1,3,5-Tris(methylthio)benzene (10): mp 63–65 °C (lit.[5] mp 61–63 °C); NMR (60 MHz) δ 6.85 (s, 1 H), 2.45 (s, 3 H).

1,2,3,4-Tetrakis(methylthio)benzene (11): mp 108–109 °C (lit.[5] mp 104–106 °C); NMR (60 MHz) δ 7.05 (s, 1 H), 2.45 (s, 3 H), 2.4 (s, 3 H).

1,2,3,4-Tetrakis(ethylthio)benzene (12): oil; NMR (90 MHz) δ 7.15 (s, 1 H), 3.0 (q, 2 H), 2.9 (q, 2 H), 1.4 (t, 3 H, J = 7.5 Hz), 1.25 (t, 3 H, J = 7.5 Hz); mass spectrum, m/e (relative intensity) 320 (20.7, M + 2), 318 (100, M), 289 (25.8, M - C_2H_5), 260 (25.8, M - C_4H_{10}), 245 (36, M - C_5H_{13}), 230 (15.5, M - C_6H_{16}).

1,2,4,5-Tetramercaptobenzene (13): mp 138–141 °C (lit.[18] mp 139–141 °C); NMR (60 MHz) δ 7.25 (s, 1 H), 3.6 (s, 2 H).

1,2,4,5-Tetrakis(methylthio)benzene (14): mp 128–130 °C (lit.[14] mp 125–126 °C); NMR (60 MHz) δ 7.1 (s, 1 H), 2.45 (s, 6 H).

Pentakis(methylthio)benzene (17): mp 103–106 °C (lit.[2] mp 103–105 °C); NMR (90 MHz) δ 6.8 (s, 1 H), 2.55 (s, 3 H), 2.5 (s, 6 H), 2.45 (s, 6 H).

Pentakis(ethylthio)benzene (18): mp 64–65 °C; NMR (90 MHz) δ 6.9 (s, 1 H), 3.1 (q, 2 H), 2.95 (q, 8 H), 1.45 (t, 6 H, J = 7.5 Hz), 1.25 (t, 9 H, J = 7.5 Hz); mass spectrum, m/e (relative intensity) 380 (25, M + 2), 378 (100, M), 349 (20, M - C_2H_5), 320 (36, M - C_4H_{10}), 305 (21.3, M - C_5H_{13}), 290 (9.3, M - C_6H_{16}).

Hexakis(methylthio)benzene (19): mp 87–88 °C (lit.[2] mp 88–90 °C); NMR (60 MHz) δ 2.5 (s).

(18) W. Reifschneir, *Chem. Abstr.*, **69**, 106244 (1968).

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Registry No. 1, 17534-15-5; 2, 2388-68-3; 3, 626-04-0; 4, 2388-69-4; 5, 624-39-5; 6, 699-20-7; 7, 17661-83-5; 8, 65516-81-6; 9, 2570-41-4; 10, 2388-71-8; 11, 70648-36-1; 12, 77520-28-6; 13, 20133-21-5; 14, 1846-35-1; 15, 70416-04-5; 16, 70416-05-6; 17, 65516-74-7; 18, 77520-29-7; 19, 58468-22-7; 20, 70398-84-4; 21, 74542-66-8; 22, 70415-95-1; 23, 74542-68-0; 24, 74542-69-1; 25, 70416-07-8; 26, 70416-15-8; 27, 7205-62-1; 28, 702-13-6; 29, 3019-20-3; 30, 371-15-3; 1,2-dichlorobenzene, 95-50-1; 1,3-dichlorobenzene, 541-73-1; 1,4-dichlorobenzene, 106-46-7; 1,2,3-trichlorobenzene, 87-61-6; 1,2,4-trichlorobenzene, 120-82-1; 1,3,5-trichlorobenzene, 108-70-3; 1,2,3,4-tetrachlorobenzene, 634-66-2; 1,2,3,5-tetrachlorobenzene, 634-90-2; 1,2,4,5-tetrachlorobenzene, 95-94-3; pentachlorobenzene, 608-93-5; hexachlorobenzene, 118-74-1; Me_2CHSNa, 20607-43-6; C_6H_5SMe, 100-68-5.

New Flavonoid and Coumarin Derivatives of *Uvaria afzelii*

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Three new compounds, 2'-hydroxydemethoxymatteucinol (6), 2-hydroxy-7,8-dehydrograndiflorone (7), and uvafzelic acid (9) have been identified in extracts of *Uvaria afzelii*. Their structures were determined mainly from interpretation of the ^{13}C NMR spectral data. 7 was unstable and was rapidly converted to emorydone (8). Four other known compounds, coumarin (3), syncarpic acid (4), demethoxymatteucinol (5), and emorydone (8), were also identified along with the previously reported constituents, vafzelin (1) and uvafzelin (2). The stabilities of 1, 7, and 8 under neutral, acidic, and basic conditions were studied by HPLC.

The genus *Uvaria* continues to be an interesting source of biologically active constitutents,[1] and this has prompted us to examine other species of this genus. Extracts of *U. afzelii* Scot Elliot (Annonaceae) showed significant antimicrobial activity against gram-positive and acid-fast bacteria although no antitumor or cytotoxic activity was noted. Fractionation of the ethanolic extract using an ethyl acetate–water partition resulted in concentration of the antimicrobial activity in the ethyl acetate soluble fraction. Chromatography of the ethyl acetate soluble fraction over silicic acid yielded a number of fractions from which a number of novel compounds were isolated. We recently reported on the identification of two of these constituents, vafzelin (1) and uvafzelin (2), by single-crystal X-ray diffraction experiments.[2] We now report the identification of the known compounds coumarin (3), syncarpic acid (4), demethoxymatteucinol (5), and emorydone (8) and three new compounds, 2'-hydroxydemethoxymatteucinol (6), 2-hydroxy-7,8-dehydrograndiflorone (7), and uvafzelic acid (9).

Coumarin (3) and syncarpic acid (4) were readily identified from spectral data and their identities confirmed by direct comparison with authentic samples. Demethoxymatteucinol (5) had spectral data consistent with a flavanone with methyl groups at C-6 and C-8 (^1H and ^{13}C NMR). Its identity was confirmed by a direct comparison with an authentic sample.

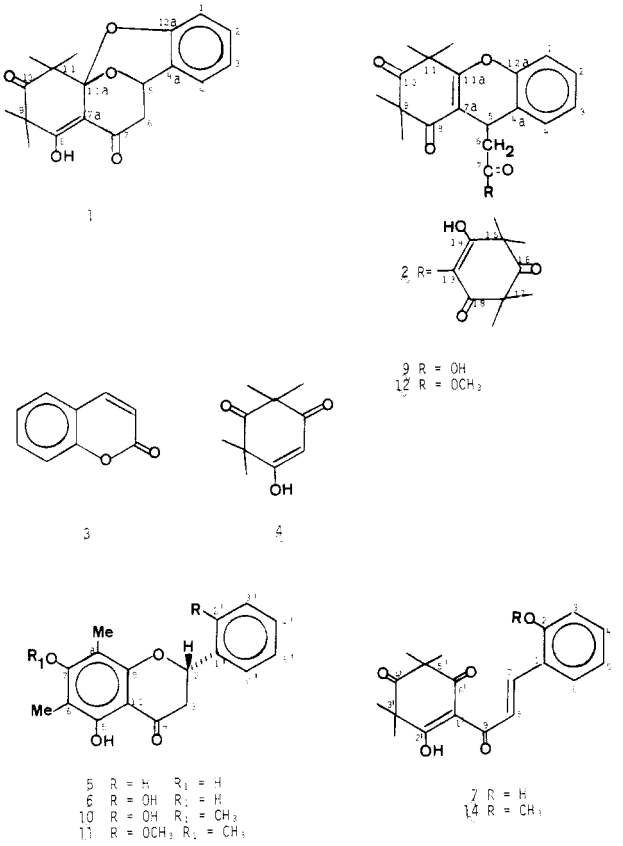
An optically active crystalline substance (6) with a molecular formula of $C_{17}H_{16}O_5$ had UV and IR data similar to those of 5. The ^1H NMR spectrum of 6 displayed the characteristic ABX pattern of flavanones (H-2 and H-3) and two aromatic methyl signals (Me at C-6 and C-8). There were three D_2O-exchangeable signals and a four-proton multiplet in the aromatic region (δ 6.73–7.60),

(1) (a) Cole, J. R.; Torrance, S. J.; Wiedhopf, R. M. *J. Org. Chem.* **1976**, *41*, 1852–1855. (b) Lasswell, W. L., Jr.; Hufford, C. D. *Ibid.* **1977**, *42*, 1295–1302. (c) Hufford, C. D.; Lasswell, W. L., Jr.; Hirotsu, K.; Clardy, J. *Ibid.* **1979**, *44*, 4709–4710. (d) El-Sohly, H. N.; Lasswell, W. L., Jr.; Hufford, C. D. *J. Nat. Prod.* **1979**, *42*, 264–270. (e) Hufford, C. D.; Oguntimein, B. O. *Phytochemistry* **1980**, *19*, 2036–2038.

(2) Hufford, C. D.; Oguntimein, B. O.; Engen, D. V.; Muthard, D.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 7365–7367.

(3) (a) Hufford, C. D.; Lasswell, W. L., Jr. *Lloydia* **1978**, *41*, 151–155. (b) Pelter, A.; Ward, R. S.; Gray, T. I. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2475–2483.

0022-3263/81/1946-3073$01.25/0



characteristic of the ortho-hydroxylation pattern of other flavanones of *Uvaria*. The mass spectrum, in addition to showing the parent ion peak at m/z 300 (59%), showed the retro-Diels–Alder fragment at m/z 180 ($M^+ - 120$, 17%), consistent with a hydroxyl group in the B ring of flavanones.[1d] The ^{13}C NMR spectral data (Table I) established that the hydroxyl group must be located at C-2′ since C-4′ is eliminated on symmetry principles and the signal for C-1′ is shifted about 13 ppm upfield from that in **5**. The absolute stereochemistry depicted in **6** (2*S*) was established from CD data.[1b,4] Methylation of **6** with excess ethereal diazomethane produced a monomethyl ether and dimethyl ether which were separated by chromatography. The monomethyl ether was assigned structure **10** based on the strongly H-bonded carbonyl signal in the IR spectrum (1630 cm^{-1}), the presence of one 3 H singlet at δ 3.76 and two D_2O-exchangeable signals at δ 12.19 and 8.76 in the ^1H NMR spectrum, and the presence of signals at 60.4 (q, OCH_3) and 199.1 ppm (s, CO) in the ^{13}C NMR spectrum (Table I). The ^{13}C NMR signal at 60.4 ppm indicates that the methoxyl group must be flanked by two ortho substituents, thus eliminating C-2′.[1d] Methylation at C-5 could be ruled out since an upfield shift of about 10 ppm in the carbonyl signal was not observed.[1d] The dimethyl ether was assigned structure **11** on the basis of similar arguments of the IR (1630 cm^{-1}, H-bonded CO), ^1H NMR [δ 3.82 and 3.72 (3 H, each) and δ 12.09 (1 H)], and ^{13}C NMR [60.0 (q), 55.4 (q), 198.1 (s)] (Table I) spectral data. Methylation of **6** using methyl iodide produced **10** as the major product. Thus, **6** represents another example of the ortho-hydroxylation pattern characteristic of the genus *Uvaria*.

Uvafzelic acid (**9**) was obtained as an oily residue which could not be obtained in crystalline form. It was pure as evidenced by TLC and spectroscopic analysis and was optically inactive. The molecular formula, $C_{19}H_{20}O_5$, was established by high-resolution mass spectrometry. The IR spectrum showed characteristic bands for a carboxylic acid in the region 2500–3200 cm^{-1} and carbonyl bands at 1715 and 1675 cm^{-1}. The UV spectral data showed similarities to those of **2**. The ^1H NMR spectrum of **9** showed a 1 H broad singlet (δ 9.30) exchangeable with D_2O, a 4 H multiplet (δ 7.00–7.67, Ar H), a 1 H triplet (δ 4.48, J = 5 Hz, H-5), a 2 H doublet (δ 2.77, J = 5 Hz, H-6), and singlets for four methyl groups [δ 1.57 (3 H), 1.50 (3 H), 1.43 (6 H)]. Data from the ^{13}C NMR spectrum were very helpful in formulating structure **9** for uvafzelic acid. A comparison of the ^{13}C NMR spectrum of **9** with those of **1** and **2** immediately suggested that **9** was closely related to **2** (Table II). Uvafzelic acid (**9**) was converted into its crystalline methyl ester (**12**) by treatment with excess ethereal diazomethane. The methyl ester (**12**) was identical in all respects with a synthetic sample.[5]

Table I. ^{13}C NMR Spectral Data (δ) for 5, 6, 10, and 11[a]

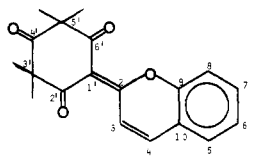
carbon no.	5[b]	6[c]	10[c]	11[d]
C-2	79.3 d	75.4 d	75.4 d	74.2 d
C-3	43.5 t	42.7 t	42.8 t	42.9 t
C-4	196.9 s	197.8 s	199.1 s	198.1 s
C-5	162.4 s^2	163.0 s^2	160.1 s^1	159.5 s^1
C-6	103.0 s^1	103.4 s^1	111.3 s^2	111.2 s^2
C-7	160.0 s^2	160.2 s^2	166.1 s	165.4 s
C-8	102.9 s^1	103.2 s^1	110.1 s^2	109.6 s^2
C-9	158.3 s^2	159.0 s^2	159.2 s^1	158.5 s^1
C-10	104.0 s^1	104.3 s^1	105.6 s	105.2 s
C-1′	140.5 s	127.0 s	126.6 s	127.9 s
C-2′	126.6 d	154.8 s	154.8 s	156.0 s^1
C-3′	129.2 d	116.4 d	116.4 d	110.6 d
C-4′	128.8 d	129.9 d	130.0 d	129.3 d
C-5′	129.2 d	120.7 d	120.7 d	121.0 d
C-6′	126.6 d	127.3 d	127.3 d	126.3 d
CH_3-C8	9.1 q^3	7.4 q^3	8.0 q^3	7.9 q^3
CH_3-C6	7.9 q^3	8.1 q^3	8.6 q^3	8.4 q^3
OCH_3-C7			60.4 q	60.0 q
OCH_3-C2′				55.4 q

[a] Assignments are based on predicted chemical shifts, previous assignments,[3] and single-frequency off-resonance decoupling. Assignments bearing the same numerical superscript may be reversed. [b] Dioxane-d_8. [c] Acetone-d_6. [d] Chloroform-d.

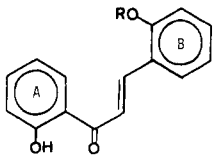
2-Hydroxy-7,8-dehydrograndiflorone (**7**) was obtained as an optically inactive yellow crystalline substance which proved to be unstable in solution. The IR spectrum showed a hydroxyl band (3420 cm^{-1}) and carbonyl bands (1720 and 1645 cm^{-1}). The ^1H NMR showed a 4 H multiplet (δ 6.93–8.00) characteristic of an ortho-oxygenated alkyl-substituted aromatic ring, an AB quartet [δ 8.07, 8.53 (J = 16 Hz)] characteristic of the protons of a *trans*-cinnamoyl moiety, and a 12 H singlet at δ 1.47 (4 CH_3). These data taken together suggested a hydroxylated cinnamoyl syncarpic acid. The ^{13}C NMR spectral data (obtained rapidly on a concentrated solution) provided further confirmation of the proposed structure as shown by **7**. In an extensive study of the ^{13}C NMR spectra of flavonoids and related compounds,[3b] a number of chalcones were reported, including examples with a hydroxyl group at C-2. One of these examples, 2,2′-dihydroxychalcone (**13**), has ^{13}C NMR data nearly identical with those of **7** (B ring only, see Table III). The placement of the hydroxyl group at C-2 clearly follows from this data since chalcones without oxygenation

(4) The sign of the Cotton effects in the CD spectra of flavanones has been correlated with absolute stereochemistry. See: Garfield, W. *Tetrahedron* **1970**, *26*, 4093–4108.

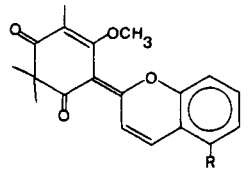
(5) Uvafzelic acid has been synthesized by Dr. J. Clardy, Cornell University, and details of this synthesis will be published separately. The methyl ester was used for the direct comparison.



8



13 R = H
15 R = CH_3



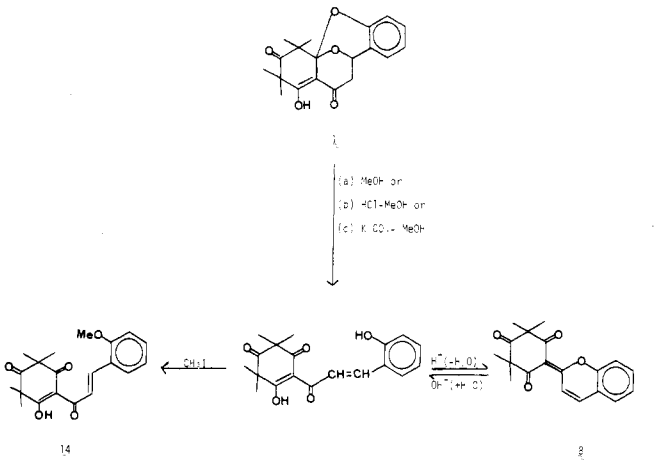
16 R = H
17 R = OCH_3

at C-2 have signals for C-1 near 134 ppm. The instability of **7** made it difficult to purify but it could be methylated with methyl iodide to form the stable crystalline methyl ether (**14**). Its ^{13}C NMR data are also reported in Table III along with 2′-hydroxy-2-methoxychalcone (**15**), for comparison.

A yellow pigment isolated as an oil was pure by TLC and spectroscopic analysis and had molecular formula $C_{19}H_{18}O_4$ (high-resolution mass spectrometry). The IR spectrum showed no hydroxyl bands, but three carbonyl bands were evident (1730, 1680, 1640 cm^{-1}). The ^1H NMR spectrum showed a 4 H multiplet [δ 7.20–7.60 (Ar-H), an AB quarter [δ 8.33, 7.70 (J = 10 Hz, H-3, H-4)], and a 12 H singlet (4 CH_3). The formulation of structure **8** for this yellow pigment arose from consideration of ^{13}C NMR data (Table III) and by observation that **7** was converted to **8**. As noted previously, **7** was unstable in solution and the conversion of **7** to **8** could be followed by ^{13}C NMR. The conversion was complete in about 24 h in an NMR tube ($CDCl_3$). The ^{13}C NMR data for **8** (Table III) as similar to those reported for dalrubone (**16**) and methoxydalrubone (**17**), red pigments isolated from *Dalea* species.[6,7] Hydrolysis of **8** using hydrobromic acid–acetic acid[7] resulted in the isolation of **3** and **4**. The spectroscopic as well as chemical evidence confirms the structure as proposed for **8**. A compound isolated as a very minor product of a biomimetic synthesis of *Dalea emoryi* was given the trivial name emorydone and assigned structure **8** based on spectroscopic data (UV, IR, ^1H, NMR, and mass spectra).[8] A direct comparison of emorydone with **8** showed the two samples to be identical. The conversion of **7** to **8** can be rationalized as the isomerization of **7** to the cis form and reaction of the C-2 OH with the carbonyl function of the cinnamoyl moiety followed by dehydration. This reaction can be prevented by methylation of **7** which produces a stable methyl ether (**14**).

Vafzelin (**1**) was observed to undergo slow decomposition in methanol or ethanol solution but not in other solvents (chloroform, ethyl acetate, acetone, benzene). The alcohol solutions gradually turned yellow and TLC analysis indicated that **8** was the major decomposition product with only traces of **7** detected. A sample of vafzelin (**1**) was warmed in methanol, and **8** was isolated as the major product. Additon of traces of hydrochloric acid to methanol solutions of **1** accelerated the rate of decomposition to **8**. When potassium carbonate was added to methanol solutions of **1**, rapid decomposition occurred and **7** was the only product formed as evidenced by TLC and HPLC. Since **7** is unstable as noted previously, its presence as a decomposition product was also established by treating a methanol–potassium carbonate solution of **1** with methyl iodide with resultant formation of **14**.

Scheme I



The instabilities of **1**, **7**, and **8** (summarized in Scheme I) were studied by dissolving each in EtOAc, MeOH, 0.1 N HCl–MeOH, and K_2CO_3–MeOH and analyzing the solutions by HPLC. The results of these studies are shown in Table IV. When **1** is dissolved in K_2CO_3–MeOH, it decomposes to **7** whereas in HCl–MeOH or MeOH **8** is the major decomposition product. Vafzelin (**1**) first decomposes to **7** which then is converted to **8**. The rates of these decompositions are about the same in 0.1 N HCl–MeOH. Emorydone (**8**) is stable in EtOAc, MeOH, and HCl–MeOH but decomposes to **7** in K_2CO_3–MeOH. 2-Hydroxy-7,8-dehydrograndiflorone (**7**) is transformed to **8** in MeOH, EtOAc, or HCl–MeOH but not in K_2CO_3–MeOH.

Since alcohol was used in the extraction process of the plant and based on the stability studies (Table IV), some questions arise as to whether **8** may be an artifact. All three compounds (**1**, **7**, and **8**) could be detected by TLC when the plant material was rapidly extracted (2 h, EtOAc) and evaporated. The isolation of the novel compounds **1**, **2**, **6**, **7**, and **9** along with the more common compounds **3–5** in *U. afzelii* further supports previous speculations on the biosynthesis of these compounds.[2,7]

Experimental Section

Melting points were determined on a Fisher-Digital Model 355 melting point apparatus. Elemental analyses were performed by Scandanavian Microanalytical Laboratories, Herlev, Denmark. IR and UV spectra were recorded on Perkin-Elmer 281b and Beckman ACTA III spectrophotometers, respectively. The CD spectra were recorded on a JASCO J-40 spectropolarimeter. ^1H NMR (60 MHz) spectra were recorded on a JEOL C-60HL, using tetramethylsilane as internal standard, or on a JEOL-FX60 FT NMR spectrometer. ^{13}C NMR (15 MHz) spectra were recorded on the JEOL FX-60 instrument with a 45° pulse angle, repetition rates between 5–10 s, and 8K data points. PND spectra were obtained by broad band (1K Hz) irradiation. Single-frequency off-resonance decoupling experiments were conducted by centering the decoupling frequency 1100 Hz downfield from tetramethylsilane. The proton-coupled data were recorded by using the gated decoupling mode (decoupler off during data acquisition). TLC analyses were conducted on Brinkmann precoated silica-gel G plates, using various percentages of ether in hexane or chloroform. The spots were visualized by UV or by spraying with 0.5% aqueous

(6) Wehrli, F. W.; Nishida, T. *Prog. Chem. Org. Nat. Prod.* **1979**, *36*, 1–229 (see p 172).
(7) Dreyer, D. L.; Munderloh, K. P.; Thiessen, W. E. *Tetrahedron* **1975**, *31*, 287–293.
(8) Roitman, J. N.; Jurd, L. *Phytochemistry* **1978**, *17*, 161–163.

Table II. ^{13}C NMR Spectral Data (δ) for 1, 2, 9, and 12[a]

carbon no.	1	2[b]	9	12
C-1	117.1 d	116.2 d	116.3 d	116.2 d
C-2	129.3 d	129.2 d[1]	128.8 d[1]	128.8 d[1]
C-3	121.4 d	125.5 d	125.5 d	125.3 d
C-4	125.5 d	128.1 d[1]	128.3 d[1]	128.2 d[1]
C-4a	122.7 s	124.6 s	123.3 s	123.6 d
C-5	68.4 d	30.0 d	29.4 d	29.6 d
C-6	39.2 t	48.4 t	41.5 t	41.6 t
C-7	198.2 s	198.8 s[2]	176.7 s	171.3 s
C-7a	105.6 s	110.1 s[3]	109.5 s	109.8 s
C-8	183.7 s	201.5 s[2]	197.9 s	197.6 s
C-9	52.0 s[1]	55.4 s	55.7 s	55.8 s
C-10	211.4 s	212.1 s[4]	211.9 s	212.0 s
C-11	53.0 s[1]	47.5 s	47.5 s	47.4 s
C-11a	98.7 s	168.8 s	168.9 s	168.5 s
C-12a	150.2 s	150.6 s	150.5 s	150.5 s
C-13		110.5 s[3]		
C-14		196.5 s[2]		
C-15		51.8 s		
C-16		209.8 s[4]		
C-17		56.9 s		
C-18		197.6 s[2]		
CH_3	15.6, 21.2, 23.3, 26.1 q	25.0, 24.8, 24.5, 24.2, 24.0, 23.8 q	25.0, 24.4 q	25.1, 24.4, 24.2 q
OCH_3				51.3 q

[a] Assignments are based on predicted chemical shifts, previous assignments,[3] and single-frequency off-resonance decoupling. Assignments bearing the same numerical superscript may be reversed. The data for 1 and 2 were previously reported[2] without complete assignments and are presented here for comparison purposes. The data for syncarpic acid (4) and its *C*-acetyl and *O*-methyl derivatives were also reported.[2] All data were obtained in chloroform-*d*. [b] The signal assignments for C-9 and C-11 were based on comparison with 9 and 12. The assignment of the signal at 47.5 ppm to C-11 was based on the assumption that this signal would be more upfield since it is in the α position to the enol ether. The assignments for C-15 and C-17 were based on similar arguments.

Table III. ^{13}C NMR Spectral Data (δ) for 7, 8, 13, 14, and 15[a]

carbon no.	7[b]	13[c]	14[b]	15[c]	8[d]
C-1	122.4	121.8 s	124.0 s	123.7 s	
C-2	156.4	157.9 s	159.1 s	159.1 s	166.8 s
C-3	116.6	116.8 d	111.4 d	111.4	119.6 d
C-4	132.6	132.1 d	132.7 d	132.3 d	139.8 d
C-5	121.0[1]	120.2 d	121.0 d[1]	120.8 d	127.5 d
C-6	129.8	130.1 d	129.2 d	129.7 d	125.8 d
C-7	142.6	142.2 d	142.0 d	140.3 d	132.9 d
C-8	121.2[1]	118.4 d	121.2 d[1]	123.3 d	117.7 d
C-9	197.7[2]	194.6 s	197.4 s[2]	194.4 s	152.6 s
C-10					120.9 s
C-1′	108.4		108.3 s		108.6 s
C-2′	186.9		186.5 s		197.1 s
C-3′	54.3		53.9 s		58.2 s
C-4′	210.4		210.1 s		210.6 s
C-5′	57.1		57.2 s		58.2 s
C-6′	202.5[2]		202.5 s[2]		197.1 s
CH_3	24.1		24.0, 24.1 q		23.1 q
OCH_3-C-1			55.7 q		

[a] Assignments are based on predicted chemical shifts, single-frequency off-resonance decoupling, and previous assignments.[3b] Assignments bearing the same numerical superscripts may be interchanged. All data were obtained in chloroform-*d*. [b] 7 proved to be too unstable to get single-frequency off-resonance decoupling data and the assignments are related to those of 14 for which these data were obtained. [c] The examples listed here are for comparison and the data were taken from the literature. Only the reported assignments for the cinnamoyl moiety are listed.[3b] [d] The assignments for C-5, C-6, C-7, and C-8 were based on those of coumarin (3).[6] The assignments for C-3 and C-4 were confirmed by selective proton decouplings (irradiation at δ_H 8.33–119.6 signal singlet; irradiation δ_H 7.70–139.8 signal singlet). The proton-coupled spectrum was also obtained and confirmed that C-4 was assigned to the signal at 139.8. The 139.8 signal appeared as a doublet of doublets ($^1J_{C\text{-}H4}$ = 170.0; $^3J_{C\text{-}H5}$ = 3.9) while the 119.6 signal appeared only as a doublet ($^1J_{C\text{-}H3}$ = 177.0). A gated decoupling experiment (decoupler on only during data acquisition) was performed and confirmed double-intensity signals at 197.1 and 58.2 ppm by integration (pulse repetition 180 s).

Table IV. Stabilities of 1, 7, and 8

compd	MeOH	0.1 N HCl-MeOH	K_2CO_3-MeOH	EtOAc
1	3% conversion to 8 and 0% 7 in 13 days	$t^{1/2}$ = 14 h; 82% 8 and 18% 7 in 13 days; 7 reaches peak concn in 3 days	$t^{1/2}$ = 8 min, 7 only	no change after 25 days
7	$t^{1/2}$ = 11 h, 8 only	$t^{1/2}$ = 11 h, 8 only	no 8 detected after 6 days	$t^{1/2}$ = 20 h, 8 only
8	no change after 48 h	1% conversion to 7 after 48 h	$t^{1/2}$ = 18 h, 7 only	no change after 25 days

solutions of $KMnO_4$ or Fast Blue B salt (Aldrich). The plant material was collected in April 1978 in Oyo State, Nigeria, and identified by Mr. Gbile, Forest Research Institute of Nigeria (FRIN). A voucher specimen has been deposited in the Herbarium of the FRIN. The antimicrobial assays were performed as previously described[9] and the extracts of *U. afzelii* were active against *Staphylococcus aureus*, *Bacillus subtilis*, and *Mycobacterium smegmatis*. The most active constituent was shown to be uvafzelin (2) and its data have been reported.[2] All of the other compounds reported here were tested but all showed activity more than 25 μg/mL (minimum inhibitory concentration). The antitumor and cytotoxicity assays were performed by the National Cancer Institute.

Isolation Procedures. The air-dried ground stems of *Uvaria afzelii* (4.0 kg) were exhaustively extracted by percolation with 95% EtOH. Evaporation of the ethanolic extract in vacuo at 40 °C yielded 450 g of residue. A portion of this residue (400 g) was partitioned between 1.5 L of ethyl acetate (5 times) and 1.5 L of water. Evaporation of the combined dried (Na_2SO_4) EtOAc layers yielded 131.5 g. A portion of this residue (43 g) was adsorbed onto 60 g of Celite 545 (Sargent-Welch) and applied to a column containing 1.3 kg of silicic acid in C_6H_6. Column fractions were monitored and combined by TLC.

Vafzelin (1). Elution with 2.5 L of C_6H_6 resulted in an oily fraction (528 mg) which upon standing became crystalline. Crystallization from *n*-hexane yielded 150 mg of **1** as colorless prisms, mp 136–138 °C. The spectral data have been published[2] and the ^{13}C NMR assignments are listed in Table II.

Demethoxymatteucinol (5). Elution with an additional 3.5 L of C_6H_6 followed by 1.5 L of 1% Et_2O–C_6H_6 resulted in a fraction from which 253 mg of **5** was crystallized from C_6H_6, mp 202–204 °C (lit.[10] mp 204 °C). A sample of **5** was compared with and found identical with an authentic sample of demethoxymatteucinol (melting point, mixture melting point, superimposable IR, TLC).

Coumarin (3). Further elution with 1 L of 1% Et_2O–C_6H_6 resulted in a 1.3-g fraction from which 455 mg of **3** was obtained from *n*-hexane, mp 65–68 °C (lit.[11] mp 68–70 °C). A direct comparison of **3** with an authentic sample of coumarin (nutritional Biochemistry Corp.) confirmed its identify (melting point, mixture melting point, TLC, ^1H NMR, superimposable IR).

Uvafzelin (2). Elution with 2 L of 2% EtO–C_6H_6 yielded an oily fraction (1.39 g) which crystallized upon standing. Crystallization from MeOH yielded 600 mg of **2** as colorless needles, mp 138–140 °C. The spectral data have been published[2] and the ^{13}C NMR assignments are listed in Table II.

2-Hydroxy-7,8-dehydrograndiflorone (7). Elution with 2.5 L of 4% Et_2O–C_6H_6 yielded a 1.73-g fraction from which **7** (150 mg, yellow needles) was obtained by crystallization from $CHCl_3$: mp 143–144 °C; IR (KBr) 3420, 1720, 1645, 1603 cm^{-1}; UV (dioxane) λ_{max} 390 nm (ϵ 3.24 × 10^4), 320 (1.03 × 10^4), 253 (1.42 × 10^4); ^1H NMR ($CDCl_3$) δ 8.53 (1 H, d, J = 16 Hz), 8.07 (1 H, d, J = 16 Hz), 8.00–6.93 (4 H, m), 7.25 (1 H, s, exchanges with D_2O), 1.47 (12 H, s); mass spectrum, m/e 328 (M^+, 5%); ^{13}C NMR, see Table III. **7** decomposed rapidly in solution.

Emorydone (8). Elution with an additional 500 mL of 4% Et_2O–C_6H_6 yielded a yellow oil (2 g) which was further purified by chromatography over silica gel G (35 g). Elution with 300 mL of 20% Me_2CO–hexane gave 209 mg of a yellow oil which was pure by TLC and ^1H NMR: IR ($CHCl_3$) 1730, 1680, 1640, 1560 cm^{-1}; UV (dioxane) λ_{max} 445 nm (sh, ϵ 2.33 × 10^4), 422 (3.41 × 10^4), 400 (3.10 × 10^4), 280 (1.86 × 10^4), 220 (3.72 × 10^4); ^1H NMR ($CDCl_3$) δ 8.33 (1 H, d, J = 10 Hz), 7.70 (1 H, d, J = 10 Hz), 7.60–7.20 (4 H, m), 1.43 (12 H, s); ^{13}C NMR, see Table III; high-resolution mass spectrum, calcd for $C_{19}H_{18}O_4$ mol wt 310.1198, found 310.1192. A direct comparison of **8** with emorydone was made by TLC (co-TLC) and HPLC and the two samples had identical chromatographic properties.

2′-Hydroxymethoxymatteucinol (6). Elution with 4 L of 8% Et_2O–C_6H_6 afforded a 1.26-g fraction from which 200 mg of **6** was obtained by crystallization from Me_2CO–CH_3CN (yellow needles): mp 198–200 °C; IR (KBr) 3300, 2920, 1640, 1600 cm^{-1}; UV (MeOH) λ_{max} 345 nm (sh, ϵ 3.30 × 10^3), 297 (1.62 × 10^4), 218 (2.09 × 10^4); CD (MeOH) $[\theta]_{314}$ +11 200, $[\theta]_{290}$ −33 600, $[\theta]_{250}$ +4000, $[\theta]_{216}$ +46 800; $[\alpha]^{25}_D$ −97.8° (*c* 1.2, MeOH); mass spectrum, m/e 300 (M^+, 59%), 282 (M^+ − 18, 100), 180 (M^+ − 120, 17%); ^1H NMR (CD_3COCD_3) δ 12.30 (1 H, s, exchanges with D_2O), 7.95 (1 H, s, exchanges with D_2O), 7.60–6.73 (4 H, m), 5.69 (1 H, dd, J = 6, 10 Hz), 3.20 (1 H, br s, exchanges with D_2O), 3.2–2.8 (2 H, AB of ABX), 2.13 (6 H, s); ^{13}C NMR, see Table I. Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.69; H, 5.79.

Syncarpic Acid (4). Elution with 4 L of 16% Et_2O–C_6H_6 gave a 2.8-g fraction from which 176 mg of **4** was obtained by crystallization from $CDCl_3$, mp 185–188 °C (lit.[12] mp 190 °C). The *C*-acetyl and *O*-methyl derivatives were prepared and had mp 53–54 (lit.[12] mp 54 °C) and 60–62 (lit.[12] mp 63 °C). The ^{13}C NMR spectral data for **4** and its derivatives have been reported.[2] Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.62; H, 7.56.

Uvafzelic Acid (9). Elution with another 6 L of 16% Et_2O–C_6H_6 gave an oily fraction (1.97 g). A portion of this (300 mg) was purified by chromatography over silica gel 60 (40 g). After elution with 300 mL of $CHCl_3$, the eluent was changed to 2% EtOH–$CHCl_3$. Elution with 100 mL gave 150 mg of **9** as an oil pure by TLC and ^1H NMR: IR ($CHCl_3$) 3200, 1715, 1675, 1590 cm^{-1}; UV (MeOH) λ_{max} 285 nm (ϵ 5.68 × 10^3), 220 (8.31 × 10^3); $[\alpha]^{25}_D$ 0°; ^1H NMR ($CDCl_3$) δ 9.30 (1 H, br s, exchanges with D_2O), 7.67–7.00 (4 H, m), 4.48 (1 H, t, J = 5 Hz), 2.77 (2 H, d, J = 5 Hz), 1.57 (3 H, s), 1.50 (3 H, s), 1.43 (6 H, s); ^{13}C NMR see Table II; high-resolution mass spectrum, calcd for $C_{19}H_{20}O_5$ mol wt 328.1308, found 328.1306.

2-Methoxy-7,8-Dehydrograndiflorone (14). A stirred suspension of 80 mg of **7** in 10 mL Me_2CO, 120 mg of K_2CO_3, and 4.5 mL of CH_3I was kept at room temperature for 24 h. The suspension was then filtered and concentrated in vacuo, and 20 mL of H_2O and 20 mL of Et_2O were added. The solution was extracted twice more with Et_2O (20 mL). The combined dried (Na_2SO_4) ether layers were evaporated and the residue was chromatographed over silica gel 60 (40 g, C_6H_6) to give 65 mg of **14** as yellow needles from hexane: mp 133–135 °C; IR (KBr) 3420, 1720, 1660, 1606 cm^{-1}; UV (dioxane) λ_{max} 385 nm (ϵ 3.08 × 10^4), 275 (2.35 × 10^4), 257 (2.35 × 10^4); ^1H NMR ($CDCl_3$) δ 8.53 (1 H d, J = 16 Hz), 8.07 (1 H, d , J = 16 Hz), 8.00–6.93 (4 H, m), 3.96 (3 H, s), 1.52 (9 H, s), 1.47 (3 H, s); ^{13}C NMR, see Table III. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.88; H, 6.71.

Uvafzelic Acid Methyl Ester (12). Methylation of **9** (120 mg) with excess ethereal diazomethane for 2 h at room temperature gave a yellow residue after evaporation of solvent. This residue was chromatographed over silica gel 60 (40 g, C_6H_6). Elution with 6% Et_2O–C_6H_6 gave 90 mg of **12** as white needles from *n*-hexane; mp 79–80 °C; IR (KBr) 1735, 1720, 1630, 1580 cm^{-1}; UV (MeOH) λ_{max} 285 nm (ϵ 7.80 × 10^3), 220 (1.10 × 10^4); ^1H NMR ($CDCl_3$) δ 7.50–6.97 (4 H, m), 4.43 (1 H, t, J = 5 Hz), 3.57 (3 H, s), 2.72 (2 H, d, J = 5 Hz), 1.63 (3 H, s), 1.53 (3 H, s), 1.47 (3 H, s), 1.43 (3 H, s); ^{13}C NMR, see Table II; mass spectrum, m/e 342 (M^+, 15%). Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.09; H, 6.52.

2′-Hydroxydemethoxymatteucinol Methyl Ethers (10 and 11). Treatment of 100 mg of **6** with excess ethereal diazomethane for 24 h at room temperature left a residue after evaporation of solvent which was chromatographed over silica gel 60 (40 g). Elution with $CHCl_3$ (100 mL) and crystallization from EtOH gave 74 mg of **11**: mp 123–126 °C; IR (KBr) 3400, 1630, 1590 cm^{-1}; UV (MeOH) λ_{max} 360 nm (ϵ 2.46 × 10^3), 282 (9.84 × 10^3), 213 (1.76 × 10^4); $[\alpha]^{25}_D$ −129° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 12.09 (1 H, s, exchanges with D_2O), 7.70–6.69 (4 H, m), 5.67 (1 H, dd, J = 6, 10 Hz), 3.82 (3 H, s), 3.73 (3 H, s), 3.15–2.68 (2 H, AB of ABX), 2.09 (6 H, s); ^{13}C NMR see Table I; mass spectrum, m/e 328 (M^+, 89%), 194 (M^+ − 134, 39%). Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; , 6.14. Found: C, 69.29; H, 6.10.

Further elution with 200 mL of $CHCl_3$ yielded an oil which on crystallization from *n*-hexane gave 23 mg of **10**: mp 184–187 °C; IR (KBr) 3270, 1630, 1600 cm^{-1}; $[\alpha]_D^{25}$ −77° (*c* 0.6, Me_2CO); UV (MeOH) λ_{max} 360 nm (ϵ 3.40 × 10^3), 283 (1.49 × 10^4), 218 (1.89

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× 10^4), ^{1}H NMR (CD_3COCD_3) δ 12.19 (1 H, s, exchanges with D_2O), 8.76 (1 H, s, exchanges with D_2O), 7.62–6.70 (4 H, m), 5.79 (1 H, dd, J = 6, 10), 3.76 (3 H, s), 3.35–2.71 (2 H, AB of ABX), 2.04 (6 H, s); ^{13}C NMR, see Table I; mass spectrum, m/e 314 (M^+, 79%), 194 (M^+ – 120, 13). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.34, H, 5.82.

The monomethyl ether (**10**) could also be prepared by methylation of **6** (100 mg) using CH_3I (5 mL) and K_2CO_3 (100 mg) in Me_2CO (10 mL). After 5 h at room temperature, the suspension was concentrated in vacuo, diluted with H_2O (15 mL), and extracted with EtOAc (4 × 15 mL). The combined dried (Na_2SO_4) EtOAc layer was concentrated to give a yellow oil from which 58 mg of **10** was obtained from *n*-hexane, mp 184–187 °C, identical with the sample prepared from CH_2N_2 (mixture melting point, TLC, IR).

Degradation of Emorydone (8). Emorydone (8, 50 mg) was dissolved in 6 mL of glacial HOAc, 6 mL of hydrobromic acid was added, and the solution was refluxed for 3 h (yellow color disappeared), cooled, diluted with H_2O (25 mL), and extracted with Et_2O (4 × 30 mL). The combined ether layers (dried over Na_2SO_4) were evaporated, and the residue was chromatographed over silica gel 60 (20 g). Elution with 20% Me_2CO–hexane yielded a fraction from which 20 mg of **3**, mp 65–68 °C (*n*-hexane), was obtained. This was identical with an authentic sample of **3** (melting point, mixture melting point, TLC, superimposable IR).

Elution with 60% Me_2CO–hexane (200 mL) yielded a crystalline residue from which 10 mg of **4**, mp 186–188 °C ($CHCl_3$) was obtained. This sample was identical with the isolated sample of **4** (melting point, mixture melting point, TLC, superimposable IR).

Transformation of Vafzelin (1). A 20-mg sample of vafzelin (**1**) was dissolved in MeOH (5 mL) and refluxed for 6 h. The yellow solution was evaporated to dryness and the yellow oil chromatographed over silica gel 60 (30 g). Elution with 200 mL of $CHCl_3$ gave 12 mg of emorydone (**8**), which was identical with the previously isolated sample [TLC, co-TLC, superimposable IR spectra ($CHCl_3$)]. Elution with an additional 100 mL of $CHCl_3$ gave 3 mg of **7** (TLC, co-TLC, HPLC).

To 20 mg of vafzelin (**1**) in 10 mL of MeOH was added 40 mg of K_2CO_3. The suspension was stirred for 0.5 h and then 3 mL of CH_3I was added. The suspension (yellow) was stirred for 24 h, filtered, concentrated, and then partitioned between Et_2O (4 × 20 mL) and H_2O (20 mL). The combined dried (Na_2SO_4) ether layers were evaporated and 14 mg of **14** was obtained from *n*-hexane, mp 133–135 °C, identical with the previously prepared sample [mixture melting point, TLC, co-TLC, superimposable IR (KBr)].

Stability Studies of Vafzelin (1), 2-Hydroxy-7,8-dehydrograndiflorone (7), and Emorydone (8) by HPLC. Kinetic studies on the interconversions of **1**, **7**, and **8** were accomplished by using high-performance liquid chromatographic analysis of the reaction mixtures. A 3.9 mm × 30 cm C_{18} reversed-phase column (μ-Bondapak C_{18}, Waters Assoc. Inc.) with a 10-μm particle size was used for the study. The mobile phase was prepared by using 6.6 g of K_2HPO_4, 9.4 g of KH_2PO_4, 2.0 L of H_2O, and 2.0 L of CH_3OH, and a flow-rate of 1.0 mL/min was used. Two ultraviolet detectors (254 and 280 nm) were used in series for the quantitation of the products and for the verification of their identities, using A_{254}/A_{280} ratios.[13] The retention times that were observed for **7**, **8**, and **1** were 4.5, 18.2, and 27.4 min and the A_{254}/A_{280} observed values were 0.38, 0.98, and 0.61, respectively.

For the stability studies, 1.0 mg/mL solutions of each of the three test compounds were prepared by using CH_3OH, 0.1 N HCl in CH_3OH, K_2CO_3-saturated CH_3OH, and ethyl acetate. The 12 solutions were stored at room temperature, and the reactions products were quantitated by using peak heights of the HPLC analysis.

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Thallium in Organic Synthesis. 60. 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane-4,8-dione Lignans by Oxidative Dimerization of 4-Alkoxycinnamic Acids with Thallium(III) Trifluoroacetate or Cobalt(III) Trifluoride[1,2]

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Oxidation of *p*-alkoxycinnamic acids either with thallium(III) trifluoroacetate in TFA/CH_2Cl_2 or with cobalt(III) trifluoride in CH_3CN, in the presence of a small amount of BF_3·Et_2O, results in instantaneous oxidative dimerization to give the bislactone lignans **1**. A mechanism for this transformation is discussed.

The fused bislactones **1** belong to a naturally occurring family of compounds, some of which have been found in a cultured mushroom, *Inonotus* sp. K-1410, and which exhibit inhibitory activity against catechol-*O*-methyl-

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