in methanol for 24 h. The filtrate and washes were evaporated to dryness: yield 77 mg, 36% by weight; 127 μmol Val, 7.7 μmol Gly (yield 32%). Total ^{14}C counts recovered in the filtrate indicated a yield of 36%. The solid was recrystallized from ether–petroleum ether. Paper electrophoresis at pH 1.5 gave a single radioactive spot at R_{Val} 0.48 (standards of Gly-Val, Asp, and cyclic Dca-Val appeared at 0.86, 0.74, and 0.66, respectively); ^1H NMR (Varian HF, 220 MHz, Me_2SO-d_6) δ 0.91 (m, 6 H), 1.3–1.4 (broad m, cyclohexyl axial), 1.6–1.8 (broad m, cyclohexyl equatorial), 2.06 (m, 1 H, Val β-CH), 3.1 (m, tertiary CH), 4.1–4.2 (m, 3 H, α-CH), 3.8 (s, 3 H, OCH_3), 7.32 (d, 2 H, J = 8 Hz, cyclohexyl NH), 7.68 (t, 1 H, J = 7 Hz, Gly NH), 8.64 (d, 1 H, J = 8 Hz, Val NH); ^{13}C NMR (Bruker HX-90, 22.6 MHz, proton decoupled, Me_2SO) (Me_4Si δ 0) δ 19.1, 19.8 (Val, C_γ), 25.5, 33.2, 51.6 (cyclohexyl), 31.0 (Val C_β), 44.8 (Gly C_α), 54.4 (OCH_3), 58.7 (Val C_α), 155 (Guan), 167.8 (Gly C=O), 169.7 (Val C=O). ^{13}C assignments were based on the standards, cyclohexylamine, Gly-Val, and Arg·HCl.

Acknowledgment. We wish to thank Mr. Arun Dhundale for his assistance during the preliminary phase of this work.

Registry No.—IV, 5874-68-0; V, 61364-31-6; VI, 61348-54-7; VII, 57944-26-0; VIII, 61364-32-7; DCC, 538-75-0; Gly-OEt HCl, 623-33-6; Gly HCl, 6000-43-7; Gly, 56-40-6; Boc-Gly, 4530-20-5; Dca-Gly HCl, 61348-85-8; DIEA, 7087-68-5; [^{14}C]urea, 594-05-8; cyclohexylamine, 108-91-8; 1-cyclohexyl-2-cyclohexylamino-4-isopropyl-4,5-dihydro-5-imidazolone, 61348-56-9; Val HCl, 17498-50-9; [^{14}C]Dca-Gly-Val, 61348-57-0; Gly-Val HCl, 61348-59-2; Dca-Gly-Val HCl, 61348-60-5; Boc-Ala, 15761-38-3; Ala-Gly-Val HCl, 61348-58-1; Boc-Leu, 13139-15-6; Boc-Ile, 13139-16-7; Boc-Val, 13734-41-3; Boc-Gly-Val, 28334-73-8; Boc-Ile-Val, 61348-61-6; Boc-Ala-Gly-Val, 56133-97-2; Boc-Leu-Ala-Gly-Val, 61165-83-1.

References and Notes

(1) Reported in part at the 170th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1975; the work was supported by Grants AM 01260 and HL 12157 from the U.S. Public Health Service and by a grant from the Hoffmann-La Roche Foundation.
(2) Abbreviations: [^{14}C]DCC, [1-^{14}C]dicyclohexylcarbodiimide; Boc, *tert*-butyloxycarbonyl; Lys(2,4-Cl_2Z), N^{ϵ}-2,4-dichlorobenzyloxycarbonyllysine; Tos, *p*-toluenesulfonyl; DIEA, diisopropylethylamine; Res, 200–400 mesh resin beads of a 1% cross-linked copolymer of styrene and divinylbenzene; Dca, *N,N'*-dicyclohexylamidino; TFA, trifluoroacetic acid; TLC, thin layer chromatography. Other nomenclature and symbols follow the Tentative Rules of the IUPAC–IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966); **242**, 555 (1967); **247**, 977 (1972).
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Cytotoxic C-Benzylated Flavonoids from *Uvaria chamae*[1]

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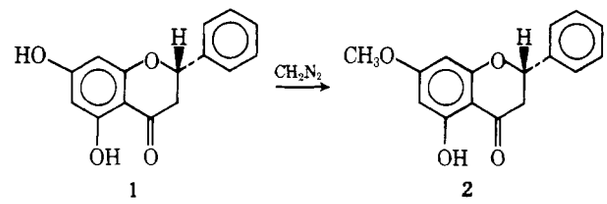
Ethanolic extracts of *Uvaria chamae* have demonstrated activity in vivo against P-388 lymphocytic leukemia in the mouse and in vitro against cells derived from human carcinoma of the nasopharynx (KB). Fractionation of these extracts yielded the known flavanones pinocembrin (**1**) and pinostrobin (**2**), the C-benzylated flavanones chamanetin (**3**), isochamanetin (**4**), and dichamanetin (**5**), and the C-benzylated dihydrochalcones uvaretin (**6**), isouvaretin (**7**), and diuvaretin (**8**). The structures were established by spectroscopic methods, chemical synthesis, and degradations.

In a previous communication[2] the isolation and structure elucidation of the cytotoxic C-benzylated flavanones chamanetin[3] (**3**) and isochamanetin (**4**) from the stem bark of *Uvaria chamae* were reported. We now wish to describe the total structure determination of these compounds. In addition, we wish to describe the isolation and structure elucidation of the known flavanone pinocembrin (**1**) and the dibenzylated flavanone dichamanetin (**5**) isolated from stem bark extracts as well as the known flavanone pinostrobin (**2**) and C-benzylated dihydrochalcones uvaretin (**6**), isouvaretin (**7**), and diuvaretin (**8**), which were isolated from root bark extracts.

Cytotoxicity[5] residing in ethanolic extracts of the stem bark was concentrated in the ethyl acetate fraction of an ethyl acetate–water partition. Silicic acid chromatography of this fraction starting with initial eluent benzene followed by ether–benzene mixtures resulted in the isolation of four flavanones (**1**, **3**, **4**, and **5**).

Scheme I



1 **2**

Compound **1** demonstrated UV, IR, and ^1H NMR[6] data consistent with a 5,7-dihydroxylated flavanone lacking B-ring[7] substituents. Comparison of the isolated product with an authentic sample of pinocembrin verified structure **1**.

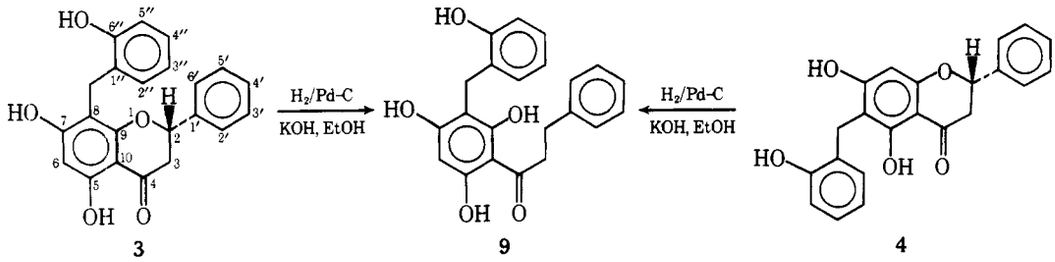
Based on spectroscopic evidence (^1H NMR data in Table I) chamanetin (**3**) and isochamanetin (**4**) were designated as isomeric *o*-hydroxybenzyl derivatives of pinocembrin.[2] Support for these assignments followed from their formation of

Table I. ^{1}H NMR Spectra of Flavanones[a]

Registry no.	Compd	H-2[b]	H-3[c]	C_5-OH	H-6	H-8	Misc
480-39-7	1	5.53, dd (3.5, 9.8)	2.67–3.60, m (14.2)	14.00	5.98	5.98	7.30–7.80,[d] m
480-37-5	2	5.50, dd (3.9, 10.2)	2.70–3.50, m (14.6)	13.90	6.13	6.13	7.50[d] 3.87[e]
	3	5.60, dd (4.5, 10.7)	2.50–3.50, m (16.5)	12.60	6.10		6.50–7.33,[d] m 3.91[f]
	4	5.68, dd (3.5, 9.8)	2.67–3.60, m (14.2)	13.33		6.26	6.67–7.50,[d] m 4.00[f]
58779-09-2	5	5.65, dd (3.9, 9.2)	2.60–3.60, m (13.7)	13.13			6.50–7.80,[d] m 3.97[f]

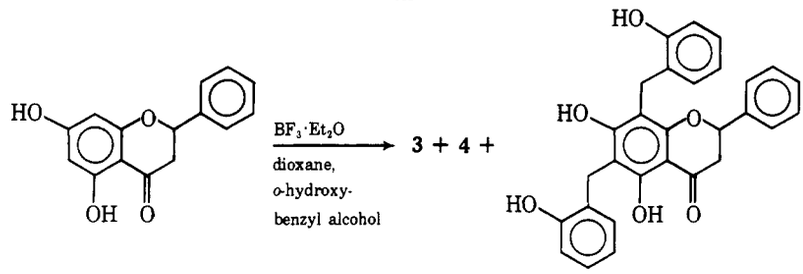
[a] Values are in parts per million in acetone-d_6 solution. Multiplicities are indicated by the usual symbols: dd, double doublet; m, multiplet. Unmarked signals are singlets. Figures in parentheses are coupling constants in hertz. [b] Center of the X portion of an ABX system; parentheses include J_{AX} and J_{BX}, respectively. [c] AB portion of an ABX system, J_{AB} is in parentheses. [d] The aromatic signals in this category represent (1) the four B-ring aromatic protons for 1 and 2, (2) the nine B-ring and o-hydroxybenzyl aromatic protons for 3 and 4, and (3) the 13 B-ring and o-hydroxybenzyl aromatic protons for 5. [e] C_7–OCH_3. [f] $ArCH_2Ar$ (two protons in 3 and 4; four protons in 5).

Scheme II



3 9 4

Scheme III



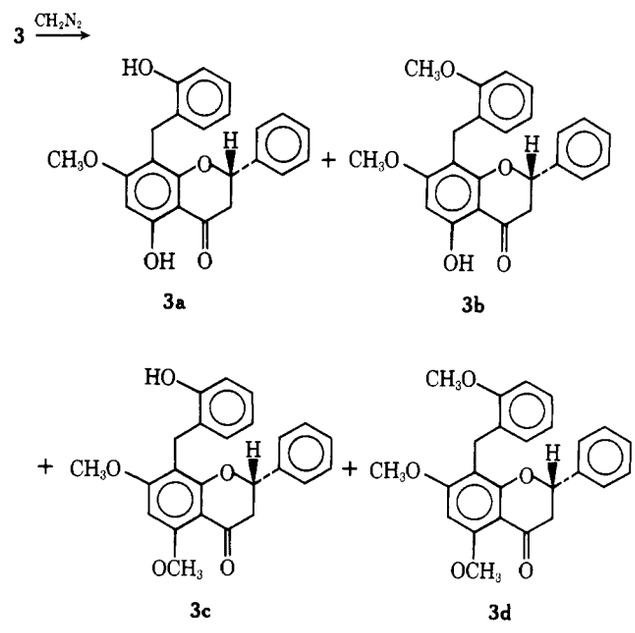
1 5

the same dihydrochalcone (9) upon catalytic hydrogenation (Scheme II) and their synthesis from pinocembrin and o-hydroxybenzyl alcohol using boron trifluoride etherate in dioxane (Scheme III). The dibenzylated product from this reaction was found to correspond to dichamanetin (5), a C-dibenzylated flavanone also isolated from stem bark extracts. The absolute stereochemistry in 3, 4, and 5 follows from CD data which allows assignment of the 2S configuration.[2,8]

Treatment of chamanetin (3) with ethereal diazomethane (Scheme IV) yielded four products: a monomethyl ether 3a, two dimethyl ethers 3b and 3c, and a trimethyl ether 3d. Treatment of isochamanetin (4) with ethereal diazomethane (Scheme V) yielded the dimethyl ethers 4a and 4b[9] and the trimethyl ether 4c. Table II lists the spectroscopic data supporting the indicated methoxyl assignments in the methyl ethers of 3 and 4.

The synthesis of chamanetin and isochamanetin established them as isomeric C-benzylated flavanones. However, placement of the o-hydroxybenzyl substituent at the C-8 and C-6 positions of 3 and 4, respectively, depended upon the interrelation of certain methyl ethers of chamanetin and isochamanetin with methyl ether derivatives of the dihydrochalcones uvaretin (6) and isouvaretin (7) which were isolated from root bark extracts.

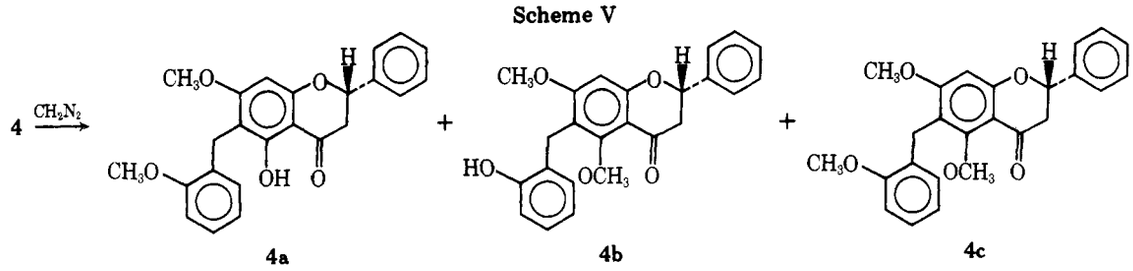
Scheme IV



3a 3b

3c 3d

Scheme V



Scheme VI

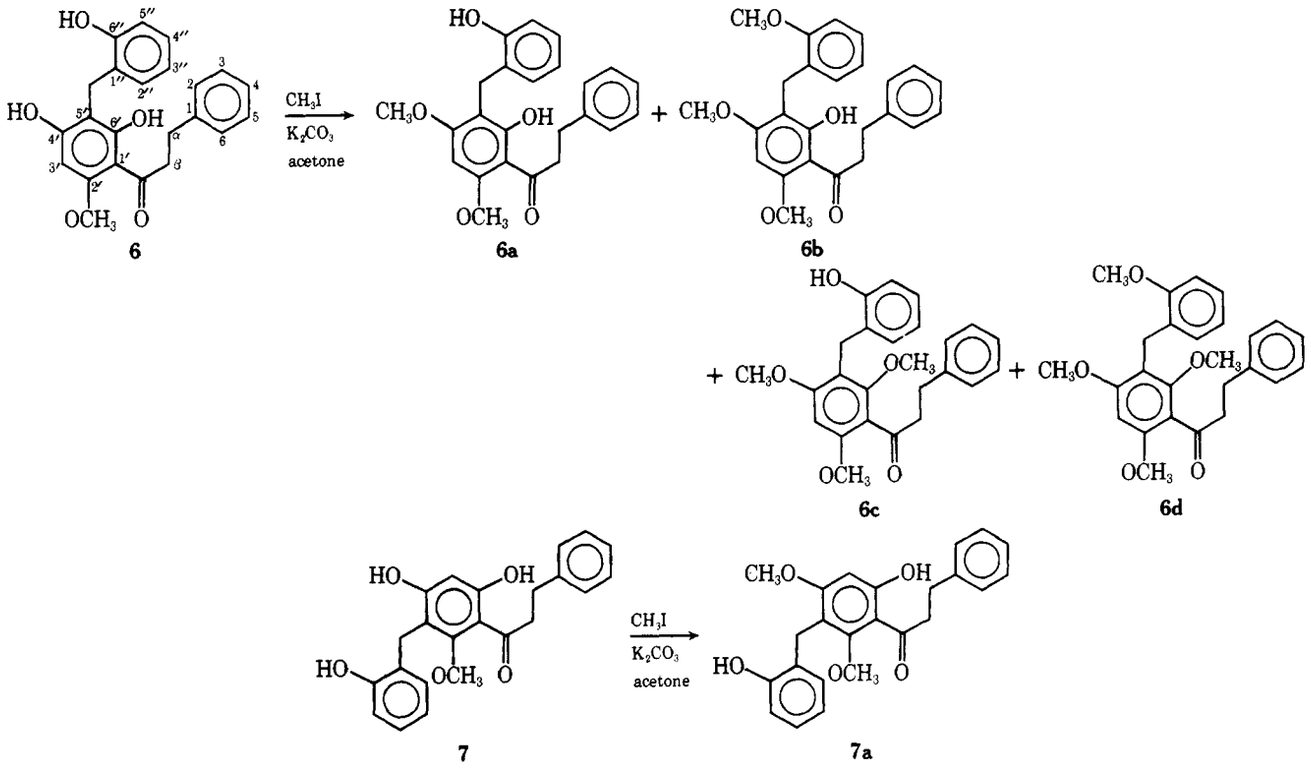


Table II. Spectral Data for 3, 4, and Their Methyl Ethers

Registry no.	Compd	^{1}H NMR[a] C_5-OH	UV NaOAc shift[b]	IR carbonyl band,[c] cm^{-1}
61462-95-1	3	12.60	+36	1630
61462-96-2	3a	13.50	*d*	1630
61462-97-3	3b	12.70	*d*	1640
61462-98-4	3c		*d*	1662
61462-99-5	3d		*d*	1680
61477-75-6	4	13.33	+28	1630
61463-00-1	4a	12.53	*d*	1640
61463-01-2	4b		*d*	1678
61463-02-3	4c		*d*	1670

[a] All signals are singlets. The presence of a low-field, exchangeable signal indicates the presence of a hydroxyl group at C-5 which is hydrogen bonded to the carbonyl function.[6] [b] Shift values refer to the 290-nm band (band II) in the UV spectrum. A shift of ~30 nm indicates a C-7 hydroxyl group.[6] [c] Carbonyl bands of unusually low value (<1640) are a result of hydrogen bonding with the C-5 hydroxyl. [d] No appreciable shift.

Silicic acid chromatography of the ethyl acetate fraction of the root bark yielded four flavonoids (**2**, **6**, **7**, and **8**). Compound **2** demonstrated spectral characteristics indicative of pinostrobin (**2**). Treatment of (−)-pinocembrin with ethereal diazomethane (Scheme I) gave a product identical with **2**.

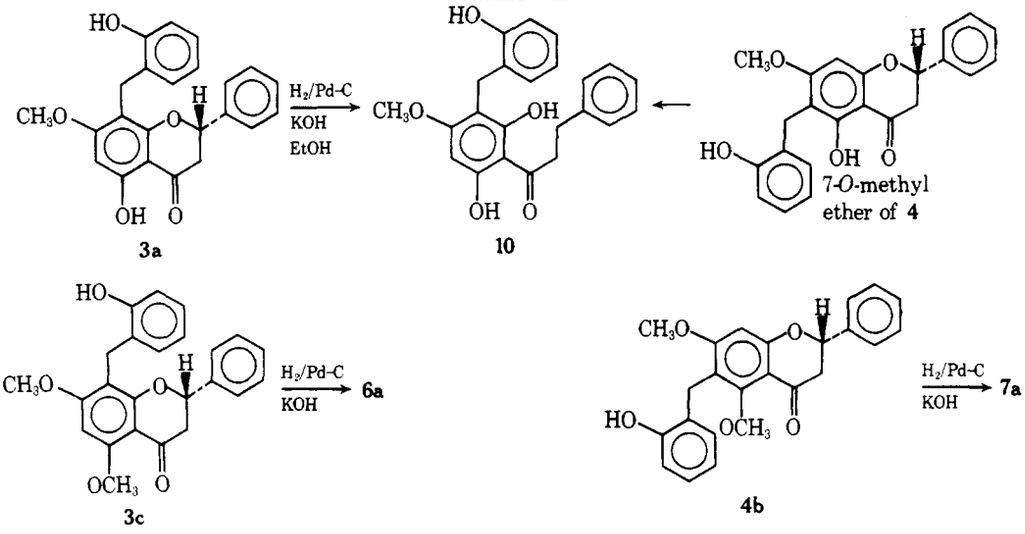
The spectral data for uvaretin (**6**) and isouvaretin (**7**) indicated them to be monomethoxylated dihydrochalcones (see ^{1}H NMR data in Table III). Uvaretin (**6**) yielded four products upon treatment with methyl iodide and potassium carbonate in acetone (Scheme VI): a monomethyl ether **6a**, two dimethyl ethers **6b** and **6c**, and a trimethyl ether **6d**.[10] Isouvaretin (**7**) formed a monomethyl ether,[11] **7a**, upon treatment with methyl iodide and potassium carbonate in acetone (Scheme VI). Recently, uvaretin has been reported from *Uvaria acuminata* and its structure has been established by x-ray crystallography.[4] Knowledge of the structure of uvaretin taken in conjunction with the following conversions (Scheme VII) allows deduction of the structures of chamanetin (**3**) and isochamanetin (**4**).

Hydrogenation of **3a** gave a product, **10**, not identical with **6** or **7**. However, similar treatment of **3c**[12] yielded the monomethyl ether of **6**, **6a**. Thus, the hydroxybenzyl substituent in **3** and **3c** must be placed at C-8. The fact that **3** and **4** have been shown to be isomeric places the hydroxybenzyl substituent of isochamanetin (**4**) at C-6.

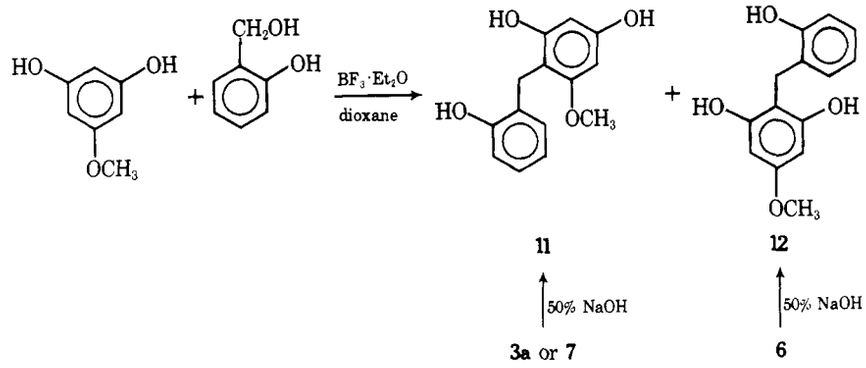
Spectroscopic evidence indicates that isouvaretin (**7**) is isomeric with **6**. Scheme VII shows that hydrogenation of **4b** gives **7a**.[13] Therefore, the same relationship that existed between **3c**, **6a**, and **6** exists between **4b**, **7a**, and **7**, thus placing the *o*-hydroxybenzyl substituent in **7** ortho to the methoxyl group. The following sequence of conversions was carried out to provide further evidence for the structure of isouvaretin (**7**).

The monomethyl ether of phloroglucinol was treated with

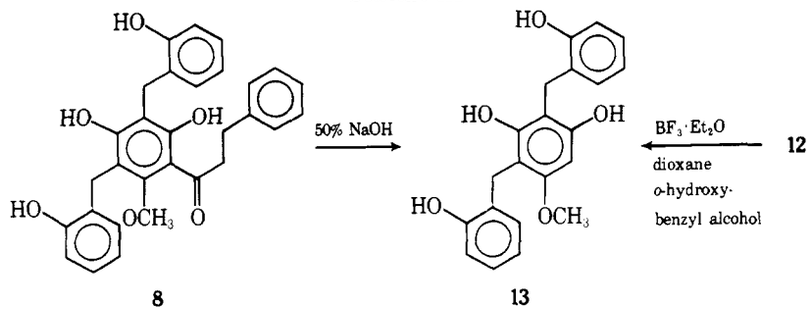
Scheme VII



Scheme VIII



Scheme IX



o-hydroxybenzyl alcohol and boron trifluoride etherate to yield two monomethoxylated, monobenzylated products **11** and **12**. Degradation of **3a** (Scheme VIII) with sodium hydroxide yielded a product identical with **11**. Thus, of the two isomeric monobenzylated products formed from the monomethyl ether of phloroglucinol, **11** is the isomer containing its benzyl group ortho to the methoxy group and **12** is the isomer with its benzyl group para to the methoxy function. As expected, similar treatment of **6** yielded **12**. Furthermore, degradation of **7** gave **11**, thus confirming structure **7** for isouvaretin.

One of the fragments of this degradative procedure, **12**, was then used to elucidate the structure of the third dihydrochalcone from the root bark, diuvaretin (**8**). The molecular formula and spectral properties (see Table III) of diuvaretin indicated it to be a 3′,5′-dibenzylated dihydrochalcone. Degradation of **8** with sodium hydroxide gave **13** which was found identical with the dibenzylated product formed from the treatment of **12** with *o*-hydroxybenzyl alcohol and boron trifluoride etherate (Scheme IX). This degradation along with spectroscopic evidence allows diuvaretin to be assigned structure **8**.

Experimental Section[14]

Isolation of Pinocembrin (1), Chamanetin (3), Isochamanetin (4), and Dichamanetin (5). The plant material used in this study was obtained and identified in Ghana by Dr. Oscar B. Dokosi, Department of Botany, University of Ghana, and Dr. Maynard W. Quimby, Department of Pharmacognosy, University of Mississippi. A voucher specimen has been deposited in the Herbarium of the Department of Pharmacognosy, School of Pharmacy, University of Mississippi.

The dried, ground stem bark (2.4 kg) was exhaustively extracted by percolation with 95% ethanol. After solvent evaporation 560 g of residue was obtained; 300 g of this residue was partitioned between 1.5 L of H_2O and 3 × 1.5 L of ethyl acetate. Evaporation of the combined ethyl acetate layers yielded 65 g of material which was adsorbed onto 50 g of Celite 545 and applied to a column containing 1 kg of silicic acid in benzene. Column fractions were monitored and combined by TLC.

Initial elution with 4 L of benzene resulted in a fraction containing 17.6 g of volatile oils. Further elution with 1.5 L of 0.1% ether in ben-

Table III. ^{1}H NMR Spectra of Dihydrochalcones[a]

Registry no.	Compd	H-α, H-β[b]	$C_{2'}$-OCH_3	$C_{6'}$-OH	H-3′	H-5′	Misc
58449-06-2	6	2.83–3.56, m	3.91	15.20	6.30		6.60–7.50[c] 3.96[d]
61463-03-4	7	2.80–3.80, m	3.77	13.13		6.25	6.50–7.50[c] 4.03[d]
61463-04-5	8	2.70–3.60, m	3.65	14.00			6.50–7.50[c] 3.93[d]

[a] Spectra for 6 and 7, were taken in acetone-d_6 while the spectrum for 8 was taken in $CDCl_3$. Unmarked signals are singlets (m = multiplet). [b] H-α and H-β form an A_2B_2 pattern. [c] These represent aromatic protons for the B-ring and *o*-hydroxybenzyl groups. [d] Singlets here represent $ArCH_2Ar$ grouping.

zene, 3 L of 0.5% ether in benzene, and 2 L of 1% ether in benzene yielded a number of semicrystalline fractions.

Dichamanetin (5). Continued elution with 5 L of 1% ether in benzene yielded a 4.07-g fraction from which 1.60 g of **5** was obtained by crystallization from ethanol: mp 118–120 °C; UV λ_{max} (MeOH) 329 nm (ϵ 1.05 × 10^4) and 273 (2.10 × 10^3); CD $[\theta]_{362}$ +3640, $[\theta]_{335}$ −3120, $[\theta]_{283}$ −10 400, $[\theta]_{244}$ −5200; $[\alpha]^{25}D$ −9.75° (*c* 1.20, acetone); IR (KBr) bands at 3060, 1620, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 468 (M$^+$, 82), 467 (M$^+$ − 1, 3), 364 (M$^+$ − 104, 22), 363 (M$^+$ − 105, 100), and 362 (M$^+$ − 106, 19).

Anal. Calcd for $C_{29}H_{24}O_6 \cdot C_2H_5O$: C, 72.33; H, 5.84. Found: C, 72.39; H, 5.89.

Isochamanetin (4). Elution with 4 L of 2% ether in benzene afforded a 5.03-g fraction from which 850 mg of **4** was obtained from benzene: mp 215–217 °C; uv λ_{max} (MeOH) 324 nm (ϵ 1.25 × 10^4), 296 (sh, 9.00 × 10^3), 218 (sh, 7.06 × 10^3), and 251 (4.04 × 10^3); CD $[\theta]_{328}$ +3800, $[\theta]_{289}$ −24 500, $[\theta]_{251}$ −24 100, $[\theta]_{219}$ +29 600; $[\alpha]^{25}D$ −10.5° (*c* 1.00, acetone); IR (KBr) bands at 3030, 1630, and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 362 (M$^+$, 100), 361 (M$^+$ − 1, 10), 344 (M$^+$ − 18, 2), 285 (M$^+$ − 77, 13), 258 (M$^+$ − 104, 22), and 256 (M$^+$ − 106).

Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.93; H, 4.97. Found: C, 72.99; H, 5.02.

Pinocembrin (1). Further elution (3 L) with 4% ether–benzene resulted in a fraction from which 240 mg of **1** was crystallized from benzene: mp 194–195 °C; UV λ_{max} (MeOH) 320 nm (sh, ϵ 7.46 × 10^3) and 287 (1.55 × 10^4); CD $[\theta]_{325}$ +9420, $[\theta]_{315sh}$ +7300, $[\theta]_{284}$ −41 300, $[\theta]_{215}$ +27 400; $[\alpha]^{25}D$ −37.8° (*c* 0.90, MeOH); IR (KBr) bands at 3020, 1630, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 256 (M$^+$, 100), 255 (M$^+$ − 1, 48), 179 (M$^+$ − 77, 84), 152 (M$^+$ − 104, 87), and 150 (M$^+$ − 106, 34). This compound was compared with and found identical with an authentic sample of pinocembrin[15] (melting point, mixture melting point, TLC, co-TLC, IR, and ^{1}H NMR).

Chamanetin (3). Elution with 2 L of 8% ether–benzene yielded a 2.47-g fraction from which 900 mg of **3** was obtained from benzene: mp 210–211 °C; UV λ_{max} (MeOH) 324 nm (ϵ 2.40 × 10^4) and 289 (1.05 × 10^4); CD $[\theta]_{355}$ +2260, $[\theta]_{314}$ +5080, $[\theta]_{288}$ −40 000, $[\theta]_{242}$ +3620, $[\theta]_{219}$ +34 600; $[\theta]^{25}D$ −52.5° (*c* 1.20, MeOH); IR (KBr) bands at 3090, 1630, and 1588 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 362 (M$^+$, 100), 361 (M$^+$ − 1, 11), 285 (M$^+$ − 77, 16), 258 (M$^+$ − 104, 37), and 256 (M$^+$ − 106, 51).

Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.93; H, 4.97. Found: C, 72.96; H, 5.02.

Isolation of Pinostrobin (2), Uvaretin (6), Isouvaretin (7), and Diuvaretin (8). The dried, ground root bark (2.4 kg) was extracted by percolation with 95% ethanol. After solvent evaporation 685 g of residue was obtained; 300 g of this residue was partitioned between 1.5 L of H_2O and 3 × 1.5 L of ethyl acetate. The combined ethyl acetate fraction was evaporated to afford 110 g of residue which was adsorbed onto 100 g of Celite 545 and chromatographed on a column containing 2 kg of silicic acid in benzene. Elution with 4 L of benzene yielded a 6.0-g fraction of volatile oils.

Pinostrobin (2). Elution with an additional 1 L of benzene yielded a 132-mg fraction from which was isolated 20 mg of **2**: mp 109–110 °C (ethanol); UV λ_{max} (MeOH) 284 nm (ϵ 1.46 × 10^4); CD $[\theta]_{328}$ +820, $[\theta]_{285}$ −3880, $[\theta]_{227}$ +5180; IR (KBr) bands at 3210, 1640, and 1580 cm^{-1}. Compound **2** was compared with and found identical with the methylation product of 1[16,17] (melting point, mixture melting point, TLC, co-TLC, IR and ^{1}H NMR).

Diuvaretin (8). Elution with an additional 3 L of benzene afforded a 12.0-g residue containing **8** as a gum which could not be induced to crystallize. Repeated chromatography over silica gel (with benzene) produced a gummy residue (9.6 g) which was pure by TLC, ^{1}H NMR, and MS: UV λ_{max} (MeOH) 331 nm (ϵ 9.40 × 10^3) and 277 (9.70 × 10^3); IR ($CHCl_3$) bands at 3600, 3310, 1620, and 1585 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 484 (M$^+$, 52), 452 (M$^+$ − 32, 6), 379 (M$^+$ − 105, 57), and 378 (M$^+$ − 106, 100).

Anal. Calcd for $C_{30}H_{28}O_6$: mol wt. 484.1886. Found: mol wt, 484.1877 (MS).

Isouvaretin (7). Elution with 4 L of 1% ether–benzene yielded 635 mg of a gummy fraction containing **7**. Repeated chromatography over silica gel (with 1% ether–benzene) yielded an oily residue which was pure by TLC, ^{1}H NMR, and MS: UV λ_{max} (MeOH) 326 nm (ϵ 8.09 × 10^3) and 278 (1.00 × 10^4); IR ($CHCl_3$) bands at 3595, 3400, 1645, and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 378 (M$^+$, 63), 347 (M$^+$ − 31, 9), 274 (M$^+$ − 104, 17), 273 (M$^+$ − 105, 100), 272 (M$^+$ − 106, 15), and 246 (M$^+$ − 132, 22).

Anal. Calcd for $C_{23}H_{22}O_5$: mol wt, 378.1467. Found: mol wt, 378.1442 (MS).

Uvaretin (6). Following elution with 3 L of 2% ether–benzene and 3 L of 4% ether–benzene a 2.65-g fraction was obtained which afforded 1.60 g of **6** from benzene: mp 164–165 °C; UV λ_{max} (MeOH) 323 nm (ϵ 1.3 × 10^4) and 295 (1.52 × 10^4); IR ($CHCl_3$) bands at 3590, 3490, 1621, and 1610 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 378 (M$^+$, 100), 274 (M$^+$ − 104, 23), 273 (M$^+$ − 105, 100), 272 (M$^+$ − 106, 29), and 246 (M$^+$ − 132, 38).

Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.01; H, 5.82. Found: C, 72.85; H, 5.96.

Methylation of Pinocembrin to Give 2. A solution of 30 mg of **1** was treated with excess ethereal diazomethane for 3 h at room temperature. After evaporation the resulting crude residue was taken up in benzene and chromatographed over 20 g of silica gel in benzene. Elution with benzene and crystallization from ethanol afforded 22 mg of pinostrobin (**2**), mp 109–110 °C.[16,17]

Methylation of Chamanetin (3) to Give 3a, 3b, 3c, and 3d. Excess ethereal diazomethane was added to a solution of 200 mg of **3** in 60 mL of ether. This mixture was allowed to stand at room temperature for 4 days. After evaporation of the solvent the residue was dissolved in benzene and chromatographed over 22 g of silica gel.

Elution with benzene yielded 58 mg of the dimethyl ether **3b** as needles from ethanol: mp 139–140 °C; UV λ_{max} (MeOH) 335 nm (ϵ 3.60 × 10^3) and 288 (7.20 × 10^3); CD $[\theta]_{329}$ +4360, $[\theta]_{311}$ +5430, $[\theta]_{287}$ −21 500, $[\theta]_{240}$ +6200, $[\theta]_{222}$ + 1300; $[\alpha]^{25}D$ −83.2° (*c* 0.90, benzene); IR (KBr) bands at 3200, 1640, and 1590 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M$^+$, 100), 389 (M$^+$ − 1, 10), 359 (M$^+$ − 31, 27), 313 (M$^+$ − 77, 16), and 286 (M$^+$ − 104, 8); ^{1}H NMR ($CDCl_3$) δ 12.70 (s, 1 H, exchanges D_2O), 7.33 (s, 5 H), 6.50–7.33 (m, 4 H), 6.17 (s, 1 H), 5.50 (X of ABX, 1 H), 3.97 (s, 2 H), 3.82 (s, 3 H), 3.79 (s, 3 H), and 2.50–3.16 (AB of ABX, 2 H).

Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.85; H, 5.64. Found: C, 73.71; H, 5.70.

Elution with 1% ether–benzene afforded the monomethyl ether **3a** as needles from methanol: mp 146–148 °C; UV λ_{max} (MeOH) 338 nm (ϵ 4.60 × 10^3) and 289 (1.87 × 10^4); CD $[\theta]_{332}$ +860, $[\theta]_{311}$ +1290, $[\theta]_{287}$ −4320, $[\theta]_{235}$ −1330, $[\theta]_{212}$ +3020; $[\alpha]^{25}D$ −107.5° (*c* 1.70, acetone); IR (KBr) bands at 3230, 1630, and 1594 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 376 (M$^+$, 100), 375 (M$^+$ − 1, 7), 299 (M$^+$ − 77, 9), 272 (M$^+$ − 104, 28), and 270 (M$^+$ − 106, 66); ^{1}H NMR (acetone-d_6) δ 13.50 (s, 1 H, exchanges D_2O), 7.52 (s, 5 H), 6.60–7.33 (m, 4 H), 6.20 (s, 1 H), 5.50 (X of ABX, 1 H), 4.00 (s, 3 H), 3.82 (s, 2 H), and 2.67–3.50 (AB of ABX, 2 H).

Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.40; H, 5.32. Found: C, 73.27; H, 5.35.

Elution with 32% ether–benzene gave 41 mg of the trimethyl ether **3d** as needles from ethanol: mp 148–150 °C; UV λ_{max} (MeOH) 323 nm (sh, ϵ 5.20 × 10^3), 285 (1.74 × 10^4), and 237 (1.79 × 10^4); CD $[\theta]_{332}$ +14 600, $[\theta]_{287}$ −32 700, $[\theta]_{241}$ −12 900; $[\alpha]^{25}D$ −73.4° (*c* 1.00, benzene);

IR (KBr) bands at 3220, 1680, and 1604 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 404 (M^+, 100), 403 ($M^+ - 1$, 7), 327 ($M^+ - 77$, 10), and 300 ($M^+ - 104$); ^1H NMR ($CDCl_3$) δ 7.37 (s, 5 H), 6.80–7.50 (m, 4 H), 6.50 (s, 1 H), 5.50 (X of ABX, 1 H), 3.93 (s, 8 H), 3.80 (s, 3 H), and 2.80–3.00 (AB of ABX, 2 H).

Anal. Calcd for $C_{25}H_{24}O_5$: mol wt, 404.1624. Found: mol wt, 404.1633 (MS).

Elution with 50% ether–benzene afforded 22 mg of the dimethyl ether **3c** as plates from methanol: mp 205–209 °C; UV λ_{max} (MeOH) 320 nm (sh, ϵ 9.80×10^3), 285 (2.91×10^4), and 238 (2.85×10^4); CD $[\theta]_{335}$ +26 300, $[\theta]_{286}$ −56 400, $[\theta]_{239}$ −25 200; $[\alpha]^{25}D$ −4.6° (*c* 3.20, benzene); IR (KBr) bands at 3130, 1662, and 1596 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M^+, 100), 389 ($M^+ - 1$, 21), 313 ($M^+ - 77$, 28), 286 ($M^+ - 104$, 70), and 284 ($M^+ - 106$, 24); ^1H NMR (Me_2SO-d_6) δ 7.60 (s, 5 H), 6.60–7.20 (m, 4 H), 6.52 (s, 1 H), 5.56 (X of ABX, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.88 (s, 2 H), and 2.80–3.10 (AB of ABX, 2 H).

Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.85; H, 5.64. Found: C, 73.70; H, 5.74.

Treatment of 40 mg of **3a** with excess diazomethane for 5 h followed by chromarography over silica gel yielded 15 mg of a compound identical with **3c** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Methylation of Isochamanetin (4) to Give 4a, 4b, and 4c. Treatment of 187 mg of **4** with excess diazomethane for 10 h, evaporation of solvent, and chromatography over 19 g of silica gel afforded three methyl ethers.

Elution with benzene gave the dimethyl ether **4a:** mp 202–204 °C (ethanol); uv λ_{max} (MeOH) 338 nm (ϵ 2.91×10^3), 290 (1.71×10^4), and 237 (ϵ 1.70×10^4); CD $[\theta]_{333}$ +7310, $[\theta]_{314sh}$ −2770, $[\theta]_{288}$ −26 400, $[\theta]_{239}$ +9320, $[\theta]_{218}$ +29 400;$[\alpha]^{25}D$ −47.1° (*c* 1.50, benzene); IR (KBr) bands at 3220, 1640, and 1610 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M^+, 100), 389 ($M^+ - 1$, 9), 359 ($M^+ - 31$, 13), 313 ($M^+ - 77$, 11), and 286 ($M^+ - 104$, 10); ^1H NMR ($CDCl_3$) δ 12.53 (s, 1 H, exchanges D_2O), 7.50 (s, 5 H), 6.70–7.60 (m, 4 H), 6.20 (s, 1 H), 5.51 (X of ABX, 1 H), 3.98 (s, 2 H), 3.93 (s, 3 H), 3.82 (s, 3 H), and 2.70–3.50 (AB of ABX, 2 H).

Anal Calcd for $C_{24}H_{22}O_5$: C, 73.85; H, 5.64. Found: C, 73.37; H, 5.65.

The trimethyl ether **4c** was eluted with 2% ether–benzene and 10 mg was crystallized from ethanol: mp 176–179 °C; UV λ_{max} 276 nm (ϵ 3.54×10^2), 237 (sh, 4.72×10^2), and 225 (7.09×10^3); CD $[\theta]_{340}$ +25 900, $[\theta]_{310}$ −34 100, $[\theta]_{280}$ +6310, $[\theta]_{237}$ +21 100; $[\alpha]^{25}D$ +14.1° (*c* 0.90, benzene); IR (KBr) bands at 1670 and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 404 (M^+, 100), 403 ($M^+ - 1$, 6), 389 ($M^+ - 15$, 71), 327 ($M^+ - 77$, 9), and 300 ($M^+ - 104$, 60); ^1H NMR ($CDCl_3$) δ 7.50 (s, 5 H), 6.70–7.60 (m, 4 H), 6.47 (s, 1 H), 5.54 (X of ABX, 1 H), 4.06 (s, 2 H), 3.97 (s, 3 H), 3.82 (s, 3 H), 3.75 (s, 3 H), and 2.70–3.50 (AB of ABX, 2 H).

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.26; H, 5.94. Found: C, 74.04; H, 6.07.

Elution with 16% ether–benzene provided 114 mg of the dimethyl ether **4b** which remained as a gum after repeated attempts at crystallization (pure by TLC, ^1H NMR, and MS): UV λ_{max} (MeOH) 324 nm (ϵ 4.32×10^3) and 288 (1.73×10^4); CD $[\theta]_{340}$ +20 000, $[\theta]_{313}$ −32 800, $[\theta]_{280}$ +8790, $[\theta]_{232}$ +21 600, $[\theta]_{214}$ +14 400; $[\alpha]^{25}D$ −7.8° (*c* 1.20, benzene); IR ($CHCl_3$) bands at 3415, 1678, and 1602 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M^+, 53), 389 ($M^+ - 1$, 4), 375 ($M^+ - 15$, 12), 359 ($M^+ - 31$, 38), 358 ($M^+ - 32$, 51), 313 ($M^+ - 77$, 5), 286 ($M^+ - 104$, 16), and 284 ($M^+ - 106$, 28); ^1H NMR ($CDCl_3$) δ 7.45 (s, 5 H), 6.70–7.60 (m, 4 H), 6.43 (s, 1 H), 5.47 (X of ABX, 1 H), 4.01 (s, 3 H), 3.93 (s, 3 H), 3.90 (s, 2 H), and 2.70–3.40 (AB of ABX, 2 H).

Anal. Calcd for $C_{24}H_{22}O_5$: mol wt, 390.1480. Found: mol wt, 390.1467 (MS).

Methylation of Dichamanetin (5). Treatment of 400 mg of **5** with excess diazomethane for 4 days yielded a residue after removal of solvent. This was chromatographed over 21 g of silica gel. Elution with 1% ether–benzene gave 95 mg of the tetramethyl ether after crystallization from ethanol: mp 122–124 °C; UV λ_{max} (MeOH) 326 nm (ϵ 3.93×10^3), 277 (sh, 1.52×10^4), and 272 (1.60×10^4); CD $[\theta]_{350}$ +25 400, $[\theta]_{314}$ −24 500, $[\theta]_{278}$ +5240, $[\theta]_{243sh}$ +2100, $[\theta]_{230}$ −2620, $[\theta]_{215}$ +18 300; $[\alpha]^{25}D$ +12.8° (*c* 1.00, benzene); IR (KBr) bands at 1685 and 1595 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 524 (M^+, 100) and 509 ($M^+ - 15$, 16); ^1H NMR ($CDCl_3$) δ 6.70–7.50 (m, 13 H), 5.67 (X of ABX, 1 H), 4.13 (s, 4 H), 3.97 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.58 (s, 3 H), and 2.85–3.10 (AB of ABX, 2 H).

Anal. Calcd for $C_{33}H_{32}O_6$: C, 75.57; H, 6.11. Found: C, 75.40; H, 6.23.

Methylation of Uvaretin (6) to Give 6a, 6b, 6c, and 6d. K_2CO_3 (10 mg) was suspended in a stirred acetone solution of 40 mg of **6.** Methyl iodide (1 mL) was added to this suspension over 2.5 h. The solvent was evaporated and 15 mL of ether added. Filtration and chromatography of the Na_2SO_4-dried ether fraction over silica gel (2% ether–benzene) provided 18 mg of the monomethyl ether **6a** as needles from ethanol: mp 138–140 °C; UV λ_{max} (MeOH) 289 nm (ϵ 1.81×10^4); IR ($CHCl_3$) bands at 3490, 1621, and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 392 (M^+, 88), 288 ($M^+ - 104$, 20), 287 ($M^+ - 105$, 100), and 260 ($M^+ - 132$, 36); ^1H NMR ($CDCl_3$) δ 15.80 (s, 1 H, exchanges D_2O), 7.33 (s, 5 H), 6.83–7.66 (m, 4 H), 6.08 (s, 1 H), 4.03 (s, 3 H), 3.93 (s, 5 H), and 2.83–3.66 (A_2B_2, 4 H).

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.47; H, 6.12. Found: 73.42; H, 6.21.

Compound **6** (90 mg) was treated with 4.5 mL of methyl iodide and 135 mg of K_2CO_3 as before. Chromatography of the resulting residue over 19 g of silica gel produced three additional methyl ethers.

The dimethyl ether, **6b** (16 mg), mp 129–131 °C (ethanol), was eluted with 2% ether–benzene: UV λ_{max} (MeOH) 288 nm (ϵ 2.01×10^4); IR ($CHCl_3$) bands at 3500, 1621, and 1598 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 406 (M^+, 62), 302 ($M^+ - 104$, 19), 301 ($M^+ - 105$, 100), and 274 ($M^+ - 132$, 34); ^1H NMR ($CDCl_3$) δ 14.53 (s, 1 H, exchanges D_2O), 7.34 (s, 5 H), 6.66–7.50 (m, 4 H), 6.10 (s, 1 H), 3.80 (s, 9 H), 3.71 (s, 2 H), and 2.83–3.67 (A_2B_2, 4 H).

Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.89; H, 6.40. Found: C, 73.99; H, 6.61.

Elution with 2% ether–benzene yielded 34 mg of the trimethyl ether **6d** as a gum (pure by TLC, ^1H NMR, and MS); UV λ_{max} (MeOH) 295 nm (sh, ϵ 3.19×10^3), 275 (6.22×10^3), and 269 (6.41×10^3); IR ($CHCl_3$) bands at 3392, 1702, and 1598 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 420 (M^+, 15), 316 ($M^+ - 104$, 25), 315 ($M^+ - 105$, 100), and 288 ($M^+ - 132$, 41); ^1H NMR ($CDCl_3$) δ 7.16 (s, 5 H), 6.50–7.33 (m, 4 H), 6.27 (s, 1 H), 3.90, 3.89, 3.80, 3.75 (s, 11 H), 3.43 (s, 3 H), and 3.07 (br s, 4 H).

Anal. Calcd for $C_{26}H_{28}O_5$: mol wt, 420.1937. Found: mol wt, 420.1920 (MS).

Elution with 4% ether–benzene yielded 43 mg of the dimethyl ether **6c** as a colorless gum (pure by TLC, ^1H NMR, and MS): UV λ_{max} 280 nm (sh, ϵ 3.93×10^3), 277 (sh, 6.26×10^3), and 271 (6.70×10^3); IR ($CHCl_3$) bands at 3392, 1695, and 1585 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 406 (M^+, 17), 302 ($M^+ - 104$, 21), 301 ($M^+ - 105$, 100), and 274 ($M^+ - 132$, 16); ^1H NMR ($CDCl_3$) δ 7.17 (s, 5 H), 6.50–7.33 (m, 4 H), 6.07 (s, 1 H), 3.80 (s, 2 H), 3.63, 3.64, 3.67 (s, 9 H), and 2.97 (s, 4 H).

Anal. Calcd for $C_{25}H_{26}O_5$: mol wt, 406.1780. Found: mol wt, 406.1769 (MS).

Treatment of 40 mg of **6a** with excess ethereal diazomethane yielded a compound identical with **6c** (TLC, co-TLC, and IR).

Methylation of Isouvaretin (7) to Give 7a. Treatment of 70 mg of **7** with 20 mg of K_2CO_3 and 0.5 mL of CH_3I in a manner similar to that of **6** afforded 35 mg of the monomethyl ether **7a** as rods from ethanol: mp 127–131 °C; UV λ_{max} (MeOH) 330 nm (ϵ 3.74×10^3), 282 (1.54×10^4), and 239 (1.20×10^4); IR (KBr) bands at 3410, 1630, and 1585 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 392 (M^+, 81), 361 ($M^+ - 31$, 6), 288 ($M^+ - 104$, 10), 287 ($M^+ - 105$, 57), 286 ($M^+ - 106$, 43), and 260 ($M^+ - 132$, 11); ^1H NMR $CDCl_3$) δ 13.51 (s, 1 H, exchanges D_2O), 7.25 (s, 5 H), 6.70–7.50 (m, 4 H), 6.33 (s, 1 H), 3.93 (s, 3 H), 3.82 (s, 5 H), and 2.80–3.70 (A_2B_2, 4 H).

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.47; H, 6.12. Found: C, 73.46; H, 6.18.

Hydrogenation of Chamanetin (3) to Give 9. Pd/C (10%, 25 mg) in 20 mL of ethanol and 10 mL of 0.1 N ethanolic KOH was prereduced with hydrogen at room temperature and atmospheric pressure. To this suspension was added 50 mg of **3** in 5 mL of ethanol. After 24 hydrogen uptake ceased and the catalyst was removed by filtration. The filtrate was acidified to pH 1 with 0.1 N HCl, evaporated, and chromatographed over 18 g of silica gel (32% ether–benzene) to afford 10 mg of **9** as crystals from benzene: mp 207–208 °C; UV λ_{max} (MeOH) 317 nm (sh, ϵ 1.30×10^3); IR (KBr) bands at 3120, 1640, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 364 (M^+, 62), 346 ($M^+ - 18$, 18), 260 ($M^+ - 104$, 10), 259 ($M^+ - 105$, 25), 258 ($M^+ - 106$, 11), and 232 ($M^+ - 132$, 27); ^1H NMR (acetone-d_6) δ 7.33 (s, 5 H), 6.70–7.60 (m, 4 H), 6.20 (s, 1 H), 3.97 (s, 2 H), and 2.85–3.80 (A_2B_2, 4 H).

Anal. Calcd for $C_{22}H_{20}O_5$: mol wt, 364.1311. Found: mol wt, 364.1332 (MS).

Hydrogenation of 3a to Give 10. Compound **3a** (40 mg) was dissolved in ethanol and added to a suspension of 20 mg of 10% Pd/C and 6 mL of 0.1 N ethanolic KOH. This was then hydrogenated in the same manner as **3** and chromatographed over silica gel (2% ether–benzene) to give 12 mg of **10:** mp 190–192 °C; UV λ_{max} 350 nm (sh, ϵ

1.29×10^3) and 283 (7.40×10^3); IR (KBr) bands at 3100, 1640, and 1594 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 378 (M^+, 62), 274 ($M^+ - 104$, 8), 273 ($M^+ - 105$, 68), 272 ($M^+ - 106$, 16), and 246 ($M^+ - 132$, 23); ^1H NMR (acetone-d_6) δ 7.30 (s, 5 H), 6.50–7.50 (m, 4 H), 6.23 (s, 1 H), 3.87 (s, 5 H), and 2.80–3.70 (A_2B_2, 4 H).

Anal. Calcd for $C_{23}H_{22}O_5$: mol wt, 378.1467. Found: mol wt, 378.1481 (MS).

Hydrogenation of 3c, 4, and 4b. Compound **3c** (40 mg in 5 mL of ethanol) in 20 mg of 10% Pd/C and 4 mL of 0.1 N ethanolic KOH was hydrogenated and worked up as before. Chromatography over 18 g of silica gel (1% ether–benzene) afforded 12 mg of a compound identical with **6a** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Compound **4** (50 mg in 5 mL of ethanol) in 25 mg of 10% Pd/C and 10 mL of 0.1 N ethanolic KOH was hydrogenated and worked up as before. Silica gel chromatography (32% ether–benzene) provided 10 mg of a compound identical with **9** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Compound **4b** (40 mg in 5 mL of ethanol) in 20 mg of 10% Pd/C and 5 mL of 0.1 N ethanolic KOH was hydrogenated and worked up as before. Silica gel chromatography (1% ether–benzene) gave 25 mg of a compound identical with **7a** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Degradation of 3a to Give 11. Compound **3a** (100 mg) was dissolved in 10 mL of 50% aqueous NaOH, refluxed for 45 min, and allowed to cool to room temperature. The mixture was then acidified to pH 1 with 6 N HCl and extracted with 3 × 20 mL of ether. After drying of the combined ether phases over Na_2SO_4 and evaporation, the residue was chromatographed over 20 g of silica gel. Elution with 16% ether–benzene gave 50 mg of **11** from ethanol–benzene: mp 180–182 °C; UV λ_{max} (MeOH) 270 nm (ϵ 3.00×10^3) and 223 (5.00×10^3); IR (KBr) bands at 3200, 1640, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 246 (M^+, 38), 245 ($M^+ - 1$, 2), and 140 ($M^+ - 106$, 100); ^1H NMR (acetone-d_6) δ 6.50–7.50 (m, 4 H), 6.00 (s, 2 H), 3.99 (s, 2 H), and 3.72 (s, 3 H).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69. Found: C, 68.13; H, 5.85.

Degradation of Uvaretin (6) to Give 12. Compound **6** (100 mg) was dissolved in 10 mL of 50% NaOH and treated in a manner similar to that described for **3a.** Chromatography over silica gel (4% ether–benzene) gave 65 mg of **12:** mp 171–173 °C; UV λ_{max} (MeOH) 269 nm (ϵ 2.88×10^3) and 219 (6.73×10^3); IR (KBr) bands at 3300, 1640, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 246 (M^+, 100), 245 ($M^+ - 1$, 2), and 140 ($M^+ - 106$, 83); ^1H NMR (acetone-d_6) δ 6.50–7.50 (m, 4 H), 5.97 (s, 2 H), 3.82 (s, 2 H), and 3.57 (s, 3 H).

Anal. Calcd for $C_{14}H_{14}O_4$: mol wt, 246.0892. Found: mol wt, 246.0862 (MS).

Degradation of Isouvaretin (7) to Give 11. Compound **7** (100 mg) was dissolved in 10 mL of 50% NaOH and treated as before (refluxed for 2 h). Chromatography over silica gel (16% ether–benzene) yielded 45 mg of a compound identical with **11** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Degradation of Diuvaretin (8) to Give 13. Compound **8** (170 mg) was dissolved in 17 mL of 50% NaOH and treated as before. Chromatography over silica gel (4% ether–benzene) gave 70 mg of a gum, **13,** pure by TLC, ^1H NMR, and MS: UV λ_{max} (MeOH) 267 nm (sh, ϵ 5.49×10^3) and 262 (5.84×10^3); IR ($CHCl_3$) bands at 3605, 3280, 1629, and 1619 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 352 (M^+, 9) and 243 ($M^+ - 109$, 100); ^1H NMR δ ($CDCl_3$) 6.60–7.70 (m, 8 H), 5.92 (s, 1 H), 3.90 (s, 2 H), 3.87 (s, 2 H), and 3.63 (s, 3 H).

Anal. Calcd for $C_{21}H_{20}O_5$: mol wt, 352.1311. Found: mol wt, 352.1292 (MS).

Synthesis of Chamanetin (3), Isochamanetin (4), and Dichamanetin (5). (±)-Pinocembrin[18] (500 mg) was dissolved in 10 mL of purified dioxane[19] and heated to 60 °C. A solution of 300 mg of *o*-hydroxybenzyl alcohol in 5 mL of dioxane and 1 mL of boron trifluoride etherate was added over 25 min. An additional 1 mL of boron trifluoride etherate in 2 mL of dioxane was then added. After standing at 60 °C for 30 min the cooled solution was diluted with 15 mL of ether and extracted with 6 × 20 mL of H_2O. The ether layer was dried over Na_2SO_4, evaporated, and applied to a column of 20 g of silica gel in benzene. Elution with 1% ether–benzene yielded 15 mg of a dibenzylated product identical with **5** (melting point, mixture melting point, TLC, co-TLC, and IR). A monobenzylated product was eluted with 2% ether–benzene and was identical with **4** (melting point, mixture melting point, TLC, co-TLC, and IR). Elution with 4% ether–benzene yielded 260 mg of pinocembrin while the 8% ether–benzene eluate yielded 10 mg of a product identical with **3** (melting point, mixture melting point, TLC, co-TLC, and IR).

Synthesis of 11 and 12. Phloroglucinol monomethyl ether[20] (1.14 g) was dissolved in 20 mL of dioxane and heated to 50 °C. A solution of 660 mg of *o*-hydroxybenzyl alcohol and 2 mL of boron trifluoride etherate dissolved in 25 mL of dioxane was added over 30 min. An additional 1 mL of boron trifluoride etherate in 5 mL of dioxane was then added. After 30 min the solution was allowed to cool, diluted with 20 mL of ether, and extracted with 6 × 20 mL of H_2O. The combined ether layers were then dried over Na_2SO_4 and evaporated. Chromatography of the resulting residue over 40 g of silica gel (4% ether–benzene) yielded 195 mg of a product identical **12** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR). Elution with 8% ether–benzene gave 272 mg of phloroglucinol monomethyl ether while elution with 16% ether–benzene gave 240 mg of a product identical with **11** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Synthesis of 13. To a solution of 400 mg of **12** in 5 mL of dioxane at 60 °C was added 200 mg of *o*-hydroxybenzyl alcohol and 2 mL of boron trifluoride etherate. After standing at 60 °C for 1 h the reaction mixture was worked up as before and the resulting residue was chromatographed over 22 g of silica gel. Elution with 8% ether–benzene gave 135 mg of a product identical with **13** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

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Registry No.—5, tetramethyl ether, 61463-05-6; **6a,** 58449-08-4; **6b,** 58449-09-5; **6c,** 61463-06-7; **6d,** 61463-07-8; **7a,** 61463-08-9; **9,** 61463-09-0; **10,** 61463-10-3; **11,** 61463-11-4; **12,** 61463-12-5; **13,** 61463-13-6; (±)-pinocembrin, 61490-55-9; phloroglucinol monomethyl ether, 2174-64-3; *o*-hydroxybenzyl alcohol, 90-01-7.

References and Notes

(1) Presented at the annual meeting of the American Society of Pharmacognosy, Cable, Wis., July 1976.
(2) C. D. Hufford and W. L. Lasswell, Jr., *J. Org. Chem.*, **41,** 1297 (1976).
(3) The names uvaretin and isouvaretin were originally chosen for these novel C-benzylated flavanones. The name uvaretin was also assigned to a C-benzylated dihydrochalcone[4] appearing in a paper published after our communication appeared in print. By mutual agreement with the authors of ref 4 we have decided to change the names of these flavanones from those originally chosen (uvaretin and isouvaretin) to chamanetin and isochamanetin since the received date of the paper in ref 4 preceded that of our communication.
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(5) Tumor-inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute by procedures described in *Cancer Chemother. Rep., Part 3,* **3,** 1 (1972). KB test values (ED_{50}, μg/mL) follow: **1,** 21 (25); **3,** 5.2 (16); **4,** 2.4 (5.3); **5,** 1.2 (4.8); **6,** 1.0 (2.6); **7,** 1.9 (2.8); **8,** 2.0 (2.4). PS cell culture values (ED_{50}, μg/mL) follow: **1,** 10.5 (19); **3,** 2.4 (2.7); **4,** 2.2 (4.1); **5,** 1.4 (1.8); **6,** 1.0 (0.83); **7,** 1.9 (2.3); **8,** 0.84 (0.96).
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(9) Brief treatment of **4** with diazomethane failed to produce a monomethyl ether.
(10) **6a** and **6b** have been reported previously.[4] However, the evidence presented in ref 4 for the monomethyl ether of **6** does not rule out the possibility that the introduced methoxyl group might be located in the hydroxybenzyl moiety. **6a** correctly represents the monomethyl ether of **6** because of the conversion of **3c** to **6a** which is described later. **6b** correctly represents one of the dimethyl ethers based on spectroscopic evidence. **6c** correctly represents one of the dimethyl ethers based on its spectroscopic properties as well as its formation from methylation of **6a.**
(11) The structure assigned to the monomethyl ether of **7** follows from the hydrogenation of **4b** to **7a** which is described later.
(12) In a separate experiment treatment of **3a** with diazomethane yielded **3c** (melting point, mixture melting point, TLC, co-TLC, and IR).
(13) Although attempts to make the 7-*O*-methyl ether of **4** failed, its hydrogenation product would be identical with **10** since **3a** and the 7-*O*-methyl ether of **4** are *o*-hydroxybenzyl isomers at the C-8 and C-6 positions, respectively.
(14) Melting points were determined on either a Thomas-Hoover or a Fisher-Johns 355 melting point apparatus and are uncorrected. Elemental analyses were performed by Scandanavian Microanalytical Laboratories, Herlev,

Denmark. Infrared spectra were obtained on either a Beckman IR-33 or a Perkin-Elmer 257 spectrophotometer and ultraviolet spectra were obtained on a Beckman Acta III spectrophotometer. The CD spectra were taken in methanol on a JASCO J-40 recording spectropolarimeter and optical rotation measurements were performed on a Perkin-Elmer 141 polarimeter. Mass spectra were obtained on a Du Pont CEC-492 mass spectrometer. ^{1}H NMR spectra were recorded on a JEOL C-60HL spectrometer using Me_4Si as internal standard. Coupling constants were calculated using first-order approximations. Column chromatography was carried out with silicic acid AR, 100 mesh (Mallinckrodt), activated by heating at 120 °C for 12 h or silica gel 60, 70–270 mesh (Brinkmann).

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Synthesis of Deoxy Sugar. Deoxygenation of an Alcohol Utilizing a Facile Nucleophilic Displacement Step

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Methyl 2-amino-2-deoxy-α-D-glucopyranoside was converted in good yield to the corresponding 3-deoxy analogue. The key steps include the facile nucleophilic displacement of a 3-*O*-trifluoromethylsulfonyl function by benzenethiolate under mild conditions and subsequent desulfurization with sodium in liquid ammonia. Desulfurization was also achieved, but in low yield, with Raney nickel or tributyltin hydride. The nucleophilic displacement step was accompanied by little, if any, neighboring group participation.

The conversion of an equatorial C-3 hydroxyl to the corresponding deoxy function in an α-linked D-hexopyranosyl glycoside, present in a number of prominent aminoglycoside antibiotics, has been of current interest because of the development of bacterial resistance by phosphorylation of this hydroxyl group.[1] Such a conversion, in several instances, was effected through the use of nucleophilic displacement as one of the key steps.[2] Recently, a reductive method proceeding through free-radical mechanism was also reported.[3] Generally speaking, nucleophilic displacement by presently available methods proceeds with difficulty, which may be accounted for by probable 1,3-diaxial interaction between the aglycone and the approaching nucleophile, as well as by complications arising from neighboring group participation. In the course of our synthetic modification studies of the antibiotic butirosin,[4] we have succeeded in such a conversion by devising a facile nucleophilic displacement. Through the combined use of the trifluoromethylsulfonyl (triflate) function, an exceedingly good leaving group,[5] and the benzenethiolate anion, one of the most powerful nucleophiles,[6] the nucleophilic displacement was achieved under extremely mild conditions. The study of this reaction in model compounds, together with subsequent desulfurization leading to the desired deoxy sugar, will be described in the present paper.

Methyl 2-deoxy-2-[[(phenylmethoxy)carbonyl]amino]-α-D-glucopyranoside (**1**) was converted to the corresponding 4,6-*O*-(1-methylethylidene) derivative (**2**) with 2,2-dimethoxypropane. Triflation of **2** with trifluoromethanesulfonic anhydride afforded the triflate (**3**) in 90% crude yield, which could be further purified by crystallization. Nucleophilic displacement of crude **3** with sodium benzenethiolate at 5 °C gave, almost exclusively (TLC evidence), the 3-(phenylthio)allopyranoside (**4**), which was subsequently isolated in crystalline form in 64% overall yield from **2**. The allo configuration of **4** was readily inferred from its 4,6-O-unsubstituted derivative **8** (cf. below). The conversion of **4** to **5** was conveniently realized by initial treatment with sodium in liquid ammonia,[8] which reductively removed both the phenylthio and the *N*-[(phenylmethoxy)carbonyl] groups, followed by hydrolytic cleavage of the 4,6-O-(1-methylethylidene) group on Dowex 50 × 4 (a strong cation exchange resin) in the hydrogen form. The product, compound **5**, was isolated by elution with aqueous ammonia and further converted to the crystalline *N*-acetyl derivative (**6**) in an overall yield of 81% from **4**. The 3-deoxy-D-ribo configuration in **6** was confirmed by NMR data, which showed a geminal coupling $J_{3a,3e}$ (ca. 11 Hz), two axial–axial couplings $J_{2a,3a}$ (ca. 12 Hz) and $J_{3a,4a}$ (ca. 11 Hz), and two axial–equatorial couplings $J_{1e,2a}$ (ca. 3.8 Hz) and $J_{2a,3e}$ (ca. 4.7 Hz each). The 4,6-di-*O*-acetate of **6** (**6**, OH = OAc) showed properties closely resembling those reported for an identical compound[9] and provided NMR data fully confirming the 3-deoxy-D-ribo configuration.

Other methods for the reductive cleavage of the phenylthio–sp^3 carbon bond in **4** were also examined. Treatment of **4** with nickel boride[10] in boiling ethanol for 12 h gave essentially unchanged starting material. Reaction of **4** with Raney nickel (previously neutralized to pH 7 with acetic acid) in boiling ethanolic solution yielded the corresponding 3-deoxy analogue, but in low yield; under these conditions the *N*-[(phenylmethoxy)carbonyl] group was preferentially hydrogenolyzed, generating the amine which was then irreversibly absorbed by the Raney nickel. Treatment of **4** with tributyltin hydride[11,12] in boiling toluene for 12 h in the presence of the radical initiator 2,2′-azobis(2-methylpropanenitrile) resulted in the isolation of the 3-deoxy compound **9** in less than 37% yield, which was characterized by eventual conversion to the crystalline compound **6**, together with ca. 12% of unreacted **4**. The side products of the reaction, showing much lower TLC mobilities, conceivably could be compounds having a free amino group at C-2 but were not further investigated.

The presence of neighboring groups, such as a hydroxyl or a [(phenylmethoxy)carbonyl]amino group, in trans orientation to the triflate leaving group, may lead to possible complications in the nucleophilic displacement step. To resolve such possibilities, the attack of the benzenethiolate ion on **7**, the 4,6-dihydroxy analogue of **3**, was studied. The product, a 3-deoxy-3-phenylthio-D-allo derivative (**8**), was isolated in crystalline form in high yield (81%) and found to be identical with the product obtained by removal of the 4,6-*O*-(1-methylethylidene) group from **4**. The C-3 configuration in **8**