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Total Synthesis of Daphneticin, a Coumarinolignoid

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Daphnetin (**3**) was transformed with excess benzyl chloride into 7,8-dibenzoyloxycoumarin (**4**), which on treatment with trifluoroacetic acid in benzene or aluminum chloride in benzene gave 8-benzoyloxy-7-hydroxycoumarin (**5**) in good yield. Condensation of **5** and ethyl 2-bromo-3-(4-acetoxy-3,5-dimethoxyphenyl)-3-oxopropionate (**9**), prepared from ethyl benzylsyngoylacetate (**7**) in two steps, in the presence of sodium hydride afforded **10** in good yield, and the condensation product (**10**) was then reduced with lithium borohydride to yield a mixture of the diols (**11a, b**). Treatment of the diols with 36% hydrochloric acid in acetic acid provided daphneticin (**1**) in 68% yield.

Keywords—coumarinolignoid; daphneticin; coumarin; daphnetin; antitumor

In the previous paper,¹⁾ we reported a convenient synthesis of cleomiscosin A, which is cytotoxic.²⁾ Five natural coumarinolignans (cleomiscosin A,^{3a-d)} cleomiscosin B,^{3a,b,d)} propacin,⁴⁾ aquillochin,^{3d,5)} and daphneticin (**1**)⁶⁾ have been reported so far. Daphneticin also showed⁷⁾ cytotoxic activity *in vitro* in the Walker-256-carcinoma-ascites system. Daphneticin, as a racemic compound, has been isolated⁶⁾ from roots and stems of *Daphne tangutica* (Thymelaeaceae) and the structure was proposed⁶⁾ on the basis of selective proton nuclear magnetic resonance (¹H-NMR) and carbon-13 nuclear magnetic resonance (¹³C-NMR) heterodecoupling studies of daphneticin diacetate (**2**). Concerning the synthesis of daphneticin, Cordell and Lin⁸⁾ reported that the treatment of daphnetin (**3**) with sinapyl alcohol under oxidative reaction conditions (horseradish peroxidase and silver oxide) gave daphneticin in low yields.

Here, we wish to describe a facile synthesis of daphneticin from a readily available compound (**7**) and commercially available daphnetin.

Alkylation of 7,8-dihydroxy-4-methylcoumarin(4-methyldaphnetin) and 7,8-dihydroxy-6-methoxycoumarin (fraxetin) occurs^{1,9)} regioselectively at the C-7 position in the phenol and results predominantly in 7-alkylated coumarins. In order to prepare the desired 8-benzylated compound (**5**), we investigated monodebenzylation of 7,8-dibenzoyloxycoumarin (**4**) under acidic reaction conditions. The compound **4** was obtained in good yield by benzylation of daphnetin with an excess of benzyl chloride in *N,N*-dimethylformamide (DMF) containing anhydrous potassium carbonate. Treatment of **4** with aluminum bromide in nitrobenzene or in carbon disulfide at room temperature gave daphnetin as a sole product, and the desired compound (**5**) was not obtained. Further, when 2% sulfuric acid in ethanol or 36% hydrochloric acid in acetic acid was used at room temperature, the starting material (**4**), monobenzyl products (**5** and **6**) and daphnetin were found in the reaction mixture. It was difficult to obtain the desired monodebenzyl product (**5**) in a large amount. Eventually, debenylation of **4** with trifluoroacetic acid (TFA) in benzene or aluminum chloride in benzene at room temperature afforded the desired compound (**5**) in good yield together with the minor regioisomer (**6**).

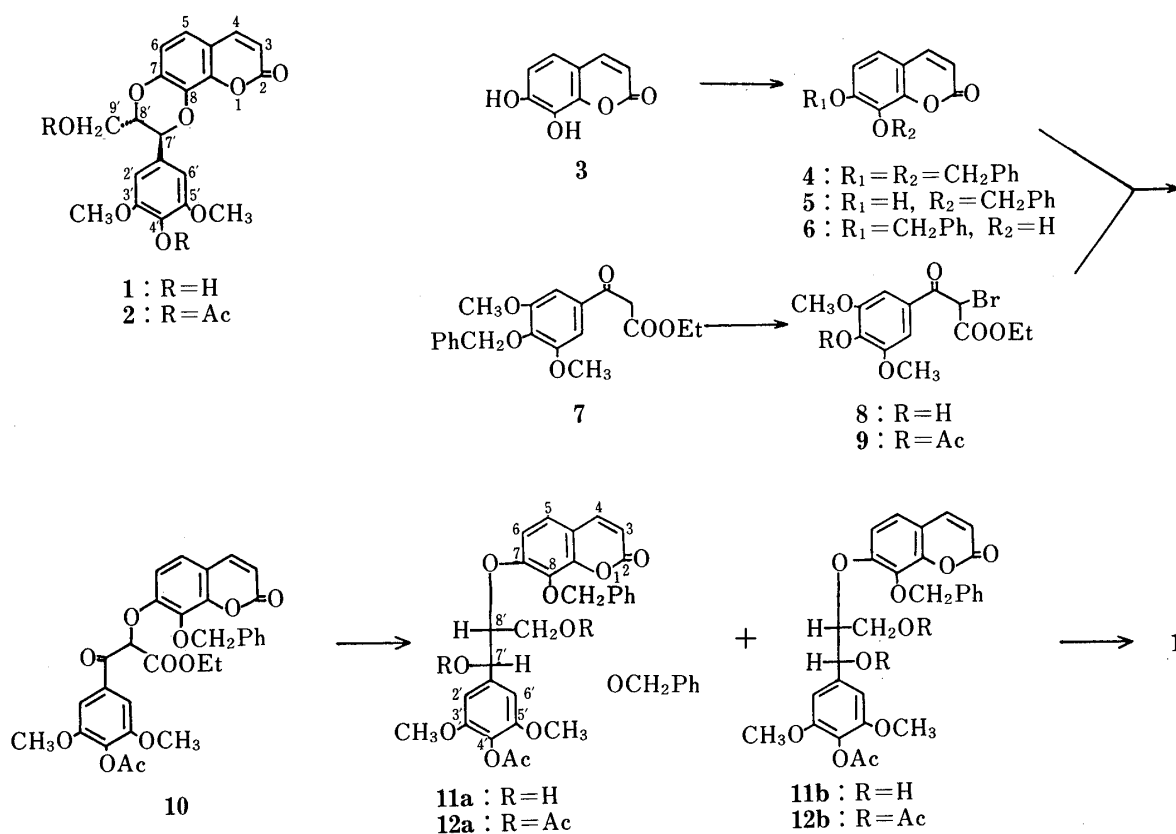


Chart 1

On the other hand, the phenylpropane segment (9) of daphneticin was synthesized as follows. Ethyl 3-(4-benzyloxy-3,5-dimethoxyphenyl)-3-oxopropionate (7),¹⁰⁾ was reacted with bromine to form a bromophenolic compound (8), which was converted into an acetyl compound (9) by acetylation with acetic anhydride and pyridine.

Next, condensation of an excess of 9 with the monobenzyl compound (5) in a mixture of DMF and tetrahydrofuran (THF) in the presence of sodium hydride gave 10 in 97% yield. The condensation product (10) was reduced with lithium borohydride in THF to afford a mixture of diols (11a, b).¹¹⁾ The infrared (IR) spectrum of the diols¹²⁾ showed a hydroxyl band at 3550 cm⁻¹, and the keto group band (1690 cm⁻¹) and the ester group band (1750 cm⁻¹) observed in 10 were absent.

Finally, the diols (11a, b) cyclized upon heating in acetic acid in the presence of 36% hydrochloric acid, presumably *via* a quinone methide intermediate such as those involved in the syntheses of cleomiscosin A¹⁾ and silybin derivatives,¹³⁾ to give daphneticin in 68% yield as a single product. The mass spectrum (MS) revealed the characteristic retro Diels–Alder fragmentation peak⁶⁾ at *m/z* 210, and in the ¹H-NMR spectrum, the C-7' proton signal was observed as a doublet at δ 5.03 whose coupling constant was 8 Hz, demonstrating that the two hydrogens of the benzodioxane moiety are *trans*-oriented.⁶⁾ The synthetic material was identical with a sample⁶⁾ of natural daphneticin in terms of MS, IR spectra and mixed melting point, and the spectral data of daphneticin diacetate (2), obtained by a usual acetylation procedure, were also identical with those reported for the diacetate⁶⁾ of natural daphneticin.

Experimental

All melting points are uncorrected. Column chromatography was run on Merck Silica gel 60 (70–230 mesh) and thin-layer chromatography (TLC) was performed on glass plates precoated with Kieselgel 60 F₂₅₄ (Merck). MS were

recorded on a Hitachi M-52 spectrometer and high-resolution MS on a Hitachi M-80 spectrometer. IR spectra were obtained on a JASCO IRA-3 spectrophotometer. ^1H -NMR spectra were recorded on a JEOL JNM-PS-100 nuclear magnetic resonance spectrometer and ^{13}C -NMR spectra on a JEOL JNM-FX-100 Fourier-transform spectrometer operating at 25.00 MHz, with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, dd=doublet-of-doublets, t=triplet, q=quartet, m=multiplet, br=broad).

7,8-Dibenzoyloxycoumarin (4)—A mixture of daphnetin (**3**) (2.33 g), benzyl chloride (4.52 ml), and anhydrous K_2CO_3 (5.38 g) in DMF (20 ml) was heated at 60°C for 13 h. The reaction mixture was filtered and the filtrate was added to AcOEt (70 ml). The organic layer was washed with 10% NaOH and water, dried over Na_2SO_4 , and evaporated. The crude product was recrystallized from benzene, yielding colorless needles (4.30 g, 92%). mp $125\text{--}126^\circ\text{C}$. Anal. Calcd for $\text{C}_{23}\text{H}_{18}\text{O}_4$: C, 77.08; H, 5.06. Found: C, 77.23; H, 4.97. MS m/z : 358 (M^+), 267, 181, 178 (100%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1720, 1605. ^1H -NMR (CDCl_3) δ : 5.11, 5.16 (4H, 2 $\times$ s, 2 $\times$ OCH_2Ph), 6.17 (1H, d, $J=9.5$ Hz, $\text{C}_3\text{-H}$), 6.84 (1H, d, $J=9$ Hz, $\text{C}_6\text{-H}$), 7.05 (1H, d, $J=9$ Hz, $\text{C}_5\text{-H}$), 7.33 (10H, br s, 10 $\times$ aromatic protons), 7.51 (1H, d, $J=9.5$ Hz, $\text{C}_4\text{-H}$).

8-Benzoyloxy-7-hydroxycoumarin (5) and 7-Benzoyloxy-8-hydroxycoumarin (6)—i) Debenzylation of **4** with TFA in Benzene: A mixture of **4** (4.55 g) in TFA (30 ml) and benzene (30 ml) was stirred at room temperature for 5 h. After the starting material had disappeared, the reaction mixture was poured into ice-water and extracted with benzene. The benzene layer was washed with water, dried over Na_2SO_4 , and evaporated to give the residual crude product. The product was chromatographed on a silica gel column with a mixture of CHCl_3 and acetone (20:1), affording **5** (2.93 g, 86%) and **6** (0.23 g, 7%). The compound **6** gave a positive Gibb's test.

Compound **5**: Recrystallized from benzene. Colorless needles. mp $168\text{--}170^\circ\text{C}$. TLC (silica gel/ CHCl_3 -acetone (20:1)), $R_f=0.25$. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{O}_4$: C, 71.63; H, 4.51. Found: C, 72.01; H, 4.30. MS m/z : 268 (M^+ , 100%), 178, 150, 121. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3370, 1705, 1610. ^1H -NMR (CDCl_3) δ : 4.63 (1H, s, OH), 5.15 (2H, s, OCH_2Ph), 6.17 (1H, d, $J=9.5$ Hz, $\text{C}_3\text{-H}$), 6.80 (1H, d, $J=9$ Hz, $\text{C}_6\text{-H}$), 6.90 (1H, d, $J=9$ Hz, $\text{C}_5\text{-H}$), 7.33 (5H, br s, 5 $\times$ aromatic protons), 7.52 (1H, d, $J=9.5$ Hz, $\text{C}_4\text{-H}$).

Compound **6**: Recrystallized from benzene. Colorless needles. mp $160\text{--}162^\circ\text{C}$ (lit.,¹⁴) $162\text{--}163^\circ\text{C}$. TLC silica gel/ CHCl_3 -acetone (20:1), $R_f=0.48$. MS m/z : 268 (M^+ , 100%), 178, 150, 121. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3360, 1705, 1610. ^1H -NMR (CDCl_3) δ : 5.19 (1H, br s, OH), 5.27 (2H, s, OCH_2Ph), 6.19 (1H, d, $J=9.5$ Hz, $\text{C}_3\text{-H}$), 6.80 (1H, d, $J=9$ Hz, $\text{C}_6\text{-H}$), 7.05 (1H, d, $J=9$ Hz, $\text{C}_5\text{-H}$), 7.32 (5H, br s, 5 $\times$ aromatic protons), 7.57 (1H, d, $J=9.5$ Hz, $\text{C}_4\text{-H}$).

ii) Debenzylation of **4** with AlCl_3 in Benzene: A suspension of AlCl_3 (51 mg) in dry benzene (4 ml) was added to a solution of **4** (100 mg) in dry benzene (1 ml). The reaction mixture was stirred at room temperature for 5 h and the mixture was worked up as described above to yield colorless needles (**5**) (64 mg, 85%) and colorless needles (**6**) (5 mg, 7%).

iii) Debenzylation of **4** with AlBr_3 in Nitrobenzene: A suspension of AlBr_3 (102 mg) in dry nitrobenzene (4 ml) was added to a solution of **4** (100 mg) in dry nitrobenzene (1 ml) under ice-cooling during less than 5 min. The reaction mixture was then poured into ice-water and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 , and evaporated. The residue was recrystallized from MeOH, giving daphnetin (**3**) (40 mg, 80%).

iv) Debenzylation of **4** with AlBr_3 in Carbon Disulfide: A suspension of AlBr_3 (102 mg) in dry CS_2 (4 ml) was added to a solution of **4** (100 mg) in dry CS_2 (1 ml) under ice-cooling during less than 5 min. The reaction mixture was then treated as described in iii) to afford daphnetin (**3**) (39 mg, 78%).

v) Debenzylation of **4** with 2% H_2SO_4 in EtOH: A solution of 2% H_2SO_4 (10 ml) was added to a solution of **4** (100 mg) in EtOH (20 ml) under ice-cooling. The mixture was stirred at room temperature for 5 h, then poured into ice-water and extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 , and evaporated. The residue was subjected to preparative TLC with a mixture of CHCl_3 and acetone (20:1), yielding **4** (18 mg, 18%), **5** (40 mg, 53%), **6** (3 mg, 4%), and daphnetin (**3**) (9 mg, 18%).

vi) Debenzylation of **4** with 36% HCl in AcOH: A solution of 36% HCl (0.5 ml) and AcOH (0.5 ml) was added to **4** (100 mg) under ice-cooling. The mixture was stirred at room temperature for 30 min, then treated in the same way as in v) to give **4** (4 mg, 4%), **5** (42 mg, 56%), **6** (3 mg, 4%), and daphnetin (**3**) (16 mg, 32%).

Ethyl 2-Bromo-3-(4-hydroxy-3,5-dimethoxyphenyl)-3-oxopropionate (8)—A solution of bromine (1.44 ml) in CHCl_3 (15 ml) was added dropwise to a solution of ethyl 3-(4-benzoyloxy-3,5-dimethoxyphenyl)-3-oxopropionate (**7**)¹⁰ (10 g) in CHCl_3 (45 ml) under ice-cooling. After the addition, the mixture was poured into ice-water and the CHCl_3 layer was washed with 5% NaHCO_3 and water. The organic layer was dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with CHCl_3 , giving a colorless oil (**8**) (8 g, 83%). High MS m/z : 347.9983 Calcd for $\text{C}_{13}\text{H}_{15}^{81}\text{BrO}_6$ ($\text{M}^+ + 2$). Found: 348.0001. High MS m/z : 346.0051 Calcd for $\text{C}_{13}\text{H}_{15}^{79}\text{BrO}_6$ (M^+). Found: 346.0053. MS m/z : 348, 346 (M^+), 267, 182, 181 (100%), 167, 153, 123, 108. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3510, 1750, 1735, 1670. ^1H -NMR (CDCl_3) δ : 1.26 (3H, t, $J=7$ Hz, OCH_2CH_3), 3.94 (6H, s, 2 $\times$ OCH_3), 4.28 (2H, q, $J=7$ Hz, OCH_2CH_3), 5.67 (1H, s, $-\text{CHBr}-$), 6.34 (1H, br s, OH), 7.29 (2H, s, 2 $\times$ aromatic protons).

Ethyl 2-Bromo-3-(4-acetoxy-3,5-dimethoxyphenyl)-3-oxopropionate (9)—A mixture of **8** (5 g), Ac_2O (3 ml), and pyridine (3 ml) was stirred at room temperature for 2 h. The reaction mixture was worked up in a usual manner and the resulting residue was chromatographed on silica gel with a mixture of CHCl_3 and acetone (20:1), affording a

colorless oil (**9**) (5.5 g, 98%). High MS m/z : 390.0137 Calcd for $C_{15}H_{17}^{81}BrO_7$ ($M^+ + 2$). Found: 390.0163. High MS m/z : 388.0156 Calcd for $C_{15}H_{17}^{79}BrO_7$ (M^+). Found: 388.0152. MS m/z : 390, 388 (M^+), 348, 346, 302, 301, 268, 239, 223, 198, 181, 167. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1760, 1750, 1735, 1685. 1H -NMR ($CDCl_3$) δ : 1.26 (3H, t, $J=7$ Hz, OCH_2CH_3), 2.33 (3H, s, $COCH_3$), 3.87 (6H, s, $2 \times OCH_3$), 4.27 (2H, q, $J=7$ Hz, OCH_2CH_3), 5.64 (1H, s, $-CHBr-$), 7.24 (2H, s, $2 \times$ aromatic protons).

Condensation of 9 with 5 (Formation of 10)—NaH (152 mg), washed twice with dry ether (5 ml), was suspended in a mixture of dry DMF (8 ml) and dry THF (2 ml). The slurry was cooled to $0^\circ C$ under an N_2 atmosphere and a solution of **5** (1.70 g) in dry DMF (12 ml) and dry THF (3 ml) was slowly added. After the addition, the solution was stirred at room temperature for 1 h, then cooled to $0^\circ C$, and a mixture of **9** (3.70 g) in dry DMF (12 ml) and dry THF (3 ml) was added dropwise. The mixture was stirred at room temperature for 8 h and then quenched by adding water (10 ml). The resulting mixture was extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 , and evaporated. The residue was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (10:1), affording a colorless oil (**10**) (3.55 g, 97%). High MS m/z : 576.1630 Calcd for $C_{31}H_{28}O_{11}$ (M^+). Found: 576.1585. MS m/z : 576 (M^+), 534, 399, 357, 353, 311, 271, 268, 244, 239, 223, 222. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1760, 1750, 1735, 1690, 1615. 1H -NMR ($CDCl_3$) δ : 1.19 (3H, t, $J=7$ Hz, OCH_2CH_3), 2.29 (3H, s, $COCH_3$), 3.80 (6H, s, $2 \times OCH_3$), 4.17 (2H, q, $J=7$ Hz, OCH_2CH_3), 5.04 (2H, s, OCH_2Ph), 5.82 (1H, s, C_8-H), 6.14 (1H, d, $J=9.5$ Hz, C_3-H), 6.81 (1H, d, $J=9$ Hz, C_6-H), 7.08 (1H, d, $J=9$ Hz, C_5-H), 7.19 (2H, s, $2 \times$ aromatic protons), 7.39 (5H, br s, $5 \times$ aromatic protons), 7.48 (1H, d, $J=9.5$ Hz, C_4-H).

Reduction of 10 with Lithium Borohydride (Formation of 11a, b)—A solution of **10** (1.0 g) in dry THF (10 ml) was added to a suspension of $LiBH_4$ (76 mg) in dry THF (5 ml) at $0^\circ C$ under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 min, then carefully quenched by adding ice, and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 , and evaporated. The residue was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (5:1), providing a colorless oil (**11a, b**) (536 mg, 58%). High MS m/z : 536.1681 Calcd for $C_{29}H_{28}O_{10}$ (M^+). Found: 536.1679. MS m/z : 536 (M^+), 494, 476, 446, 294 (100%), 269, 210, 189, 182. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 3550, 1760, 1730, 1610. 1H -NMR ($CDCl_3$) δ : 2.26 (3H, s, $COCH_3$), 3.37–4.41 (3H, m, C_8-H and C_9-H), 3.71, 3.72 (6H, $2 \times$ s, $2 \times OCH_3$), 5.18 (2H, s, OCH_2Ph), 5.29 (3/7H, d, $J=8$ Hz, C_7-H), 5.34 (4/7H, d, $J=3$ Hz, C_7-H), 6.22 (1H, d, $J=9.5$ Hz, C_3-H), 6.69 (2H, br s, C_2-H and C_6-H), 6.91 (1H, d, $J=9$ Hz, C_6-H), 7.15 (1H, d, $J=9$ Hz, C_5-H), 7.37 (5H, br s, $5 \times$ aromatic protons), 7.58 (3/7H, d, $J=9.5$ Hz, C_4-H), 7.59 (4/7H, d, $J=9.5$ Hz, C_4-H).

Acetylation of 11a, b—A mixture of **11a, b** (20 mg), Ac_2O (1 ml), and pyridine (1 ml) was stirred at room temperature for 13 h. The reaction mixture was worked up in a usual manner. The residue was subjected to preparative TLC with a mixture of $CHCl_3$ and acetone (10:1), affording **12a** (6 mg, 26%) and **12b** (11 mg, 48%).

Compound 12a: Colorless oil. TLC (silica gel/ $CHCl_3$ -acetone (10:1)), $R_f=0.48$. High MS m/z : 620.1892 Calcd for $C_{33}H_{32}O_{12}$ (M^+). Found: 620.1922. MS m/z : 620 (M^+), 578, 518, 458, 428, 369, 354, 281, 268, 251 (100%). IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1760, 1735, 1610. 1H -NMR ($CDCl_3$) δ : 1.90, 1.91, 2.25 (9H, $3 \times$ s, $3 \times COCH_3$), 3.70 (6H, s, $2 \times OCH_3$), 3.80 (1H, dd, $J=11, 5$ Hz, C_9-H), 4.29 (1H, dd, $J=11, 4$ Hz, C_9-H), 4.87 (1H, m, C_8-H), 5.11 (2H, s, OCH_2Ph), 6.15 (1H, d, $J=8$ Hz, C_7-H), 6.19 (1H, d, $J=9.5$ Hz, C_3-H), 6.58 (2H, s, C_2-H and C_6-H), 6.84 (1H, d, $J=9$ Hz, C_6-H), 7.08 (1H, d, $J=9$ Hz, C_5-H), 7.34 (5H, m, $5 \times$ aromatic protons), 7.53 (1H, d, $J=9.5$ Hz, C_4-H).

Compound 12b: Colorless oil. TLC (silica gel/ $CHCl_3$ -acetone (10:1)), $R_f=0.52$. High MS m/z : 620.1892 Calcd for $C_{33}H_{32}O_{12}$ (M^+). Found: 620.1879. MS m/z : 620 (M^+), 578, 518, 458, 428, 369, 354, 281, 268, 251 (100%). IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1760, 1735, 1610. 1H -NMR ($CDCl_3$) δ : 1.86, 2.09, 2.27 (9H, $3 \times$ s, $3 \times COCH_3$), 3.71 (6H, s, $2 \times OCH_3$), 4.28 (1H, dd, $J=11, 3$ Hz, C_9-H), 4.54 (1H, dd, $J=11, 7$ Hz, C_9-H), 5.02 (1H, m, C_8-H), 5.14 (2H, s, OCH_2Ph), 6.20 (1H, d, $J=3$ Hz, C_7-H), 6.21 (1H, d, $J=9.5$ Hz, C_3-H), 6.62 (2H, s, C_2-H and C_6-H), 6.84 (1H, d, $J=9$ Hz, C_6-H), 7.10 (1H, d, $J=9$ Hz, C_5-H), 7.34 (5H, br s, $5 \times$ aromatic protons), 7.54 (1H, d, $J=9.5$ Hz, C_4-H).

Daphneticin (1)—A mixture of **11a, b** (200 mg) in 36% HCl (1 ml) and AcOH (1 ml) was heated at $60^\circ C$ for 30 min. The mixture was poured into water and extracted with AcOEt. The AcOEt extract was washed with water, dried over Na_2SO_4 , and evaporated. The crude product was recrystallized from MeOH, affording colorless needles (**1**) (98 mg, 68%). mp $233-235^\circ C$ (lit.,⁶) mp $235-238^\circ C$. Anal. Calcd for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70. Found: C, 61.94; H, 4.69. MS m/z : 386 (M^+), 368 (100%), 354, 311, 219, 210, 178, 167, 150. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3450, 1720, 1610, 1565. 1H -NMR ($DMSO-d_6$) δ : 3.48 (2H, m, C_9-H), 3.78 (6H, s, $2 \times OCH_3$), 4.32 (1H, m, C_8-H), 5.03 (1H, d, $J=8$ Hz, C_7-H), 6.31 (1H, d, $J=9.5$ Hz, C_3-H), 6.75 (2H, s, C_2-H and C_6-H), 6.94 (1H, d, $J=9$ Hz, C_6-H), 7.18 (1H, d, $J=9$ Hz, C_5-H), 7.96 (1H, d, $J=9.5$ Hz, C_4-H), 8.55 (1H, br s, OH). ^{13}C -NMR (pyridine- d_5) δ : 160.4 (s, C-2), 149.2 (s, C-9), 149.2 (s, C-3'), 149.2 (s, C-5'), 147.6 (s, C-7), 144.4 (d, C-4), 138.4 (s, C-8), 132.2 (s, C-4'), 126.5 (s, C-1'), 119.8 (d, C-5), 113.6 (d, C-3), 113.6 (d, C-10), 113.2 (d, C-6), 106.2 (d, C-2'), 106.2 (d, C-6'), 79.9 (d, C-8'), 77.8 (d, C-7'), 60.6 (t, C-9'), 56.3 (q, OCH_3).

This compound was identical with an authentic specimen⁶ on the basis of mixed melting point determination and direct comparison of IR (KBr) spectra and MS.

Daphneticin Diacetate (2)—A mixture of **1** (50 mg), Ac_2O (1.5 ml), and pyridine (1.5 ml) was stirred at room temperature for 13 h. The reaction mixture was worked up in a usual manner and the resulting residue was recrystallized from MeOH, yielding colorless needles (**2**) (60 mg, 99%). mp $206-208^\circ C$ (lit.,⁶) $208-209^\circ C$. MS m/z :

470 (M^+), 428 (100%), 368, 252. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1720, 1610, 1570. $^1\text{H-NMR}$ (CDCl_3) δ : 2.03 (3H, s, aliphatic COCH_3), 2.29 (3H, s, aromatic COCH_3), 3.81 (6H, s, $2 \times \text{OCH}_3$), 3.99–4.51 (3H, m, $\text{C}_8\text{-H}$ and $\text{C}_9\text{-H}$), 4.98 (1H, d, $J=8$ Hz, $\text{C}_7\text{-H}$), 6.28 (1H, d, $J=9.5$ Hz, $\text{C}_3\text{-H}$), 6.59 (2H, s, $\text{C}_2\text{-H}$ and $\text{C}_6\text{-H}$), 6.88 (1H, d, $J=9$ Hz, $\text{C}_6\text{-H}$), 7.01 (1H, d, $J=9$ Hz, $\text{C}_5\text{-H}$), 7.62 (1H, d, $J=9.5$ Hz, $\text{C}_4\text{-H}$).

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References and Notes

- 1) H. Tanaka, I. Kato, and K. Ito, *Chem. Pharm. Bull.*, **33**, 3218 (1985).
- 2) S. S. Handa, A. D. Kinghorn, G. A. Cordell, and N. R. Farnsworth, *J. Nat. Prod.*, **46**, 359 (1983).
- 3) a) A. B. Ray, S. K. Chattopadhyay, C. Konno, and H. Hikino, *Tetrahedron Lett.*, **1980**, 4477; b) *Idem*, *Heterocycles*, **19**, 19 (1982); c) M. Arisawa, S. S. Handa, D. D. McPherson, D. C. Lankin, G. A. Cordell, H. H. S. Fong, and N. R. Farnsworth, *J. Nat. Prod.*, **47**, 300 (1984); d) A. B. Ray, S. K. Chattopadhyay, S. Kumar, C. Konno, Y. Kiso, and H. Hikino, *Tetrahedron*, **41**, 209 (1985).
- 4) M. D. G. B. Zoghbi, N. F. Roque, and O. R. Gottlieb, *Phytochemistry*, **20**, 180 (1981).
- 5) P. Bhandari, P. Pant, and R. P. Rastogi, *Phytochemistry*, **21**, 2147 (1982).
- 6) L.-G. Zhuang, O. Seligmann, and H. Wagner, *Phytochemistry*, **22**, 617 (1983).
- 7) Z. Lin-Gen, O. Seligmann, K. Jurcic, and H. Wagner, *Planta Medica*, **45**, 172 (1982).
- 8) L.-J. Lin and G. A. Cordell, *J. Chem. Soc., Chem. Commun.*, **1984**, 160.
- 9) V. K. Ahluwalia, G. P. Sachdev, and T. R. Seshadri, *Indian J. Chem.*, **7**, 59 (1969); H. Tanaka, I. Kato, and K. Ito, *Heterocycles*, **23**, 1991 (1985).
- 10) W. Bradley and R. Robinson, *J. Chem. Soc.*, **1928**, 1541.
- 11) The products each gave a single spot on TLC in various solvents.
- 12) In the $^1\text{H-NMR}$ spectrum, the methine proton at the C-7' position was observed as two doublets at δ 5.29 and 5.34; the coupling constant of the doublet at δ 5.29 was 8 Hz and that of the doublet at δ 5.34 was 3 Hz. It is known¹⁾ that the vicinal coupling constant of the *threo* form is larger than that of the *erythro* form. Accordingly, the signal at δ 5.29 was ascribed to the *threo* isomer (**11a**) and that at δ 5.34 was attributed to the *erythro* isomer (**11b**). The ratio of the *threo* and *erythro* isomers was about 3 : 4 from the $^1\text{H-NMR}$ spectral analysis. Acetylation of the diols (**11a, b**) in a usual manner provided the triacetates (**12a, b**) which were separated chromatographically and individually characterized spectroscopically.
- 13) R. Hänsel, J. Schulz, and A. Pelter, *Chem. Ber.*, **108**, 1482 (1975).
- 14) V. K. Ahluwalia, I. Mukherjee, and N. Rani, *Indian J. Chem.*, **20B**, 918 (1981).