found that the daily consumption of 1 g of dried *S. jacobeae* (kg of body weight)$^{-1}$ day^{-1} causes illness and death of the animals within a few months. From the PA content of 15 mg/kg of hay, measured in our case, one may calculate ~0.5% *S. alpinus* to be present in the hay. The daily consumption of the cattle was probably around 0.5 g of *S. alpinus* (kg of body weight)$^{-1}$ day^{-1}, an amount which can easily explain the liver damages detected in 10 animals which were described earlier (Pohlenz et al., 1980).

Of special importance to the consumer is the fate of these compounds in the animal. In the urine of a cow from the same area we were able to detect ~0.5 mg of PA metabolites/L, giving a positive Mattocks (1967) reaction. The distribution in the body and the chemical and toxicological properties of these PA metabolites are presently under study.

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Structure–Taste Correlations for Flavans and Flavanones Conformationally Equivalent to Phyllodulcin

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Preparation of a conformationally defined series of compounds related to phyllodulcin allows more accurate correlations of structural features with taste. Four flavans (3,4-dihydro-2*H*-1-benzopyrans) and their parent flavanones (2,3-dihydro-4*H*-1-benzopyran-4-ones) were prepared from chalcones derived from 2-hydroxy-, 2,4-dihydroxy-, 2,6-dihydroxy-, or 2,4,6-trihydroxyacetophenone and isovanillin (3-hydroxy-4-methoxybenzaldehyde). These compounds can exist as both semiplanar and bent conformers, equivalent to those of phyllodulcin, permitting a close comparison of structural features with taste. Semiplanar conformations were established for phyllodulcin and the analogous compounds by ^{1}H NMR. Evidence for bent conformations was lacking. Flavans derived from 2-hydroxy- and 2,4-dihydroxyacetophenone were sweet, the latter intensely so, whereas the 2,6 analogue was intensely bitter. Comparisons with phyllodulcin and derivatives demonstrated the effects of nonaromatic ring heteroatom location and A-ring hydroxylation and carbonyl group effects.

Investigators seeking intensely sweet analogues of natural compounds have tended to focus on the effects of specific molecular functional groups on taste, and simple compounds containing various groups have been synthesized. Such research has succeeded in producing several sweet compounds structurally related to phyllodulcin (Yamato et al., 1972a–c, 1973, 1974a,b, 1975, 1977a–d, 1978; Yamoto and Hashigaki, 1979) and an extensive literature relating similar structures of dihydrochalcone derivatives to taste.

Assessments of how tastant molecules and their specific structural features interact with receptors to produce or modify perceived tastes are much less complete. While the above dihydrochalcones and substituted 1,2-diphenylethanes are sweet, they differ markedly from the parent model in terms of taste qualities, intensities, and predicted abilities to undergo conformational alterations when binding to a receptor. There is no way to predict or demonstrate that they achieve equivalent conformations in the bound state or that their structural features interact with identical sensitive areas of the taste receptors. The well-known proposal by Kier (1972) that the AH–B sites (Shallenberger and Acree, 1967) and a third, distant, hydrophobic site must achieve critical geometric relationships with one another for production of intense sweetness underscores the need to determine solution-average conformations for phyllodulcin analogues and to predict their abilities to achieve the Kier (1972) requirements when bound to taste receptors.

For the present, however, only the solution-average conformations of molecules possessing the structural features for intense sweetness can be established. For molecules that do not meet the Kier (1972) requirements in solution, investigators are limited to model studies and subjective evaluations of bond flexibilities for predictions of bound conformers. In the absence of any firm understanding of how sweet molecules are bound within or onto a receptor, variation of structural characteristics within relatively limited conformational arrangements could lead to an improved understanding of receptor–tastant interactions. Compounds that mimic the size and structure of phyllodulcin are attractive, in that the basic structural featues associated with AH–B and distant bonding have been proposed (Yamato et al., 1972a,b, 1973, 1974b, 1977a,c,d; Yamoto and Hashigaki, 1979).

Further, the molecules can serve as vehicles for varying positions of structural features not believed necessary for

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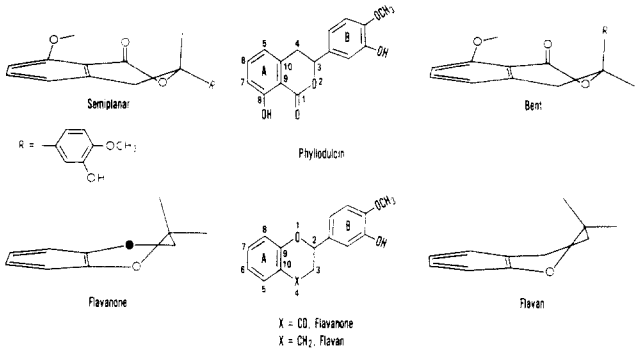

Figure 1. Stereomodel projections of phyllodulcin and related compounds.

sweetness, but whose interactions with unmapped receptor sites may alter perceived taste by cumulative or multiple stimulation effects. For this study, effects of A-ring hydroxylation, interactions with carbonyl groups on the dihydropyran rings, and dihydropyran ring heteroatom location were evaluated.

RESULTS AND DISCUSSION

Stereomodel comparisons suggested the approximate conformational equivalence of phyllodulcin with substituted flavanones (2,3-dihydro-4*H*-1-benzopyran-4-ones) and their derived flavans (3,4-dihydro-2*H*-1-benzopyrans). Discounting simple rotations of the B ring about its attachment point, conformational alterations are limited to bond flexing within the dihydropyran ring, producing a limited number of puckered conformers. Two major types of conformers are predicted, a semiplanar (quasi-equatorial) form and a family of bent (quasi-axial) forms differing primarily in the angle of bending achieved. In the most extreme bent form, the angle of bending with respect to the A-ring plane is approximately 80–85° for phyllodulcin and 60–65° for the flavanones and flavans. It is interesting to note that while the semiplanar forms fit well within the hemihedral cavity model proposed recently for a sweet receptor (Temussi et al., 1978), the Kier (1972) bonding requirements are met only in the bent forms. DuBois et al. (1977a) proposed a bent phylloculcin conformer as the active form for sweetness. Stereomodel projections are shown in Figure 1.

The premise that the three types of compounds have nearly equivalent conformational capabilities can be tested by NMR, using the coupling of the vicinal methine and methylene protons of the dihydropyran ring. It was expected that the relatively low energy inputs needed to produce bent conformers would result in equilibrium mixtures of more than one form. However, the report (Suzuki et al., 1977) that H-3 of phyllodulcin was a doublet of doublets with identical 5 Hz values for $J_{3,4}$ and $J_{3,4'}$ seemed unlikely. A check of authentic phyllodulcin isolated from Amacha in methanol-d_4 and $CDCl_3$ gave values of 4 and 5 Hz for $J_{3,4}$, and 10 and 11 Hz for $J_{3,4'}$, consistent with a semiplanar conformation. All other spectral data matched the original report, suggesting an uncorrected typographical error.

The finding of a semiplanar solution-average conformation for phyllodulcin, a form in which the Kier (1972) binding requirements are not met, is consistent with the premise that such intense sweeteners undergo conformational alteration during binding to a receptor. Four flavanones and their derived flavans were selected and prepared to test the effects of non-Kier (1972) bonding substituents on taste and solution conformation. Syntheses are shown in Figure 2. Products are listed in groups of

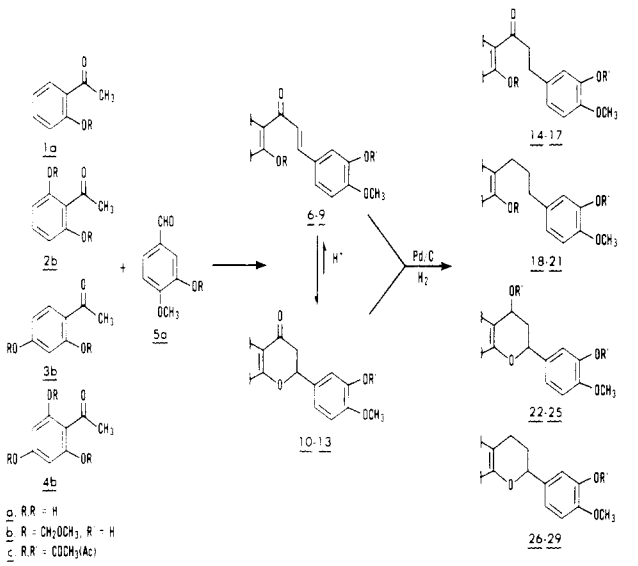

Figure 2. Synthesis of flavanones, flavans, and related compounds.

four numbered compounds, the order of any given group corresponding to the order of their parent acetophenones (1–4); e.g., **1** yields **6**, **10**, **14**, ..., and **26**. See Experimental Section for nomenclature.

Chalcone preparations for all but **6a** required preliminary conversion of the di- and trihydroxyacetophenones to the corresponding methoxymethyl ethers (**2b–4b**) before condensation with isovanillin (**5a**). Yields were excellent, with facile separation of the crystalline chalcones from byproducts.

Acidic cyclizations of the chalcones with BF_3-etherate in methanol provided the known flavanones (**10a–13a**), which were subsequently converted into the corresponding flavans (**26–29**) by catalytic hydrogenations with palladium on carbon. Substantial quantities of **6a** and **8a** re-formed from the corresponding flavanones by equilibration before the hydrogenations were complete, yielding dihydrochalcones (**14a**, **16a**) and 1,3-disubstituted propanes (**18a**, **20a**) as well as the desired flavans (**26a**, **28a**).

Hydrogenations of **11** and **13** were difficult; neither **11a** nor **13a** was reduced under conditions found effective for **10a** and **12a**, and **11c** reacted sluggishly only after hydrogen bonding of the C-5 hydroxyl with the neighboring carbonyl group (C-4) was prevented by acetoxylation. Formation of **29c** by catalytic hydrogenation required a preliminary conversion to the intermediate 4-hydroxyflavan triacetate, formed by the action of sodium borohydride on **13c**. This step should be useful generally for flavan syntheses in that equilibrium reversals as well as hydrogen-bonding problems are eliminated for all the flavanone reductions.

Identification of reduction products was accomplished by gas–liquid chromatography–mass spectrometry (GLC–MS) analysis before isolation and characterization. Separations on neutral silica gel were straightforward, except for **28a** and **28c**, which proved to be extremely light sensitive and unstable during thin-layer chromatography (TLC) unless the developments were brief.

Each of the flavanones, flavans, and derived acetates was examined by ^1H NMR to establish the solution-average conformation. As shown in Table I, coupling constants for $J_{2,3}$ and $J_{2,3'}$ are consistent for the semiplanar conformers of Figure 1, allowing for small differences in ring strain for the two groups. Given the equivalence in solution-average conformations, and assuming that conformational altera-

Table I. Coupling Constant Comparisons[a]

compd	$J_{2,3}$	$J_{2,3'}$	solv	compd	$J_{2,3}$	$J_{2,3'}$	solv	compd	$J_{2,3}$	$J_{2,3'}$	$J_{3,4}$	$J_{3',4}$	$J_{3,4'}$	solv
10a	4.5	12	C	26a	4	8.6	C	22a	2	10	2	8		D
								22a	2.3	11.3	2	6.9		A
								22c	2.3	11.5	7	10		C
11a	4	12	C	27a	3	10	A	phyl[b]			4		11	C
11c	3.8	12.5	C	27c	3	10	C	phyl			5		10	M
12a	4.1	13	A	28a	3.5	10	A							
12c	4.5	12	C	28c	3.5	9.5	C							
13a	3.8	13	A	29a	3	10	A							
13c	3.5	12.2	A	29c	3.5	10	C							

[a] In hertz, at 100 MHz. A = acetone-d_6; C = $CDCl_3$; D = methyl sulfoxide-d_6; M = methanol-d_4. [b] Phyl = phyllodulcin.

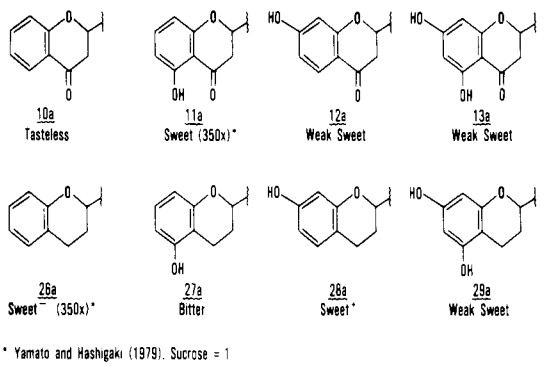

Figure 3. Flavanone and flavan structure–taste comparisons.

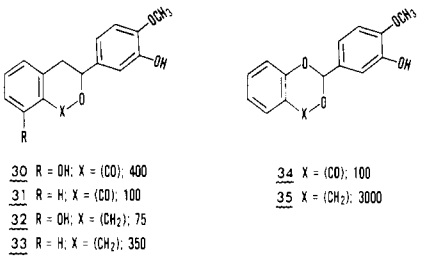

Figure 4. Structures and sweetness of phyllodulcin and analogues, relative to sucrose.

tions, if any, when binding to the receptor will be approximately equal, then differences in taste should reflect the effects of stimulating different areas of the receptor.

The general fragmentation patterns established for electron impact mass spectroscopy of flavanones and flavans (Pelter et al., 1965; Pelter and Stainton, 1967; Radford et al., 1979) were used to predict the ions formed by **10–13** and **26–29** (**a** and **c** for all). Empirical formulas and ring plus double bond (R + DB) calculations, obtained by high-resolution techniques, were used to predict ion structures.

Fragmentations of **10a** were typical for the flavanones, the two predicted cleavages providing A-ring fragments m/e 147 and the series pair 121, 92, as well as the companion fragment m/e 124 and the ion series m/e 150, 135, 107. Oxyhomologue A-ring fragments were found for **11–13** in the same patterns as for **10**. In addition to the predicted ions above, the flavanones also formed significant quantities of m/e 137 ($C_8H_9O_2$) and M - 43 mass unit ions as well, possibly an effect of cleavages not reported previously. For **11** and **12**, the fragment m/e 137 also included the A ring ($C_7H_5O_3$) as well as the above $C_8H_9O_2$.

Flavan fragmentations paralleled those of the flavanones, in that **26a** formed the predicted m/e 106 + (150, 135, 107), 131 + 123, and 119 + 137. As seen for the flavanones, formation of m/e 150 dominated other cleavage patterns for the flavans. A minor cleavage unique to the flavans examined was signaled by the presence of m/e 162 ($C_{10}H_{10}O_2$, R + DB = 6) in each spectrum. Only loss of the A ring accounts for the ion, with a bicyclic structure incorporating the 3-hydroxy-4-methoxyphenyl group satisfying the R + DB value of 6.

Qualitative taste comparisons of the flavans and parent flavanones at 20 mg % (0.02%) are listed in Figure 3. Flavanones **10a**, **11a**, and **13a** served as references: **10a** being tasteless, **11a** reported to be 350 times sweeter than sucrose (Yamato et al., 1978), and **13a** considered weakly sweet. For comparative purposes, **11a** was considered to be moderately sweet at 20 mg %. Tasting at 1% accentuated medicinal and methanol-like flavors that degraded the quality of sweetness.

For the flavans, all but **26a** were strongly medicinal in taste, and all were at least slightly bitter; **27a** was intensely bitter without any discernible sweetness. As this work was being completed, Yamato and Hashigaki (1979) reported **26a** to be ~350 times sweeter than sucrose, matching the level they reported for **11a**. At 20 mg %, **26a** seemed less sweet than **11a**, compared to the substantially sweeter **28a** which compared favorably to **11a** in intensity. Interestingly, **28a** lost the medicinal flavor when diluted to 4 and 12 mg % levels without losing the pleasant sweetness observed at higher levels. The taste of **26a** was the most pleasant of the flavans, matching that of **11a**, but none of the flavanones or flavans of Figure 2 matched the pleasant quality of phyllodulcin's sweetness. All were bound strongly to the taste receptors, as indicated by prolonged taste sensations (3–5 min).

Samples of **18a** and **20a**, as syrupy eluates from silica gel columns, were tasteless, matching the results reported for the 2′-deoxy analogue of **18a** (Yamato et al., 1972b, 1975). Tastes of the dihydrochalcones of Figure 2 have been summarized (DuBois et al., 1977a).

Taste findings for the flavanones and flavans were compared to those reported for phyllodulcin and derivatives (**30–34**, Figure 4; Yamato et al., 1972a,c, 1975, 1977a; Yamoto and Hashigaki, 1979) and to the taste of an intensely sweet 1,3-benzodioxan analogue (**35**; Dick and Hodge, 1978). Compounds **31–35** were assumed to be conformationally equivalent to the semiplanar forms established for **10a–13a**, **26a–29a**, and **30** by NMR, based on stereomodel comparisons. Although straightforward assignments of structure–taste relationships are often clouded by multiple effects, some patterns are evident for carbonyl group interactions, A-ring hydroxylations, and heteroatom presence (site and number) within the nonaromatic ring.

Carbonyl group effects are among the more easily demonstrated. The often-reported suppression of sweetness by a carbonyl group unless H bonded to a suitably placed aromatic hydroxyl group, as recorded for **10a**:**11a**, **30**:**31**, and various dihydrochalcones, can be extended. The presence of the carbonyl group is sufficient to suppress sweetness for **10a**:**26a**, **12a**:**28a** and the phyllodulcin analogues **31**:**33** and **34**:**35** as well. The sharp loss of sweetness

for **11a:27a** and **30:32** is possibly a multiple effect including A-ring hydroxylation, as discussed below.

Further compounds **11a–13a** can be considered as conformationally limited models of hydroxylated 2-alkoxydihydrochalcones. The weak sweetness of **13a** mimics that seen for dihydrochalcones analogues not bearing bulky glycosidic or ionic ether substituents on the A ring. Increased sweetness in the dihydrochalcones, conferred by such bulky or altered A-ring substituents, could be simply a matter of improved solubility, but likely reflects conformational alterations necessary to minimize steric interferences with the receptor as well.

The taste comparisons of the conformationally limited flavanone glycoside derivatives of **13a**, neohesperidin and hesperidin 7-β-D-glucoside, with the analogous dihydrochalcone glycosides of **17a** tend to support the importance of conformational considerations. The flavanone glycosides above are intensely bitter, while the dihydrochalcones are intensely sweet (Horowitz and Gentili, 1969). Although Reichel and Steudel (1942) prepared the 7-β-D-glucosyl derivative of **12a** without noting the taste, its relationship with the intensely sweet dihydrochalcone analogue prepared from **16a** (Antus et al., 1978) is probably similar to that for the **13a** and **17a** glycosides. Preparation and comparison of carboxyalkylated and sulfoalkylated derivatives of **12a** and **13a** to the dihydrochalcone analogues (DuBois et al., 1977a,b; Farkas et al., 1976) would also be of interest.

Where solubility is not a potential problem, A-ring hydroxylations can cause pronounced changes in perceived taste. Depending on the ring site, monohydroxylation can enhance (**10a:12a, 26a:28a**) suppress (**32:33**), or eliminate sweetness (**26a:27a**). Taste shifts are strong for all, especially when the ability of an isolated carbonyl group to reduce sweetness is considered (**12a**). Although binding interference could account for suppression or elimination of sweetness, the intensification seen for **26a:28a** and **10a:12a** seems more likely to reflect a strong interaction with the receptor.

The intense bitterness of **27a** demonstrates a problem encountered in relating structural features of racemic mixtures to taste, i.e., selective or simultaneous activation of bitter receptors. Given a number of known bitter–sweet relationships for enantiomeric pairs, used by Temussi et al. (1978) to propose similar structures for sweet and bitter receptors, racemic models are more likely to trigger undesired bitterness than are single isomers of natural origin. Fortunately, only traces of bitterness were observed for the flavans and flavanones of Figure 2 other than **10a** and **27a**, which were bitter free and intensely bitter, respectively.

Dihydroxylation effects, however, cannot be assessed readily. The pair **13a:29a** are essentially identical in taste. Based on taste effects observed for **27a** and **28a**, the taste of **29a** could reflect a cancellation process. However, relatively intense sweetness should be present for **13a**, due to favorable hydroxyl–carbonyl interactions and the presence of the 7-hydroxyl seen to been effective in **28a**. The relatively weak sweetness of both then may result from effects such as low solubilities in aqueous media or steric interferences with binding on or within the receptor.

Taste effects related to heteroatom(s) within the nonaromatic ring are often masked by other structural features in the tastant. Comparisons of **10a:31** and **11a:30** are influenced by resonance interactions of the ester carbonyl group with the ring oxygen or by differing abilities of keto and ester carbonyl groups to engage in hydrogen bonding with a nearby aromatic hydroxyl group. Further, the strong A-ring hydroxylation effects discussed above can be expected to alter the taste comparisons of **27a** to **32**. Only **26a:33** offers a simple comparison of ring oxygen site and taste, the sweetness of each nearly matching that of phyllodulcin (**30**) and **11a**. This suggests that electronegativity effects at those ring locations are nearly equivalent in intensity for oxygen atoms. Taste quality of **33**, with respect to phyllodulcin (**30**) is unknown. Given the taste inferiority of **26a**, the question of taste quality is important in terms of assessing ring heteroatom location effects. Interestingly, the sharply intensified sweetness of **35** (Dick and Hodge, 1978) and its near equivalence of phyllodulcin in quality may demonstrate both an effect of additive receptor interactions and quality improvements for ring oxygens.

If an additive effect is operating for **35**, stable analogues bound in an equivalent fashion may offer a promising alternative to dihydrochalcones as healthful, intense sweeteners.

EXPERIMENTAL SECTION

General. ^1H NMR spectra were measured at 100 MHz on a Varian HA-100 spectrometer and ^{13}C NMR spectra on a Bruker WH-90 with tetramethylsilane (δ 0.0) as the internal standard. Solute concentrations were ~20% (w/v). Aromatic substitution patterns were confirmed by the method of Zanger (1972); ^{13}C resonance lines were assigned by comparisons with related spectra (Wagner et al., 1976; Pelter et al., 1976) and theoretical calculations (Levy and Nelson, 1972). A Nuclide 1290 DF mass spectrometer was used for high-resolution MS with sample introduction by inlet probe. A Du Pont 21-491 mass spectrometer coupled to a Bendix 2600 gas chromatograph was used for GLC–MS analyses. Samples having more than two free hydroxyl groups were analyzed as trimethylsilyl (Me_3Si) or acetyl derivatives. Both spectrometers were operated at 70 eV. A 2 mm i.d. × 1.22 m length of glass tubing packed with 3% OV-1 on 100–120-mesh Gas-Chrom Q was used for GLC analyses, with helium as the carrier gas and with flame ionization detection. Precoated activated plates of silica gel F-254 (E. Merck, Darmstadt, Germany) were used for TLC. Layer thicknesses were 0.25 and 2.0 mm for analytical and preparative separations. For column chromatography, Baker analyzed silica gel (80–200 mesh, J. T. Baker Chemical Co., Phillipsburg, NJ) was used without pretreatment. All chromatographic solvents were proportioned on a volume per volume basis. All reagents and solvents were used as received when purchased except for *N,N*-dimethylformamide (DMF), which was dried over calcium hydride. Water solubles were removed from organic phases by repeated water washes, using dilute cupric sulfate to extract pyridine, and acetic acid was removed with aqueous sodium hydrogen carbonate. Moist solutions were dried over anhydrous sodium sulfate. All evaporations were carried out below 40 °C under diminished pressure. Melting points were determined in capillary tubes. Acetylations were carried out by adding 5 mL of 3:2 pyridine–acetic anhydride solution/g of material and storing 3 days at 25 °C. Flavanones containing a C-5 hydroxyl, or chalcones having an equivalent C-2′ hydroxyl, were difficult to substitute fully. Heating flavanone solutions at 40–60 °C to promote acetylation caused partial reformation of the parent chalcone. Excess reagent was destroyed by adding methanol; the solution was diluted with ethyl acetate and then freed of water solubles.

Methoxymethylation of 2–4a. Solutions containing 100 mmol of **2a**, **3a**, or **4a** in 200 mL of benzene and 20 mL of DMF were stirred and refluxed 0.5 h in a 1000-mL

round-bottom flask connected to a Soxhlet extractor and protected from moisture. The 33 × 94 mm extraction thimble contained Davison 4A molecular sieve (50 g, 14–30 mesh). Each solution was cooled to 25 °C and then added dropwise over 0.5 h to a stirred slurry of 225 mmol (325 mmol for **4a**) of sodium hydride and 130 mL of DMF that was held below 10 °C and covered with nitrogen. The mixture was then stirred at 30–35 °C until gas evolution ceased, rechilled below 10 °C, and treated dropwise with chloromethyl methyl ether (225 mmol; 325 mmol for **4a**) over a 0.5-h period. The final mixture was stirred 18 h at 25 °C, neutralized with a slight excess of acetic acid, diluted to 1500 mL with ethyl acetate, and freed of water solubles. TLC (benzene–diethyl ether, 9:1, one or two ascents) showed essentially complete formation of **2–4b**, with traces of monosubstituted analogues. Product syrups were satisfactory for further use without purification.

Chalcone Preparations. Cold mixtures containing potassium hydroxide (20 g in 65 mL of water) and **1a** or **2–4b** (100 mmol, product syrups derived from 100 mmol of **2–4a**) were covered with nitrogen and stirred 5 min before adding **5a** (110 mmol). The mixture was stoppered and stirred 18–20 h at 25 °C before adding a solution of acetic acid (22 mL) in ethyl acetate (1000 mL). Water solubles were removed, and the organic phase was dried and evaporated. Chalcones were formed in 75–85% yields, as judged by TLC or GLC.

1-(2-Hydroxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-2-propen-1-one (***6a***). Extraction of the solid product mixture with 350 mL of warm diethyl ether gave two crops of **6a** (18.5 g, 68%), mp 155–156 °C [156 °C (Hörhammer et al., 1965)], after one recrystallization from acetone. No effort was made to recover the additional 2–2.5 g estimated to remain in the liquors and extracted product solids. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material (see paragraph at end of paper regarding supplementary material). High-resolution mass spectrum (calcd for ^{12}C): theor $C_{16}H_{14}O_4$ 270.0892, found 270.0892, R + DB = 10; theor for $C_9H_{10}O_2$ 150.0680, found 150.0684, R + DB = 5; theor for $C_9H_7O_2$ 147.0446, found 147.0454, R + DB = 6; theor for $C_8H_9O_2$ 137.0602, found 137.0614, R + DB = 4; theor for $C_7H_5O_2$ 121.0289, found 121.0292, R + DB = 5.

1-[2,6-Bis(methoxymethoxy)phenyl]-3-(3-hydroxy-4-methoxyphenyl)-2-propen-1-one (***7b***). Extraction of the reaction mass with warm diethyl ether (350 mL) removed the bulk of the byproducts. Crude **7b** was recrystallized from methanol; mp 138–140 °C (26 g, 69%). Liquors were retained for future cyclization and processing. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor $C_{20}H_{22}O_7$ 374.1365, found 374.1377, R + DB = 10; theor for $C_{19}H_{18}O_6$ 342.1103, found 342.1102, R + DB = 11; theor for $C_{18}H_{17}O_6$ 329.1025, found 329.1031, R + DB = 10; theor for $C_{17}H_{13}O_5$ 297.0763, found 297.0768, R + DB = 11; theor for $C_{16}H_{13}O_4$ 269.0813, found 269.0809, R + DB = 10; theor for $C_{12}H_{17}O_4$ 225.1126, found 225.1130, R + DB = 4; theor for $C_{11}H_{14}O_3$ 194.0942, found 194.0930, R + DB = 5; theor for $C_9H_9O_4$ 181.0500, found 181.0502, R + DB = 5; theor for $C_{10}H_{13}O_3$ 181.0864, found 181.0862, R + DB = 4; theor for $C_{10}H_{12}O_3$ 180.0786, found 180.0789, R + DB = 5.

1-[2,4-Bis(methoxymethoxy)phenyl]-3-(3-hydroxy-4-methoxyphenyl)-2-propen-1-one (***8b***). Crude product solids were warmed with 250 mL of diethyl ether and filtered, and the precipitate was recrystallized from methanol to yield **8b** (24.8 g, 71%), mp 100–102 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{20}H_{22}O_7$ 374.1365, found 374.1357, R + DB = 10; theor for $C_{18}H_{17}O_6$ 329.1025, found 329.1023, R + DB = 10; theor for $C_{17}H_{17}O_5$ 301.1076, found 301.1077, R + DB = 9; theor for $C_{10}H_{13}O_3$ 181.0864, found 181.0852, R + DB = 4; theor for $C_9H_9O_4$ 181.0500, found 181.0499, R + DB = 5; theor for $C_{10}H_{12}O_3$ 180.0786, found 180.0788, R + DB = 5.

1-[2,4,6-Tris(methoxymethoxy)phenyl]-3-(3-hydroxy-4-methoxyphenyl)-2-propen-1-one (***9b***). Extraction of the reaction mixture with warm diethyl ether (350 mL) removed the bulk of **9b** and unreacted **4b** and **5a**. When held 18 h at −5 °C, the extract deposited a dark oil that was combined with the original ether-insoluble residue and fractionated by preparative TLC, (hexane–ethyl acetate, 1:1, two ascents). Crystallization from diethyl ether gave 14.1 g of **9b**, mp 108–110 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{22}H_{26}O_9$ 434.1576, found 434.1564, R + DB = 10; theor for $C_{20}H_{21}O_8$ 389.1236, found 389.1128, R + DB = 10; theor for $C_{19}H_{17}O_7$ 357.0794, found 357.0964, R + DB = 11; theor for $C_{12}H_{14}O_6$ 254.0790, found 254.0791, R + DB = 6; theor for $C_{12}H_{17}O_4$ 225.1126, found 225.1125, R + DB = 4; theor for $C_{10}H_{13}O_3$ 181.0846, found 181.0856, R + DB = 4; theor for $C_9H_9O_4$ 181.0500, found 181.0502, R + DB = 5; theor for $C_{10}H_{12}O_3$ 180.0786, found 180.0785, R + DB = 5. The bulk diethyl ether extract was approximately 80% **9b**, as judged by TLC, and weighed 26 g after evaporation. The mixture was cyclized without further purification, with heavy losses of product.

Chalcone Cyclizations. Chalcone samples (20 g; **6a**, **7–9b**) were added to 15% aqueous methanol solutions (500 mL) containing 5 mL of boron trifluoride etherate and refluxed gently (bumps!) on the steam bath for 18 h. The dark mixtures were cooled, stirred 1 h with 30 g of sodium acetate trihydrate, evaporated and extracted with 1500 mL of ethyl acetate, and then freed of water solubles.

2,3-Dihydro-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (***10a***). Crude **10a** (12 g, 60%) was obtained by fractional crystallization from dilute aqueous methanol, affording material pure enough for further experimentation. Pure **10a** was obtained by silica gel column chromatography ($CHCl_3$); mp 134–135 °C [132–133 °C (Hörhammer et al., 1965)]. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{14}O_4$ 270.0892, found 270.0890, R + DB = 10; theor for $C_9H_{10}O_2$ 150.0680, found 150.0683, R + DB = 5; theor for $C_8H_9O_2$ 137.0602, found 137.0611, R + DB = 4; theor for $C_8H_7O_2$ 135.0466, found 135.0451, R + DB = 5; theor for $C_7H_5O_2$ 121.0289, found 121.0291, R + DB = 5.

2,3-Dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (***11a***). Conversion of **7b** to **11a** was essentially complete, as judged by TLC (benzene–diethyl ether, 9:1, two ascents). The crude mixture was treated with 250 mL of diethyl ether, held 18 h at −5 °C, and decanted to extract the bulk of **11a** (14 g). The extract contained only traces of **7a** and was sufficiently pure for further use. Pure material was obtained by silica gel column chromatography ($CDCl_3$) and crystallized from methanol; mp 136–137 °C [136 °C (Yamato et al., 1978)]. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{14}O_5$ 286.0841, found 286.0832, R + DB = 10; theor

for $C_9H_7O_3$ 163.0395, found 163.0391, R + DB = 6; theor for $C_9H_{10}O_2$ 150.0680, found 150.0683, R + DB = 5; theor for $C_8H_9O_2$ 137.0602, found 137.0612, R + DB = 4; theor for $C_7H_5O_3$ 137.0238, found 137.0250, R + DB = 5; theor for $C_8H_7O_2$ 135.0446, found 135.0448, R + DB = 5.

2,3-Dihydro-5-acetoxy-2-(3-acetoxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**11c**). In addition to **11c**, acetylation of crude **11a** formed small amounts of a monoacetyl analogue (5-hydroxy?) and **7c**, as established by GLC–MS analysis (200–250 °C at 2 dpm). Preparative TLC (benzene–diethyl ether, 9:1, two ascents) gave pure **11c**, which was crystallized from methanol; mp 141.5–142.5 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{20}H_{18}O_7$ 370.1052, found 370.1047, R + DB = 12.

2,3-Dihydro-7-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**12a**). At equilibrium, approximately equal amounts of **8a** and **12a** are formed, as judged by TLC (benzene–diethyl ether, 4:1, two ascents). Chromatographic separation was not practicable because of **8a** and **12a** interconvertibility, but **12a** (2 g) was obtained by fractional crystallization from ethanol; mp 201–203 °C [203–205 °C (Rao and Seshadri, 1941)]. Ethanolic liquors were saved for acetylation. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{14}O_5$ 286.0841, found 286.0838, R + DB = 10.

2,3-Dihydro-7-acetoxy-2-(3-acetoxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**12c**). After acetylation, a ratio of 2:1 for **12c** and **8c** was estimated by TLC (benzene–diethyl ether, 9:1, two ascents) for the cyclization liquors above. Crude **12c** sufficiently pure for subsequent reduction was obtained by precipitation from cold ethanol. Pure material was obtained by preparative TLC (benzene–diethyl ether, 8:1, two ascents); mp 134.5–135.5 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{20}H_{18}O_7$ 370.1052, found 370.1049, R + DB = 12.

1-(2-Hydroxy-4-acetoxyphenyl)-3-(3-acetoxy-4-methoxyphenyl)-2-propen-1-one. A byproduct in the acetylated mixture of **8c** and **12c**, running just ahead of **12c** on the preparative TLC plates, was isolated during purification of **12c**. Crystallization from ether gave the pure chalcone, mp 162–163 °C. NMR and high-resolution mass spectroscopy were consistent with the assigned structure. Detailed NMR data, structural assignements, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{20}H_{18}O_7$ 370.1052, found 370.1049, R + DB = 12.

2,3-Dihydro-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**13a**). Chloroform (100 mL) extraction of the dark cyclization mixture removed the bulk of **13a**. Evaporation and extraction with two 150-mL portions of boiling diethyl ether gave an ~90% pure syrup of **13a**, the bulk of which was reserved for acetylation. A 1.2-g sample of **13a** was obtained by preparative TLC (chloroform–acetone, 9:1, two ascents); mp 228–229 °C [227–228 °C (Shinoda and Kawagoye, 1928)]. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{14}O_6$ 302.0790, found 302.0792, R + DB = 10.

2,3-Dihydro-5,7-diacetoxy-2-(3-acetoxy-4-methoxyphenyl)-4H-1-benzopyran-4-one (**13c**). Crude, syrupy **13a** (14 g) was acetylated, and the crude isolate was purified by silica gel column chromatography (60 × 750 mm, packed and eluted with chloroform). Crystallization from diethyl ether gave **13c** (16.9 g, overall yield of **13a** and **13c** from **4b** was 31.6%), mp 143–144 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{22}H_{20}O_9$ 428.1107, found 428.1112, R + DB = 13.

Hydrogenations. Hydrogenations were accomplished with a Paar shaker, using hydrogen at 50–60 psi, 200 mL of methanol containing 5–10 g of substrate, catalyst (10% Pd on activated carbon, Matheson Coleman and Bell) at a ratio of 1:10 w/w with substrate, and a 40 °C reaction temperature. Reductions of **10a** and **12a** were facile, although a portion of each re-formed the precursor chalcone before undergoing reduction unless the samples were acetylated. Compositions were determined by GLC–MS. Where silylation was not employed, thermal dehydration of aliphatic hydroxyl products was observed during GLC–MS analyses. Principal reduction products for the chalcones were the dihydrochalcones (**14–17**) and 1,3-disubstituted propanes (**18–21**), the flavanones forming 4-hydroxyflavans (**22–25**) and flavans (**26–29**). Samples of **11a** and **13a** were unreactive unless the C-5 hydroxyl groups were acetylated (**11c**, **13c**), and **13c** required a preliminary sodium borohydride treatment to produce a 4-hydroxyflavan before catalytic hydrogenation. For reactive flavanones, such intermediate 4-hydroxyflavans tend to accumulate at 25 °C.

3,4-Dihydro-2-(3-hydroxy-4-methoxyphenyl)-2H-1-benzopyran (**26a**). A 5-g crude sample of **10a** (**6a**:**10a**, 18:72 by GLC) was reduced 4.5 h, filtered, and examined by TLC (chloroform, two ascents). Four major components were **14a** (7.5%), **18a** (28.3%), **22a** (2.1%), and **26a** (44.5%), as determined by GLC–MS (185 °C, isothermal). Three unsaturated compounds were seen also, formed in part by dehydration of **22a** and unknown chalcone-derived compounds. The entire mixture was fractionated on a 40 × 700 mm column of silica gel packed and eluted with chloroform. Pure **26a** (1.6 g, 44%), was crystallized from methanol; mp 91–93 °C. Samples of **14a**, **18a**, and **22a** were retained for future use. Detailed NMR data, structural assignements, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{16}O_3$ 256.1099, found 256.1102, R + DB = 9; theor for $C_{10}H_{10}O_2$ 162.0680, found 162.0682, R + DB = 6; theor for $C_9H_{10}O_2$ 150.0680, found 150.0685, R + DB = 5; theor for C_7H_7O 107.0496, found 107.0494, R + DB = 4.

3,4-Dihydro-4-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2H-1-benzopyran (**22a**). A 2-g sample of crude **10a** was dissolved in 50 mL of 1,2-dimethoxyethane, cooled in an ice bath, and then treated with 0.5 g of sodium borohydride. After 0.5 h, the bath was removed, 10 mL of DMF was added, and the mixture was allowed to stir 18 h at 25 °C before adding 2 mL of acetic acid. The mixture was taken up in 500 mL of ethyl acetate, freed of water solubles, dried, and evaporated. Extraction with two 50-mL portions of diethyl ether removed most impurities. Recrystallization from ethanol gave pure **22a**, mp 188–189 °C, identical with that isolated from palladium on carbon hydrogenations of **10a**. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{16}O_4$ 272.1048, found 272.1050, R + DB = 9. Substitution of GLC–MS with a 250 °C transfer line for the inlet probe technique caused

extensive dehydration with formation of M – 18 (*m/e* 254) ions.

3,4-Dihydro-4-acetoxy-2-(3-acetoxy-4-methoxyphenyl)-2H-1-benzopyran (**22c**). A 1-g sample of **22a** was acetylated 48 h at 25 °C, taken up in ethyl acetate and freed of water solubles, and then crystallized from ethanol; mp 135–137 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{20}H_{20}O_6$ 356.1259, found 356.1258, R + DB = 11.

3,4-Dihyro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2H-1-benzopyran (**27a**). Direct reduction of **11a** formed less than 10% **27a**, as judged by GLC (200–250 °C, 2 dpm). A 10-g sample of **11a** was acetylated, and the mixture of **11c** and a C-5 hydroxy(?) monoacetate reduced. GLC–MS analysis of the reduction mixture showed approximately equal amounts of **27c** (40%) and an unsaturated artifact (*m/e* 354) possibly formed by dehydration during analysis. Additionally, a small quantity of **26c** was detected, suggesting **1a** was present in the original sample of **2a**. The reduction mixture was deacetylated with barium methoxide in methanol (0.25 N, 100 mL held at –5 °C), neutralized with acetic acid, evaporated, and then extracted with three 150-mL portions of warm ether. The extract was fractionated on a 60 × 750 mm column of silica gel packed and eluted with chloroform. Flavan (**27a**, 2.1 g) and unchanged **11a** were recovered, but the low R_f component believed to be **23a** was lost. Pure **27a** was obtained by sublimation (155 °c, 20 mtorr); mp 155–157 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{16}O_4$ 272.1048, found 272.1042, R + DB = 9; theor for $C_9H_{10}O_2$ 150.0680, found 150.0683, R + DB = 5; theor for $C_8H_9O_2$ 137.0602, found 137.0607, R + DB = 4; theor for $C_8H_7O_2$ 135.0446, found 135.0448, R + DB = 5.

3,4-Dihydro-5-acetoxy-2-(3-acetoxy-4-methoxyphenyl)-2H-1-benzopyran (**27c**). A 2-g sample of crude **11c** was reduced and fractionated by preparative TLC and **27c** crystallized from methanol; mp 149–150 °C. Detailed NMR data, structural assignements, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{20}H_{20}O_6$ 356.1259, found 356.1256, R + DB = 11; theor for $C_{18}H_{18}O_5$ 314.1154, found 314.1160, R + DB = 10; theor for $C_{16}H_{16}O_4$ 272.1048, found 272.1041, R + DB = 9; theor for $C_{16}H_{15}O_4$ 271.0970, found 271.0970, R + DB = 9; theor for $C_9H_{10}O_2$ 150.0680, found 150.0680, R + DB = 5; theor for $C_8H_7O_2$ 135.0446, found 135.0443, R + DB = 5.

3,4-Dihydro-7-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2H-1-benzopyran (**28a**). An equilibrated mixture of **8a** and **12a** (3:2, 10 g) was hydrogenated 6 h and then examined by GLC–MS (150–250 °C, 4 dpm as Me_3Si ethers). The mixture contained **16a** (19%), **20a** (46%), and **28a** (32%). In solvents such as ether, benzene, or ethyl acetate, the mixture was photosensitive, rapidly forming a material that did not move on TLC plates. Additionally, prolonged exposure to silica gel destroyed **28a**, preventing large-scale column fractionations unless **16a** and **20a** were sought. Preparative TLC separations required a preliminary treatment of the product mixture with sodium borohydride in DMF (3.5 g, 50 mL) to avoid cochromatography of **16a** and **28a**. Addition of acetic acid (0.5%) to the irrigant (chloroform–acetone, 9:1, one ascent) minimized losses of **28a** which was isolated as an oil (2 g, 21%) that crystallized after distillation (230 °C/10 mtorr); mp 158–160 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{16}O_4$ 272.1048, found 272.1046, R + DB = 9.

1-(2,4-Dihydroxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-2-propan-1-one (**16a**). A 35-g mixture of equilibrated **8a** and **12a** was acetylated, reduced, and then deacetylated with barium methoxide in methanol. Attempted fractionation of the mixture on a 60 × 750 mm column of silica gel packed and eluted with chloroform yielded 7.5 g of **16a** and 2.5 g of **20a**, identified by GLC–MS (150–250 °C, 4 dpm as Me_3Si ethers). Distillation (190 °C/10 mtorr) gave pure **16a**, mp 131–132 °C [115–116 °C (Farkas et al., 1976)]. ^1H NMR spectra of the product before and after distillation were identical, with aromatic proton patterns consistent for the assigned structure. Detailed NMR data, structural assignements, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{16}H_{16}O_5$ 288.0997, found 288.0994, R + DB = 9.

3,4-Dihydro-7-acetoxy-2-(3-acetoxy-4-methoxyphenyl)-2H-1-benzopyran (**28c**). A 6-h reduction of **12c** gave **28c**, which was isolated by preparative TLC (benzene–diethyl ether, 9:1, two ascents); mp 106–107 °C from diethyl ether. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{20}H_{20}O_6$ 356.1259, found 356.1250, R + DB = 11.

3,4-Dihydro-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2H-1-benzopyran (**29a**). A 1.2-g sample of **29c** crystallization liquors was deacetylated in 25 mL of 0.15 N barium methoxide in methanol, neutralized with acetic acid, evaporated, and extracted with ethyl acetate. Pure **29a** was obtained as an oil by preparative TLC (ethyl acetate, one ascent) as judged by GLC (150–250 °C, at 4 dpm, as Me_3Si ether). Detailed NMR data are listed in the supplementary material.

3,4-Dihydro-5,7-diacetoxy-2-(3-acetoxy-4-methoxyphenyl)-2H-1-benzopyran (**29c**). Preparative TLC (benzene–diethyl ether, 7:3, one ascent) of a 27-h reduction of crude **13c** gave unchanged starting material and a small amount of **28c**, identified by mixed mp and ^1H NMR. A 3.5-g sample of pure **13c** was dissolved in 50 mL of cold 1,2-dimethoxyethane, treated with 0.8 g of sodium borohydride, and held 18 h at 25 °C before adding 5 mL of methanol. After 0.5 h, the mixture was evaporated, extracted with 300 mL of ethyl acetate, and freed of water solubles. A 7-h hydrogenation completed the conversion to **29c**, as judged by TLC (benzene–diethyl ether, 7:3, one ascent). Pure **29c** (2.5 g, 74%) was isolated by preparative TLC (chloroform–acetone, 9:1, one ascent) after the mixture was reacetylated. Crystallization from ether and recrystallization from methanol gave mp 105–106 °C. Detailed NMR data, structural assignments, and MS fragmentations are listed in the supplementary material. High-resolution mass spectrum (calcd for ^{12}C): theor for $C_{22}H_{22}O_8$ 414.1255, found 414.1303, R + DB = 12.

3,4-Dihydro-8-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-1H-2-benzopyran-1-one (**30**). A 58-g sample of Amacha (dried leaves of *Hydrangea thunbergii* Sieb.) was serially extracted at 25 °C with chloroform–methanol (3:2, 1000 mL, 18 h under nitrogen atmosphere), with acetone (2 h, 1000 mL), and finally with boiling water (1000 mL). Five fluorescent components were detected by TLC (chloroform–methanol, 15:1, one ascent) in the crude isolate (10 g). Preparative TLC (chloroform–methanol, 19:1, one ascent) gave phyllodulcin (**30**) and hydrangenol frac-

tions contaminated with small quantities of chlorophyll. Percolation of each fraction through a 3 × 50 cm column silica gel packed and eluted with 1,2-dichloromethane gave pure components (phyllodulcin, 600 mg; hydrangenol, 1.05 g); mp 118–120 °C [120.5–121.5 °C (Suzuki et al., 1977)]. Detailed NMR data are listed in the supplementary material.

Taste Tests. Flavanones **10a**, **11a**, and **13a** served as references for personal taste appraisals, **10a** being tasteless, **11a** reported as 350 times sweeter than sucrose (Yamato et al., 1978) and **13a** considered as weakly sweet. Critical evaluations by a trained taste panel were not done because the compounds would have required extensive preliminary testing for toxicologic properties. Stock solutions in ethanol were prepared for each sample at 4% (4000 mg %) or 2%, as solubility permitted. Solutions were diluted to 1% and 20 mg % levels with distilled water before tasting by the author, each sample being evaluated for bitterness or medicinal taste as well as sweetness. **10a**: no taste. **11a**: moderately sweet at 20 mg %, with slight bitterness developing; sweetness appeared to increase with repeated tasting, as noted for **35**; pleasant sweetness remained at 1%. **12a**: weak sweetness at 20 mg % with slight bitterness developing; no improvement in taste at 1%. **13a**: weakly sweet at 20 mg %, sweet at 1%; slight bitterness developing, becoming medicinal also at 1%; prolonged aftertaste noted. **26a**: weakly sweet at 20 mg %, with slight bitterness developing; moderately sweet at 1%, with prolonged aftertaste noted; at 20 mg %, appears less sweet than **11a**; reported isosweet (Yamato and Hashigaki, 1979). **27a**: no sweetness, strongly bitter and medicinal at 20 mg %; taste intensities increased at 1%. **28a**: moderately sweet and slightly bitter at 20 mg %, with prolonged sweet aftertaste; very medicinal unless diluted to 4 or 12 mg % levels, at which weakly sweet only. **29a**: at 20 mg %, weakly sweet, medicinal and slightly bitter with prolonged aftertaste; no improvement at 1%. Syrupy samples of **18a** and **20a**, isolated by silica gel column chromatography (chloroform) from reduction mixtures and identified by GLC–MS, were tasteless. The 4-hydroxyflavan derivative, **22a** was also tasteless.

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Supplementary Material Available: NMR data, structural assignments, and electron-impact MS fragmentations (13 pages). Ordering information is given on any current masthead page.

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