natural product (TLC, IR, ^{1}H and ^{13}C NMR).[3] Also isolated was methyl 3,4-

di-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-benzoate (**8**) (130 mg, 18%): TLC (40% EtOAc−hexane) R_f 0.47 (dark green with vanillin−H_2SO_4); *anal.* C 76.27%, H 9.35%, calcd for $C_{28}H_{40}O_4$, C 76.36%, H 9.09%; IR (film) 2920, 1720, 1596, 1514, 1438, 1267, 1208, 1132, 1009, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.59 (6H, br s, 7′-Me), 1.66 (6H, br s, H-8′), 1.73/1.76 (each 3H, br s, 3′-Me), 2.08 (8H, m, H-4′,5′), 3.87 (3H, s, 1-COOMe), 4.66/4.69 (each 2H, d, J = 8 Hz, H-1′), 5.08 (2H, m, H-6′), 5.50 (2H, br t, J = 7 Hz, H-2′), 6.87 (1H, d, J = 8 Hz, H-5), 7.56 (1H, d, J = 2 Hz, H-2), 7.63 (1H, dd, J = 2, 9 Hz, H 6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.7 (2 × q, 3′-Me), 17.7 (2 × q, 7′-Me), 25.6/26.2 (each q, C-8′), 26.2/26.3 (each t, C-5′), 39.5/39.6 (each t, C-4′), 52.0, (q, 1-COO*Me*), 66.1 (2 x t, C-1′), 112.3 (d, C-5), 114.5 (d, C-2), 119.5/119.6 (each d, C-2′), 122.4 (s, C-1), 123.5 (d, C-6), 123.8/123.9 (each d, C-6′), 131.7/131.8 (each s, C-7′), 140.7/140.8 (each s, C-3′), 148.2 (s, C-3), 152.9 (s, C-4), 167.0 (s, 1-*C*OOMe).

Methyl 3-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-4-hydroxybenzoate (9): methyl 3,4-dihydroxybenzoate (278 mg, 1.65 mmol); geranyl bromide (358 mg, 1.65 mmol); NaH (60%, 66 mg, 1.65 mmol) in dry DMF (2 mL); 20 °C; 48 h; flash chromatography (5% EtOAc−hexane) gave (**8**) (196 mg, 27%) and **9** (245 mg, 49%); mp 34−37 °C; TLC (30% EtOAc−hexane) R_f 0.45 (dark green with vanillin−H_2SO_4); *anal.* C 71.05%, H 7.89%, calcd for $C_{18}H_{24}O_4$, C 71.05%, H 7.89%; IR (film), 3388, 2921, 1709, 1595, 1512, 1438, 1286, 1211, 1126, 988, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.62 (3H, br s, 7′-Me), 1.68 (3H, br s, H-8′), 1.77 (3H, br s, 3′-Me), 2.11 (4H, m, H-4′,5′), 3.89 (3H, s, COOMe), 4.66 (2H, d, J = 7 Hz, H-1′), 5.09 (1H, m, H-6′), 5.49 (1H, br t, J = 7 Hz, H-2′), 6.12 (1H, s, 4-OH), 6.94 (1H, d, J = 8 Hz, H-5), 7.57 (1H, d, J = 2 Hz, H-2), 7.63 (1H, dd, J = 2, 8 Hz, H-6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.7 (q, 3′-Me), 17.8 (q, 7′-Me), 25.7 (q, C-8′), 26.3 (t, C-5′), 39.6 (t, C-4′), 52.0 (q, 1-COO*Me*), 66.0 (t, C-1′), 113.1 (d, C-5), 114.1 (d, C-2), 118.6 (d, C-2′), 122.8 (s, C-1), 123.7 (d, C-6), 124.1 (d, C-6′), 132.0 (s C-7′), 142.7 (s, C-3′), 145.5 (s, C-4), 150.4 (s, C-3), 167.0 (s, 1-*C*OOMe).

Methyl 3-[{(2*E*)-3,7-dimethyl-2,6-octadienyl}oxy]-4-methyoxybenzoate (10): methyl 3-hydroxy-4-methoxybenzoate (1230 mg, 6.76 mmol); geranyl bromide (1779 mg, 8.19 mmol); NaH (60%, 295 mg, 7.37 mmol) in dry DMF (8.2 mL); 20 °C; 26 h; flash chromatography (3% EtOAc−hexane) gave **10** (1503 mg, 70%) (14); mp 40−42 °C; TLC (30% EtOAc−hexane) R_f 0.36 (green with vanillin−H_2SO_4); *anal.* C 71.43%, H 8.17%, calcd for $C_{19}H_{26}O_4$, C 71.70%, H 8.18%; IR (Nujol) 1720, 1594, 1513, 1463, 1376, 1267, 1218, 1131, 1011, 835, 726 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (3H, br s, 7′-Me), 1.66 (3H, br s, H-8′), 1.77 (3H, d, J = 1 Hz, 3′-Me), 2.09 (4H, m, H-4′,5′), 3.89 (3H, s, 1-COOMe), 3.92 (3H, s, 4-OMe), 4.67 (2H, d, J = 7 Hz, H-1′), 5.08 (1H, m, H-6′), 5.52 (1H, br t, J = 7 Hz, H-2′), 6.88 (1H, d, J = 8 Hz, H-5), 7.56 (1H, d, J = 2 Hz, H-2), 7.67 (1H, dd, J = 2, 8 Hz, H-6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.7 (q, 3′-Me), 17.7 (q, 7′-Me), 25.7 (q, C-8′), 26.3 (t, C-5′), 39.7 (t, C-4′), 52.0 (q, 1-COO*Me*), 56.0 (q, 4-OMe), 65.9 (t, C-1′), 110.4 (d, C-5), 113.8 (d, C-2), 119.3 (d, C-2′), 122.6 (s, C-1), 123.5 (d, C-6), 123.9 (d, C-6′), 131.8 (s, C-7′), 141.4 (s, C-3′), 147.9 (s, C-4), 153.4 (s, C-3), 167.0 (s, 1-*C*OOMe).

Methyl 4-[{(2*E*)-3,7-dimethyl-5-oxo-2,6-octadienyl}oxy]-3-methoxybenzoate (1). Pyridinium chlorochromate−alumina[6] (1402 mg, 1.14 mmol) was added to solution of **7** (127 mg, 0.38 mmol) in dry hexane (10 mL). After stirring for 24 h, the mixture was filtered and washed with Et_2O (3 × 10 mL). The combined Et_2O solutions were evaporated. Flash chromatography (elution with EtOAc−hexane 5:95) yielded **1** (37.8 mg, 30%), identical to the natural product (TLC, IR, ^1H and ^{13}C NMR).[1]

Methylation of 3 and 9. A mixture of K_2CO_3 (48.4 mg, 0.35 mmol), CH_3I (26.0 mg, 0.18 mmol), and **3** (35.6 mg, 0.12 mmol) in DMF (1.0 mL) was stirred at 20 °C for 17 h. The reaction mixture was diluted with H_2O and extracted with Et_2O. The Et_2O layer was washed with H_2O and saturated aqueous NaCl and the H_2O before drying over $MgSO_4$ and evaporation. Preparative TLC gave **2** (20 mg, 54%). Likewise, reaction of **9** (90 mg) gave **2** (50 mg, 50.4%).

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