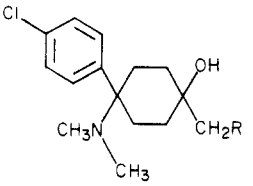
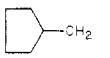
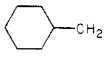
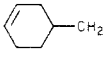
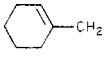
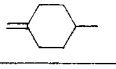
Table VI. *N,N*-Dimethyl-1-(*p*-chlorophenyl)-4-(cycloalkylalkyl)-4-hydroxycyclohexylamines



no.	R	isomer	salt	mp, °C	recrystn solv	% yield	formula
4r		trans	HCl	243.0-244.5	MeOH-$CHCl_3$	28	$C_{21}H_{33}Cl_2NO$
5r		cis		134.5-135.5	MeOH-H_2O	19	$C_{21}H_{32}ClNO \cdot {}^1/_3H_2O$
4q		trans	HCl	243.0-244.0	MeOH-EtOAc	30	$C_{22}H_{35}Cl_2NO$
5q		cis	HCl	245.0-246.0	MeOH-EtOAc	32	$C_{22}H_{35}Cl_2NO \cdot {}^2/_3H_2O$
4o		trans	HCl	240.0-241.0	MeOH-EtOAc	25	$C_{22}H_{33}Cl_2NO$
5o		cis	HCl	235.0-236.0	$CHCl_3$-EtOAc	32	$C_{22}H_{33}Cl_2NO \cdot {}^1/_3H_2O$
4p		trans	HCl	236.0-236.5	MeOH-EtOAc	20	$C_{22}H_{33}Cl_2NO \cdot 0.5H_2O$
5p		cis	HCl	210.0-214.0	$CHCl_3$-EtOAc	13	$C_{22}H_{33}Cl_2NO \cdot 1.5H_2O$
4s		trans	HCl	213.0-215.0	CH_2Cl_2-EtOAc	5	$C_{22}H_{33}Cl_2NO \cdot {}^2/_3H_2O$

The residue was taken up in water and methylene chloride. The organic layer was washed with water and brine and taken to dryness. The residual solid was recrystallized twice from acetone to afford 1.21 g (30%) of product, mp 148–150.5 °C. Anal. ($C_{14}H_{20}ClNO$) C, H, N.

1-Alkyl-4-Aryl-4-(dimethylamino)cyclohexan-1-ols (2 and 3; Table V). In a typical experiment, a solution of 6 mmol of the 4-aryl-4-(dimethylamino)cyclohexanone was added to a solution of 30 mmol of the appropriate Grignard reagent in 40 mL of THF. Following 40 h of standing at room temperature under nitrogen, the mixture was cooled in ice and treated with 25 mL of saturated aqueous $NaHCO_3$ and benzene. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was then chromatographed on 250 mL of silica gel. The appropriate fractions were combined and recrystallized either as the free base or the hydrochloride salt.

***N,N*-Dimethyl-1-(*p*-chlorophenyl)-4-(cycloalkylalkyl)-4-hydroxycyclohexylamines (4 and 5; Table VI).** To a nitrogen-covered, ice-cooled solution of the Grignard reagent prepared from 0.03 mol of the appropriate cycloalkyl bromide and 0.73 g of Mg in 40 mL of THF there was added 1.50 g (6 mmol) of 4-(*p*-chlorophenyl)-4-(dimethylamino)cyclohexanone. The mixture was stirred overnight at room temperature, again cooled in ice, and treated with 25 mL of saturated NH_4Cl and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness. The residue was chromatographed on 250 mL of silica gel. Elution with 5% MeOH in CH_2Cl_2 afforded the amino alcohol, which on the basis of the earlier work was assigned the trans configuration. The cis isomer was obtained by elution of the column with 20% MeOH–CH_2Cl_2. Each of the amino alcohols was then recrystallized either as the free base or as the appropriate salt.

Biology. Methods. The biological testing consisted of a battery of standard assays.[7] Briefly, CF-1 female mice were dosed sc with a suspension (or solution) of the test compound in 0.25% aqueous methylcellulose and 15 min later subjected to a series of procedures to detect analgesia, sedation, and narcotic antagonism. The tail-flick, tail-pinch, and HCl writhing procedures were used to detect analgesia, whereas the inclined screen test was used to measure sedation. After the completion of the tests (about 45 min postinjection), 6.3 mg/kg morphine sulfate was given subcutaneously, and 15 min later the mice were retested on the tail-flick procedure to determine if the compound might have narcotic antagonist properties. Blockade of morphine-induced elevation of tail-flick latency was scored as antagonism. Six mice were tested at each dose in this battery of assays. When multiple doses were examined, the ED_{50} values were calculated by the method of Spearman and Karber.[8]

Acknowledgment. The authors acknowledge the technical assistance of R. A. Lewis. Special thanks are due to Dr. David J. Duchamp for making available for publication the results of the X-ray crystallographic determination on compounds **2b** and **4n**.

(8) D. J. Finney, "Statistical Method in Biological Assay", Hafner, New York, 1952.
(9) Skellysolve B, a petroleum fraction of bp 60 °C sold by The Skelly Oil Co.

Dihydrochalcone Sweeteners. A Study of the Atypical Temporal Phenomena

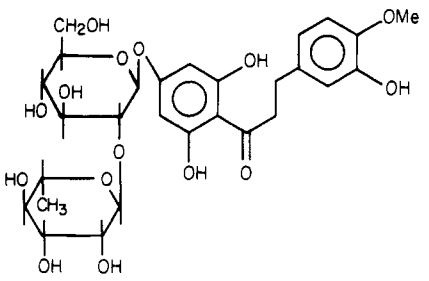
Grant E. DuBois,* Guy A. Crosby, and Rebecca A. Stephenson

Chemical Synthesis Laboratory, Dynapol, Palo Alto, California 94304. *Received July 31, 1980*

Neohesperidin dihydrochalcone (NHDHC), known since 1963 as an intensely sweet compound, is determined to be 340 ± 60 ($p < 0.05$) times more potent than sucrose. The unusual temporal properties of this material are hypothesized as being due to the effects of metabolism, conformation, chelation, or hydrophobicity. Forty-four analogues are synthesized to test the four hypotheses, none of which are strongly supported. A method of quantitation of temporal characteristics of tastant molecules is developed so as to allow comparison of taste appearance time (AT) and extinction time (ET) of experimental compounds. Four of the new compounds, **40** and **43–45**, exhibit high sweetness potencies, ranging from 280 to 440 times sucrose, and may be useful in selected food systems. The temporal taste characteristics remain unimproved over NHDHC, however.

In 1963, Horowitz and Gentili reported the discovery of a new nonnutritive sweetener called neohesperidin dihydrochalcone (NHDHC; **1**), which was derived from a natural flavonoid found in the rinds of the Seville orange.[1]

0022-2623/81/1824-0408$01.25/0



1

Sensory analysis of this compound indicated a potency 612 times that of sucrose, where the taste character was almost purely sweet.[2a,3] NHDHC suffers a major drawback, however, in that the taste, relative to that of sucrose, is slow to develop and shows a lingering, menthol or licorice-like aftertaste. These poor temporal characteristics render this compound unacceptable for use in most food products. Since the original report of 1, nearly 200 structural analogues have been prepared in the hope of obtaining an analogue with sucrose-like taste-timing properties.[2] Very early in our studies, we learned that the disaccharide moiety of 1 was not necessary for intense sweetness and, in fact, could be replaced by hydrophilic side chains, such as carboxyalkyl and sulfoalkyl, with some apparent improvement in sweet taste-timing behavior.[2a,2i]

However, the problem in development of a commercially useful nonnutritive sweetener is one of mimicking the taste of sucrose, and, since the best tasting of our NHDHC analogues still exhibited significant sweet taste linger, we were encouraged to undertake a fundamental study of the taste-timing phenomena, with the ultimate goal of developing a sucrose mimic. In order to facilitate the design of sucrose-like NHDHC analogues, it was hypothesized that the nonsucrose-like temporal properties of NHDHC could be due to the effects of (A) metabolism, (B) conformation, (C) chelation, or (D) hydrophobicity. In this paper, we report the synthesis and sensory evaluation of compounds which were designed to test each of these four hypotheses.

Sensory Evaluation. Experimental compounds were evaluated by a human sensory panel by the method of Swartz.[4] Prior to sensory analysis, new compounds were required to be ≥95 weight percent pure, as shown by a combination of HPLC, proton titration, and Karl Fischer analyses, and to exhibit an absence of toxicity. Compounds were screened for mutagenicity with five *Salmonella typhimurium* tester strains, with and without microsomal activation,[5,6] and were also subjected to limited scale, single oral dose, toxicity testing in mice. Results of these tests were reviewed by an Institutional Medical Review Board, and only compounds showing absence of mutagenicity or other toxicity were then evaluated by human volunteers. All experimental compounds were given a preliminary evaluation by tasting a dilute aqueous solution of concentration 250–2000 ppm. At 2000 ppm, sweeteners as weak as 2.5 times sucrose would be detectable, since the threshold for sucrose detection for our panel was determined to be 5100 ppm.[4] Samples exhibiting detectable sweetness, as well as some others, were then submitted for evaluation by a trained panel of judges. Experimental compound concentrations were adjusted so as to taste approximately the intensity of a 0.25 M (85 500 ppm) sucrose solution.

The panel members were trained in the recognition of the basic tastes of sweet (sucrose), sour (citric acid), salty (NaCl), and bitter (quinine sulfate), as well as in the technique of magnitude estimation, which consists of ranking the *total* intensity of a test solution relative to a sucrose standard. Judges showing consistency in training sessions were selected to evaluate experimental compounds. Panelists were asked to taste the test solution and estimate its *total* taste intensity (perceived intensity; I_p) relative to that of a 85 500 ppm (0.25 M) sucrose reference solution. The panelists were then asked to determine the "taste character" as to degree of sweetness, sourness, saltiness, bitterness or any other detected taste such that the total equaled 100%. Each panelist was also asked to describe the presence or absence and, if present, the quality of any aftertaste. Data showing excessive deviation at the 95% level of confidence were rejected by the *t*-value method.[7] Arithmetic means were then computed for the taste

(1) (a) Horowitz, R. M.; Gentili, B. U.S. Patent 2 087 821, 1963. (b) Horowitz, R. M.; Gentili, B. *J. Agric. Food Chem.* **1969**, *17*, 696–700. (c) Horowitz, R. M.; Gentili, B. "Sweetness and Sweeteners"; Birch, G. G.; Green, L. F.; Coulson, C. B., Eds.; Applied Science: London, 1971; pp 69–80.

(2) (a) DuBois, G. E.; Crosby, G. A.; Stephenson, R. A.; Wingard, R. E. *J. Agric. Food Chem.* **1977**, *25*, 763–772. (b) Krbechek, L.; Inglett, G.; Holik, M.; Dowling, B.; Wagner, R.; Riter, R. *Ibid.* **1968**, *16*, 108–112. (c) Okada, S. *Kagaku To Seibutsu* **1973**, *11*, 712. (d) Van Niekerk, D. M.; Koeppen, B. H. *Experientia* **1972**, *28*, 123. (e) Esaki, S.; Kamiya, S.; Konishi, F. *Agric. Biol. Chem.* **1975**, *39*, 1385–1389. (f) Kamiya, S.; Esaki, S.; Konishi, F. *Ibid.* **1975**, *39*, 1757. (g) Kamiya, S.; Esaki, S.; Konishi, F. *Ibid.* **1976**, *40*, 1731–1741. (h) Kamiya, S.; Esaki, S. *Nippon Shokuhin Kogyo Gakkaishi* **1976**, *23*, 432–443. (i) DuBois, G. E.; Crosby, G. A.; Saffron, P. *Science* **1977**, *195*, 397–399. (j) Kamiya, S.; Konishi, F.; Esaki, S. *Agric. Food Chem.* **1978**, *42*, 941–950. (k) Farkas, L.; Nogradi, M.; Gottsegen, A.; Antus, S. German Patent 2 258 304, 1973. (l) Farkas, L.; Nogradi, M.; Pfliegel, T.; Antus, S.; Gottsegen, A. German Patent 2 506 356, 1975. (m) Antus, S.; Farkas, L.; Gottsegen, A.; Nogradi, M.; Strelisky, J.; Pfliegel, T. *Acta Chim. Acad. Sci. Hung.* **1978**, *98*, 231–240. (n) Antus, S.; Farkas, L.; Gottsegen, A.; Nogradi, M.; Pfliegel, T. *Ibid.* **1978**, *98*, 225–230. (o) Kamiya, S.; Konishi, F.; Esaki, S. *Agric. Biol. Chem.* **1974**, *38*, 1785–1790. (p) Kamiya, S.; Konishi, F.; Esaki, S. *Ibid.* **1976**, *40*, 1887–1888. (q) Yamato, M.; Hashigaki, K.; Kuwano, Y.; Koyama, T. *Yakugaku Zasshi* **1972**, *92*, 535–538. (r) Yamato, M.; Hashigaki, K.; Honda, E.; Sato, K.; Koyama, T. *Chem. Pharm. Bull.* **1977**, *25*, 695–699. (s) Yamato, M.; Hashigaki, K.; Tsukiok, A.; Koyama, T. *Ibid.* **1977**, *25*, 700–705. (t) Yamato, M.; Sato, K.; Hashigaki, K.; Koyama, T. *Ibid.* **1977**, *25*, 706–713. (u) Yamato, M.; Kitamura, T.; Hashigaki, K.; Kuwano, Y.; Murakami, S.; Koyama, T. *Yakugaku Zasshi* **1972**, *92*, 850. (v) Yamato, M.; Hashigaki, K.; Venishi, K.; Yamakawa, I.; Sato, N.; Koyama, T. *Chem. Pharm. Bull.* **1975**, *23*, 3101. (w) Yamato, M.; Hashigaki, K.; Mito, K.; Koyama, T. *Ibid.* **1977**, *25*, 1484. (x) Yamato, M.; Hashigaki, K. *Chem. Senses Flavour* **1979**, *4*, 35–47. (y) Dick, W. E.; Hodge, J. E. *J. Agric. Food Chem.* **1978**, *26*, 723–725. (z) Sweeny, J. G.; Iacobucci, G. A. *Ibid.* **1979**, *27*, 467–469.

(3) Sensory analysis of 1 by the volunteer panel used for the present study gave a potency estimate (weight basis) of 340 ± 60 times sucrose ($p < 0.05$) when compared to a 0.25 M sucrose standard. This value should be accepted as a more precise estimate of NHDHC potency.

(4) Swartz, M. L.; Furia, T. E. *Food Technol. (Chicago)* **1977**, *11*, 51–67.

(5) Ames, B. N.; McCann, J.; Yamasaki, E. *Mutat. Res.* **1975**, *31*, 347.

(6) Brown, J. P.; Brown, R. J. *Mutat. Res.* **1976**, *40*, 203.

(7) Gordon, A. J.; Ford, R. A. "The Chemist's Companion: A Handbook of Practical Data, Techniques, and References"; Wiley: New York, 1972; pp 481–492.

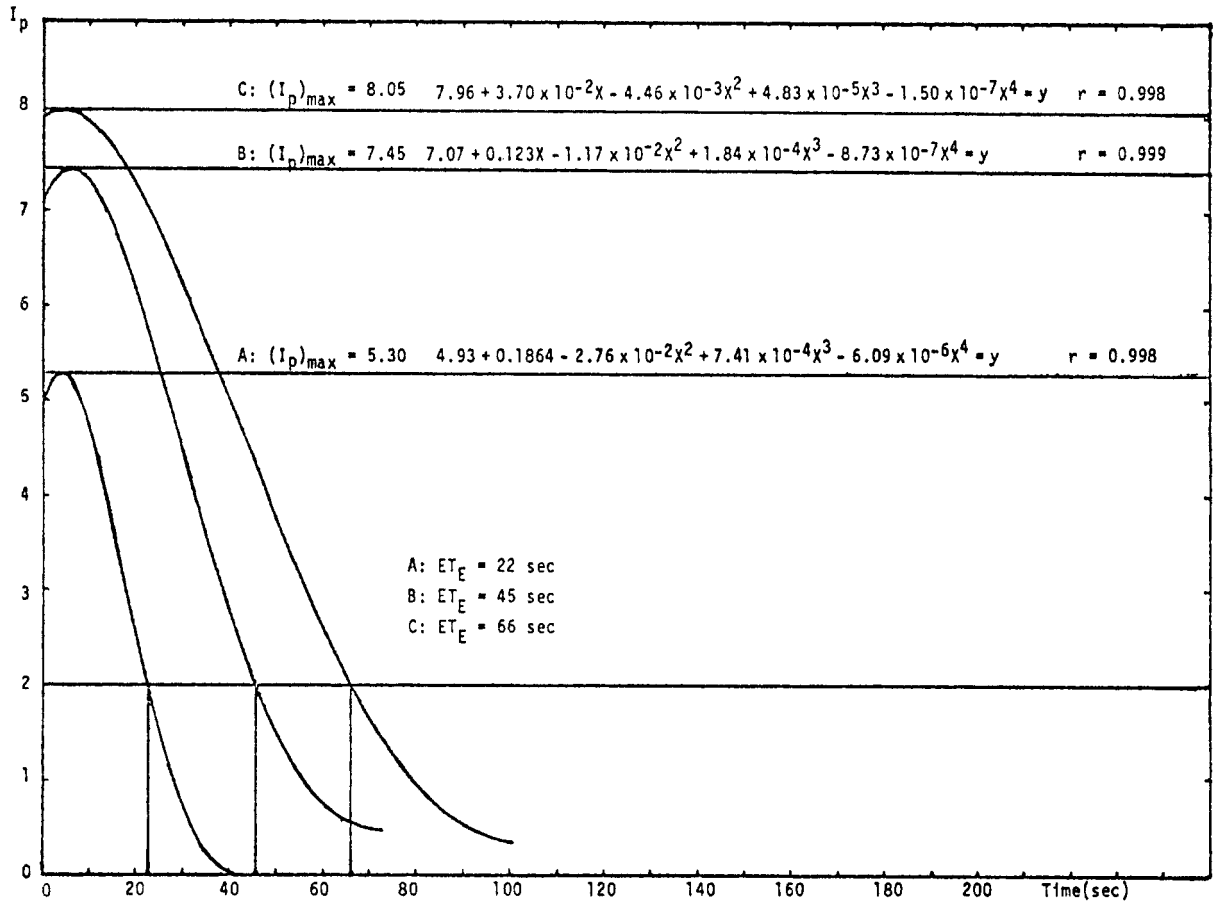


Figure 1. TI curves for 4% sucrose (A), 10% sucrose (B), and 15% sucrose (C).

character and perceived intensity data and are reported with limits of 2 standard deviations about the mean (±-$2S_m$). Calculated intensity was determined on both a weight and molar basis through use of eq 1 and 2 and also

$$I_w = I_p\left(\frac{85\,500 \text{ ppm}}{X}\right) \quad (1)$$

$$I_m = I_p\left(\frac{0.25 \text{ M}}{Y}\right) \quad (2)$$

is reported with limits of $2S_m$, where I_w = intensity calculated on a weight basis relative to an 85 500 ppm sucrose solution, I_p = experimentally determined perceivied intensity, X = experimental compound concentration in parts per million, I_m = intensity calculated on a molar basis relative to a 0.25 M sucrose solution, and Y = experimental compound molar concentration.

The above type of analysis provided a very useful method for screening compounds and also, through aftertaste response, yielded preliminary information on taste-timing behavior of promising compounds. For the case of the latter, which shall be defined as having $I_w \geq 100$ times sucrose and taste character ≥ 70% sweet, a more quantitative method was required for judging temporal characteristics. This was achieved by the general approach of Larson-Powers and Pangborn,[8] which was further developed by Swartz.[9] Methods of analysis of data obtained by this time–intensity (TI) technique are developed further in this paper. In essence, the method involves trained panelists plotting curves of I_p vs. time with the aid of a strip chart recorder. Perceived intensity was divided into 10 units, where the verbal descriptors "no taste" (0), "faint" (2), "weak" (4), "moderate" (6), "strong" (8), and "very strong" (10) are associated with the indicated numerical values of I_p. A 10% sucrose solution was used as reference and defined as having a maximum $I_p = 7.0$. Values of I_p were obtained from the curves at 4- or 6-s intervals and mean values ($\bar{I}_p$) were determined. Data showing excessive deviation at the 95% level of confidence were rejected by the t-value method.[7] Standard deviations about $\bar{I}_p$ were calculated and the data then reported as $\bar{I}_p$ ($2S_m$) for each value of time (t). The three data sets, ($\bar{I}_p - 2S_m$, t), ($\bar{I}_p$, t), and ($\bar{I}_p + 2S_m$, t), were then fit to fourth-degree polynomial equations, with excellent correlation ($r > 0.99$), by the method of least-squares using a Tektronix 31 computer and a Tektronix Statistics 4-1 curve-fitting program. The resultant equations were then plotted using a Tektronix 4661 XY plotter. The TI curves thus obtained were useful in providing information on both (1) the *time* required for taste maxima *appearance* (AT)[10a,b] and (2) the *time* required for taste *extinction* (ET), which shall be defined as the time required for decay of taste to a level of faint ($I_p = 2.0$). A significant problem exists in that the experimentally determined extinction time (ET_E) is highly dependent on the sample $(I_p)_{max}$, as shown by the data for sucrose (Figure 1). Further complicating the determination of ET is the observation that the relationship between $(I_p)_{max}$ and ET is nonlinear, as shown by a plot of these parameters for three sucrose solutions (Figure 2).[10a,11]

(8) Larson-Powers, N.; Pangborn, R. M. *J. Food Sci.* **1978**, *43*, 41.
(9) Swartz, M. L. *J. Food Sci.* **1980**, *45*, 577–581.

(10) (a) Birch, G. G.; Latymer, Z.; Holloway, M. *Chem. Senses* **1980**, *5*, 63–78. (b) The results of ref 10a show negligible dependence of taste maxima appearance time (AT) on sample concentration within moderate ranges of the latter variable. Therefore, AT results need not be normalized.

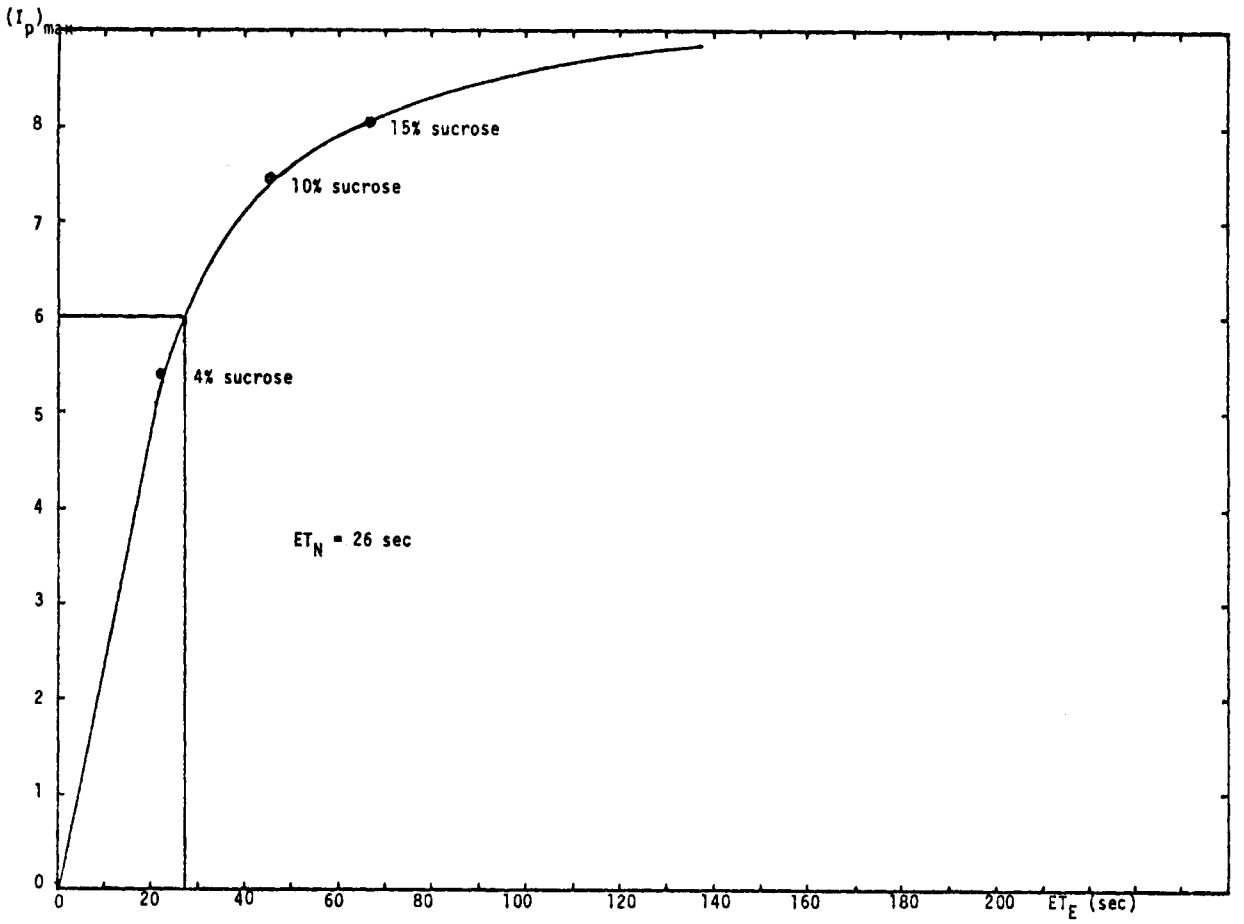


Figure 2. Plot of perceived intensity maxima, $(I_p)_{max}$, vs. experimental extinction time, ET_E, for three concentrations of sucrose.

However, from Figure 2 it can be determined that a sucrose solution exhibiting $(I_p)_{max} = 6.0$ would have an ET of 24 s. Therefore, all ET_E values for the various compounds were normalized to provide ET_N values, which would represent extinction times of solutions having $(I_p)_{max} = 6.0$. It was assumed that the function relating $(I_p)_{max}$ with ET_E values for sucrose is like that of the other compounds, differing only in minimum value of ET_E. The sucrose data curve (Figure 2) was thus used in conjunction with eq 3

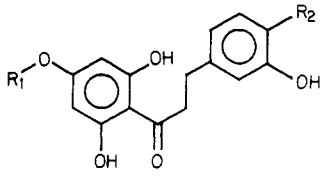
$$ET_N = ET_E + [ET_{(I_p)_{max}=6.0} - ET_{(I_p)_{max}=\text{exptl value}}]_{\text{sucrose}} \quad (3)$$

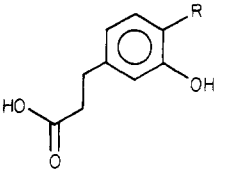
where $[ET_{(I_p)_{max}=6.0}]_{\text{sucrose}} = 24$ s

to calculate ET_N values for all experimental compounds. As an example, a 330 ppm saccharin solution, exhibiting $(I_p)_{max} = 7.0$ and $ET_E = 54$ s (Figure 3) was calculated to have $ET_N = 54 + (24 - 36) = 42$ s. Inspection of the $(\bar{I}_p - 2S_m, t)$ and $(\bar{I}_p + 2S_m, t)$ data curves indicates this value to have limits of 12 s for a confidence level of 95%. Thus, the ET_N value for saccharin is found to be 42 ± 12 s.

Results

Analogue Design and Sensory Evaluation. (A) Metabolism Effects Hypothesis. NHDHC and related flavonoid compounds are known to undergo a variety of degradation reactions when exposed to the enzymes of the small intestine. The works of Booth,[12] Scheline,[13] Honohan,[14] and others have shown hydrolytic lability of bonds A, B, and C and reductive lability of bond D, as illustrated in Figure 4. It is reasonable that enzymes present in the oral cavity may be capable of similar metabolism such that NHDHC could be converted to products of type A, B, C, or D cleavage in a time-dependent reaction. Thus, the delayed taste onset may find its rationale in that nonsweet NHDHC must first be converted to a metabolite which is the active sweetener. Strong hydrophobic binding forces may then retain the sweet metabolite in the receptor pocket. Alternatively, NHDHC may be strongly bound to nonreceptor material and slowly be enzymatically processed to produce the sweet compound. To test this hypothesis, the products of A–D type cleavage, **3**–**8**, were





2, $R_1 = CH_2COONa$; $R_2 = OMe$
3, $R_1 = H$; $R_2 = OMe$
4, $R_1 = CH_2COONa$; $R_2 = OH$
5, $R_1 = CH_2COONa$; $R_2 = H$

6, R = OMe
7, R = OH
8, R = H

synthesized and subjected to sensory evaluation. The NHDHC types C and D cleavage products **4** and **5** were prepared as carboxymethyl derivatives for synthetic reasons, a substitution which seems reasonable in view of the

(11) (a) Lawless, H. T.; Skinner, E. Z. *Percept. Psychophys.* **1979**, *25*, 180–184. (b) Similar dependencies were observed for sucrose and thaumatin by the workers cited in ref 10a and again for sucrose by the workers of ref 11a.

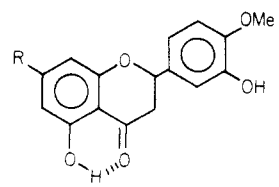
(12) (a) Booth, A. N.; Emerson, O. H.; Jones, F. T.; DeEds, F. *J. Biol. Chem.* **1957**, *229*, 51. (b) Booth, A. N.; Jones, F. T., DeEds, F. *Ibid.* **1958**, *230*, 661.

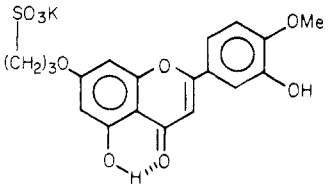
(13) Scheline, R. R. *Acta Pharmacol. Toxicol.* **1968**, *26*, 332.

(14) Honohan, T.; Hale, R. L.; Brown, J. P.; Wingard, R. E. *J. Agric. Food Chem.* **1976**, *24*, 906–911.

comparable sensory properties of NHDHC and its carboxymethyl analogue **2**. Sensory results are summarized in Table I.

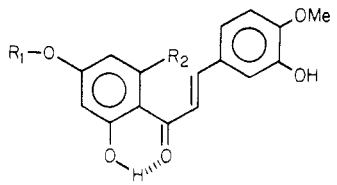
(B) Conformational Effects Hypothesis. If the conformation of NHDHC required for efficacious receptor interaction is significantly above ground state in energy, taste-eliciting binding may occur only after conformational changes are induced in both NHDHC and the receptor protein. The time required for this process could result in a taste lag. Strong hydrophobic binding forces may then retain NHDHC in the receptor area so as to prolong taste response. To test the likelihood of this hypothesis, analogues **9–18** were synthesized and subjected to sensory evaluation, the results of which are shown in Table I.

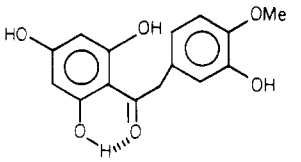




9, R = H
10, R = OCH_2COONa
11, R = $O(CH_2)_3SO_3K$

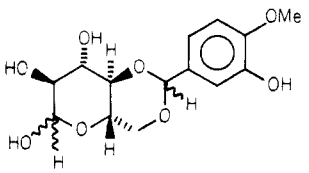
12



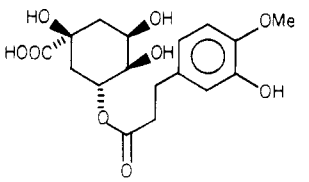


13, R_1 = CH_2COONa; R_2 = H
14, R_1 = CH_2COONa; R_2 = OH
15, R_1 = $(CH_2)_3SO_3K$; R_2 = H

16



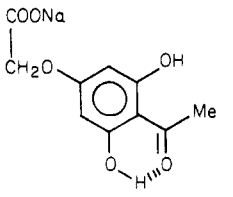
17



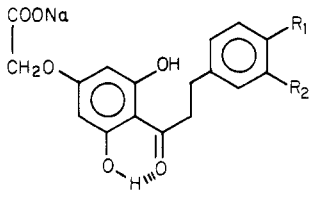
18

(C) Chelation Effects Hypothesis. The act of engagement of an active molecule with its receptor involves a significant negative entropy effect. This results in reduction of binding free energy and, therefore, a lowered association constant. Any molecule having a less negative binding entropy would therefore exhibit a higher association constant. Compounds having two binding sites may bind very intensely, much as chelating ligands interact strongly with metal ions.[15] However, such a chelating glucophore may require increased time for an induced fit with the protein receptor, after which release of the chelating molecule is retarded by the high association constant. In order to gain insight into the validity of this hypothesis, analogues **4**, **5**, and **19–33** were prepared and evaluated by the sensory panel, the results of which are summarized in Table I.

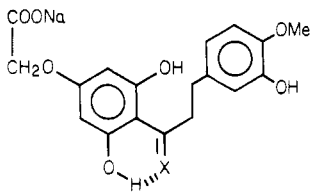
(D) Hydrophobic Effects Hypothesis. A sweet taste response can occur only after an active molecule reaches



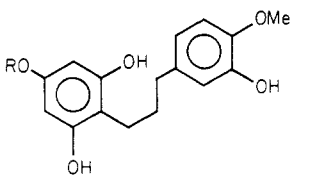
19



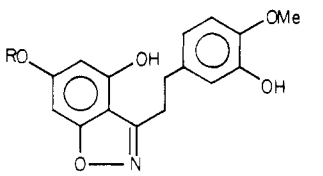
20, R_1 = R_2 = H
21, R_1, R_2 = OCH_2O
22, R_1 = $OCH_2CH_2CH_3$; R_2 = OH
23, R_1 = OCH_3; R_2 = NH_2
24, R_1 = Cl; R_2 = OH
25, R_1 = $NHCH_3$; R_2 = OH



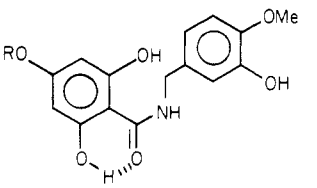
26, X = NOH
27, X = NH



28, R = H
29, R = CH_2COONa

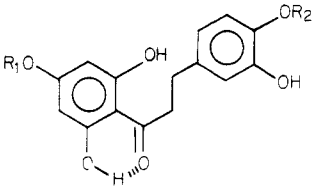


30, R = CH_2COONa
31, R = $(CH_2)_3SO_3K$



32, R = H
33, R = CH_2COONa

the receptor site. If this process is delayed by the compound undergoing nonspecific hydrophobic binding interactions with other hydrophobic material in the oral cavity, the concentration of compound in the vicinity of the receptor would build gradually over a period of time in the fashion of a Gaussian curve. Perceived taste intensity would follow a similar curve, reaching a maxima as glucophore concentration in the receptor cavity reaches a maximum and then decaying in an asymmetric manner. The lack of symmetry in the second half of this curve could be due to an increase in specific and/or nonspecific interactions in the receptor pocket. In order to judge the likelihood of this type of effect, analogues **22** and **34–45** were synthesized and evaluated by the sensory panel, the results of which are summarized in Table I. Inspection of these data indicate four of these compounds, **40** and **43–45**, to be "promising" with regard to the definition of



34, R_1 = $CH(COONa)_2$; R_2 = CH_3
35, R_1 = $CH(COONa)CH_2CH_2COONa$; R_2 = CH_3
36, R_1 = $CH(COONa)CH_2CH_2COONa$; R_2 = $CH_2CH_2CH_3$
37, R_1 = $CH(COONa)CH_2CHOHCH_2OH$; R_2 = CH_3
38, R_1 = $CH(COONa)CH_2CHOHCH_2OH$; R_2 = $CH_2CH_2CH_3$
39, R_1 = $CH(COONa)CH_2CH_2CH_2OH$; R_2 = CH_3
40, R_1 = CH_2COCH_2COONa; R_2 = CH_3
41, R_1 = $(CH_2)_2NH_2$; R_2 = CH_3
42, R_1 = $(CH_2)_3NH_2$; R_2 = CH_3
43, R_1 = $(CH_2)_3PO(OH)(OK)$; R_2 = CH_3
44, R_1 = $(CH_2)_2NHSO_3K$; R_2 = CH_3
45, R_1 = $(CH_2)_2CHOHCOONa$; R_2 = CH_3

"promising" given earlier. TI analyses for **40**, **43**, and **44**,

(15) For a discussion of the marked effects of bidentate ligands on association constants with metal ions in biological systems, see Mahler, H. R.; Cordes, E. H. "Biological Chemistry"; Harper and Row: New York, 1971; pp 16–18 and references cited therein.

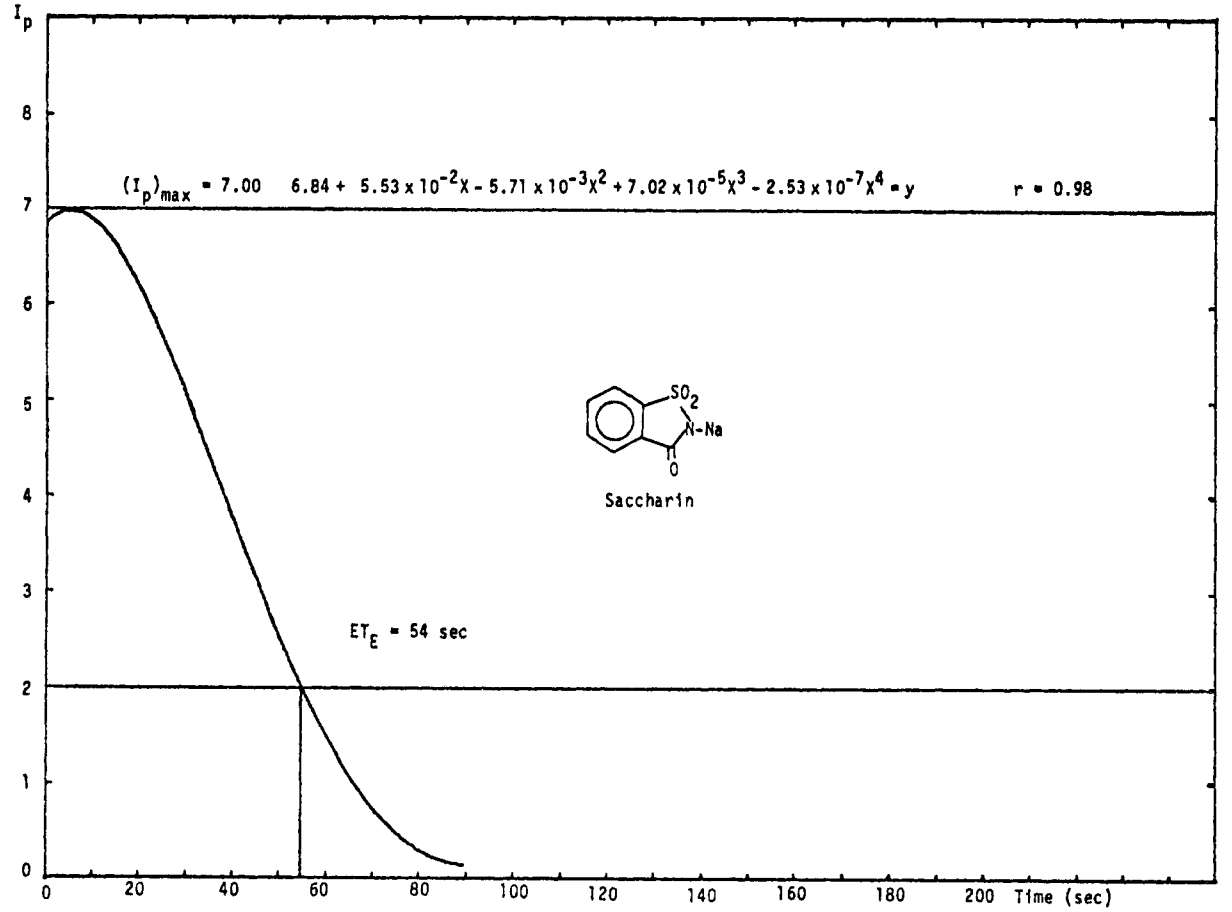


Figure 3. TI curve for 330-ppm of saccharin.

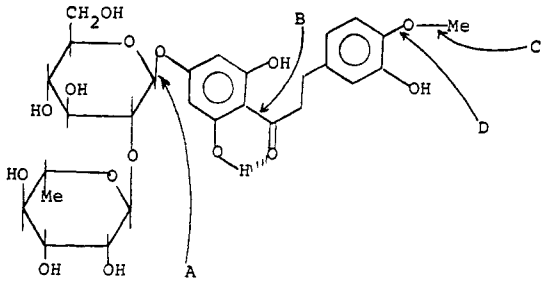


Figure 4. Cleavage sites of NHDHC exposed to gut microflora.

as well as for NHDHC, **2**, and monoammonium glycyrrhizinate (MAG), were carried out in the manner discussed above for saccharin. The TI data for all compounds and the I_p vs. time plots for **40**, **43**, and **44**, as well as for **2**, NHDHC, and MAG, are available as supplemental material (see paragraph at end of paper concerning supplementary material). The experimentally determined taste appearance times (AT) and normalized extinction times (ET_N) are given in Tables II and III, respectively.

Synthesis. The development of general synthetic methods capable of generating a large number of congeners is crucial to any structure–activity relationship (SAR) study. Ten of the fourty-four NHDHC analogues reported are available via alkylation of hesperetin (**46**) with the appropriate alkylating agent, followed by reductive cleavage of the flavanone ring, as illustrated in Scheme I. Thus, preparation of **2** involved ethyl chloroacetate alkylation; **34**, diethyl chloromalonate; **35**, dimethyl 2-bromoglutarate; **39**, 2-bromobutyrolactone; **40**, methyl 3-methoxy-4-iodo-2-butenoate; **41**, benzyl 2-bromoethylcarbamate; **42**, benzyl 3-bromopropylcarbamate; and **45**, methyl 2-acetoxy-4-bromobutyrate. The sulfamic acid salt **44** was obtained from the amine **41** by a novel sulfamation procedure, the details of which have been published elsewhere.[16] The two flavanones, **10** and **11**, are available by alkylation of **46** with ethyl chloroacetate and 1,3-propane sultone, respectively, followed by ester hydrolysis in the case of **10**. Chalcone **14** is obtained following ester hydrolysis and flavanone ring cleavage of the hesperetin–ethyl chloroacetate alkylation product. Flavone **12** was obtained via alkylation of diosmetin (**47**) with 1,3-propane sultone.

The previously reported[2a] protected dihydrochalcone **48** has been found to be generally useful for the production of C_4-OH substituted dihydrochalcones. Scheme II illustrates its utility for preparation of the dihydroxycarboxylic acid **37** and the phosphonic acid salt **43**.

Another method which was developed and found to be of general utility for synthesis of congeners having varied B-ring functionality is depicted in Scheme III. Condensation of acetophenone **51**, obtained as illustrated from naringin (**49**), with the appropriate aromatic aldehyde thus leads to the eight dihydrochalcones **4**, **5**, and **20–25**. The substituted acetophenone **19** is obtained in a straightforward fashion from intermediate **50**.

A general method which was developed for the preparation of 4′-propoxy-4-substituted-dihydrochalcones, using 4′-propoxychalcone (**52**), is illustrated in Scheme IV for the cases of congeners **36** and **38**.

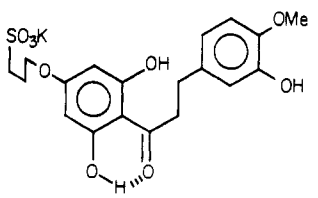
The isoxazoles **30** and **31** were obtained easily in high yield via condensation of hydroxylamine with the corresponding 2-hydroxy aromatic ketones **2** and **53**, respec-

(16) DuBois, G. E.; Stephenson, R. A. *J. Org. Chem.* **1980**, *45*, 5371–5373.

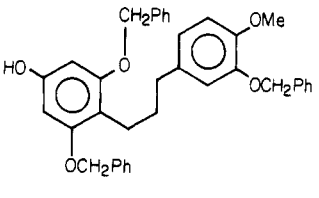
Table I. Sensory Evaluation of NHDHC and Analogues[a]

no.	judgments	concn, ppm	I_P	I_W	I_M	taste character						aftertaste[b]
						sweet	sour	salty	bitter	other	sweet/bitter	
1[c]	12	240	0.94 (0.17)	340 (60)	600 (110)	77 (14)	0 (0)	0 (0)	8 (5)	15 (10)	90/10	100 (s)
2	12	260	0.90 (0.10)	300 (30)	330 (40)	76 (6)	0 (0)	0 (0)	5 (6)	19 (7)	94/6	100 (s)
3	10	90	0.89 (0.17)	850 (160)	750 (140)	83 (5)	0 (0)	5 (5)	8 (7)	4 (2)	91/9	70 (s)
4	12	248	0.15 (0.08)	52 (27)	56 (20)	3 (2)	0 (0)	0 (0)	33 (19)	64 (23)	8/92	38 (b)
5	12	246	0.22 (0.08)	76 (28)	79 (29)	38 (22)	0 (0)	0 (0)	49 (25)	13 (10)	44/56	62 (bs)
6	8	244	0.60 (0.28)	210 (100)	120 (60)	0 (0)	69 (29)	0 (0)	28 (16)	3 (3)	0/100	50 (b)
7	8	250	0.73 (0.32)	250 (110)	130 (60)	0 (0)	76 (29)	0 (0)	15 (14)	9 (11)	0/100	50 (b)
8	8	252	0.46 (0.28)	160 (100)	80 (50)	0 (0)	96 (30)	0 (0)	4 (2)	0 (0)	0/100	38 (b)
9	8	33.4	0.68 (0.31)	1700 (800)	1400 (700)	62 (24)	6 (7)	0 (0)	32 (17)	0 (0)	66/34	42 (s)
10	12	251	0.79 (0.15)	270 (50)	300 (60)	15 (8)	0 (0)	0 (0)	78 (12)	7 (6)	16/84	100 (b)
11[d]	1	1090	0.5	40	50	75	0	0	25	0	75/25	0
12	1	4100	0									
13	1	2000	0									
14	1	690	0									
15	12	1013	0.45 (0.13)	38 (11)	50 (14)	23 (12)	0 (0)	0 (0)	59 (12)	18 (12)	28/72	100 (bs)
16	12	54	0.11 (0.10)	170 (160)	150 (130)	11 (9)	0 (0)	0 (0)	70 (25)	19 (13)	14/86	0
17[d]	1	2000	0.3	10	10	0	0	0	100	0	0/100	0
18	1	1000	0									0
19[d]	1	2000	0.25	10	0	0	0	0	100	0	0/100	0
20	12	501	0.91 (0.16)	160 (20)	150 (30)	0 (0)	0 (0)	0 (0)	79 (11)	21 (12)	0/100	100 (b)
21	12	497	0.83 (0.15)	140 (20)	160 (30)	0 (0)	0 (0)	0 (0)	79 (12)	21 (12)	0/100	100 (b)
22	12	251	0.72 (0.16)	240 (60)	300 (60)	39 (12)	0 (0)	0 (0)	38 (5)	23 (8)	51/49	100 (bs)
23	12	252	0.08 (0.10)	200 (30)	230 (40)	5 (9)	0 (0)	1 (2)	79 (16)	15 (12)	6/94	58 (b)
24	12	250	0.28 (0.06)	27 (19)	31 (13)	11 (5)	0 (0)	0 (0)	70 (20)	19 (6)	14/86	0
25	1	2000	0									0
26	12	210	0.20 (0.19)	110 (90)	130 (100)	0 (0)	26 (17)	0 (0)	74 (27)	0 (0)	0/100	0
27	1	2000	0									0
28	12	240	0.25 (0.20)	89 (71)	76 (60)	7 (4)	0 (0)	0 (0)	88 (24)	5 (4)	7/93	0
29	12	240	0.01 (0.01)	4 (4)	4 (4)	0 (0)	0 (0)	0 (0)	100 (28)	0 (0)	0/100	0
30	12	1001	0.38 (0.11)	32 (10)	36 (9)	66 (13)	0 (0)	0 (0)	22 (12)	12 (7)	75/25	100 (s)
31	12	1011	0.49 (0.13)	41 (11)	56 (15)	41 (17)	0 (0)	0 (0)	38 (18)	21 (12)	52/48	100 (bs)
32	1	1000	0									0
33	1	2000	0									0
34	1	495	0									0
35	1	2400	0									0
36	1	2000	0									0
37	1	2000	0									0
38[d]	1	2000	0.5	20	30	20	0	0	80	0	20/80	100 (bs)
39	4	250	0.10 (0.11)	34 (38)	43 (47)	69 (31)	0 (0)	0 (0)	31 (35)	0 (0)	69/31	0
40	24	249	0.89 (0.08)	310 (30)	380 (30)	85 (6)	0 (0)	0 (0)	3 (3)	12 (6)	97/3	100 (s)
41[d]	1	1000	1.0	86	87	75	0	0	25	0	75/25	100 (bs)
42[d]	1	720	1.5	180	190	50	0	0	50	0	50/50	100 (bs)
43	12	251	0.83 (0.11)	280 (40)	380 (50)	80 (8)	0 (0)	0 (0)	7 (6)	13 (6)	92/8	100 (s)
44	12	250	1.03 (0.10)	350 (30)	480 (50)	89 (5)	0 (0)	0 (0)	6 (5)	5 (3)	94/6	100 (s)
45	4	250	1.28 (0.20)	440 (70)	550 (90)	92 (8)	0 (0)	0 (0)	8 (6)	0 (0)	92/8	100 (s)

[a] Sensory data are reported as follows: mean value ($2S_m$); statistical calculations were carried out as described by Gordon and Ford.[7] [b] Percentage of judgments reporting an aftertaste and character thereof. Abbreviations used: s, sweet; b, bitter; bs, bitter-sweet. [c] NHDHC. [d] Not evaluated by panel due to quantities available.



53



54

tively. Hydrogenation of isoxazole **30** over Pd/C catalyst quantitatively yielded the hydrolytically unstable imine **27**. The norketo compounds **28** and **29** were obtained by standard methods from **54**, which in turn was obtained in quantitative yield from the $LiAlH_4$ reduction of ketone **48**. Interestingly, incomplete reduction reaction mixtures were found to contain only **48** and **54**; no alcohol intermediate reduction product was detectable, thus suggesting a two-step reduction involving a slow addition of the first hydride followed by rapid addition of the second hydride, as illustrated in Scheme V. This is analogous to the $LiAlH_4$ reduction of tertiary amides.[17]

The carboxamide analogues **32** and **33** were prepared via an interesting series of reactions outlined in Scheme VI. Selective alkylation of **32** at the C_4-OH proved a difficult problem, the desired product being obtained in only 2% yield. Protection of the much more reactive C_6-OH was easily affected through introduction of the oxazolone ring system by the general method of Crum and Franks.[18] Regioselective C_4-OH alkylation was then easily carried out.

The taste-modifying agent chlorogenic acid (**55**), which is reported to give a sweet taste to water,[19] was converted to **18**, which contains an NHDHC-type functionality, as illustrated in Scheme VII. The deoxybenzoin (**16**) was prepared via the Hoesch reaction of phloroglucinol and 3-(benzyloxy)-4-methoxybenzyl cyanide, while the glucose acetal **17** was prepared via condensation of 1-*O*-benzyl glucopyranoside with 3-(benzyloxy)-4-methoxybenzaldehyde, dimethyl acetal, according to the general procedure of Dick and Hodge.[2y] Other compounds were prepared via standard synthetic methods. All procedures and relevant data are included under Experimental Section.

Discussion

Four hypotheses have been proposed in an attempt to rationalize the non-sucrose-like temporal properties of NHDHC and its analogues. Hypothesis A, which proposes that NHDHC is not in itself sweet but is metabolized in the mouth to another intensely sweet compound, seems unlikely in view of the sensory results on compounds **3–8**. Hydrocinnamic acids **6–8**, resulting from type B cleavage of NHDHC (see Figure 1) with subsequent type C and D cleavage, show only sour taste with no observable sweet taste, while the dihydrochalcones **4** and **5**, designed to be models for the NHDHC type C and D cleavage products, respectively, show only weak bittersweet tastes. Only **3**, the product of type A cleavage, shows "promising" sensory properties. DHC **3**, for reason of low water solubility, was not submitted to TI analysis. However, the fact that a high aftertaste response (Table I) was observed in initial studies suggests the lingering sweet aftertaste of **3** to be comparable to NHDHC. Thus, the presence or absence of the carbohydrate moiety in NHDHC seems to have no pronounced effect on lingering sweet aftertaste. A comparison of the calculated molar potencies of **3** and NHDHC, its disaccharide conjugate, is quite interesting. The values of 750 ± 140 and 600 ± 110 for **3** and NHDHC, respectively, suggest, as has not been previously recognized, that the carbohydrate portion of NHDHC is totally without effect on either taste quality or *potency*.

Hypothesis B, which suggests that the delay in taste onset and, indirectly, the lingering taste property of sweet DHC's may be affected by the closeness in energy of the compounds' ground-state conformation with that required for efficacious receptor interaction, was probed by sensory studies on compounds **9–18**. The observation that flavanones **9–11** are capable of eliciting intense sweet taste strongly suggests that the active conformation of sweet DHC's is a "folded" conformation, fixed as in a flavanone rather than other "elongated" conformers, as illustrated in Figure 5. This suggestion was made earlier as a result of the similarity in structure between DHC's and the sweet dihydroisocoumarin, phyllodulcin.[2a] Neither flavanones **10** nor **11** were studied by the TI technique, since both exhibited substantial bitter taste, while poor water solubility (33.4 mg/L at 20 °C) eliminated **9** from further consideration. All properties considered, however, all three compounds appear to offer no improvement over NHDHC. Thus, it appears that fixing DHC functionality in a

Table II. Taste Appearance Times (AT) for Sucrose, Saccharin, MAG, NHDHC, and NHDHC Analogues as Determined by the TI Technique

compound	AT,[a] s
sucrose	5 (1)
saccharin	5 (1)
MAG	23 (2)
NHDHC	7 (2)
2	11 (1)
40	9 (2)
43	11 (1)
44	6 (1)

[a] Appearance time, defined as the time required for perceived taste intensity (I_p) to reach a maxima, is reported as AT ($2S_m$).

Table III. Taste Extinction Times (ET) for Sucrose, Saccharin, MAG, NHDHC, and NHDHC Analogues as Determined by the TI Technique

compound	ET,[a] s
sucrose	24 (7)
saccharin	42 (11)
MAG	133 (24)
NHDHC	57 (9)
2	60 (12)
40	59 (8)
43	56 (9)
44	68 (13)

[a] Extinction time, defined as the time required for perceived taste intensity (I_p) to decay to a level of faint (I_p = 2.0), is reported as ET ($2S_m$).

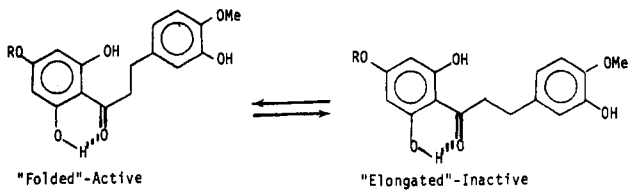
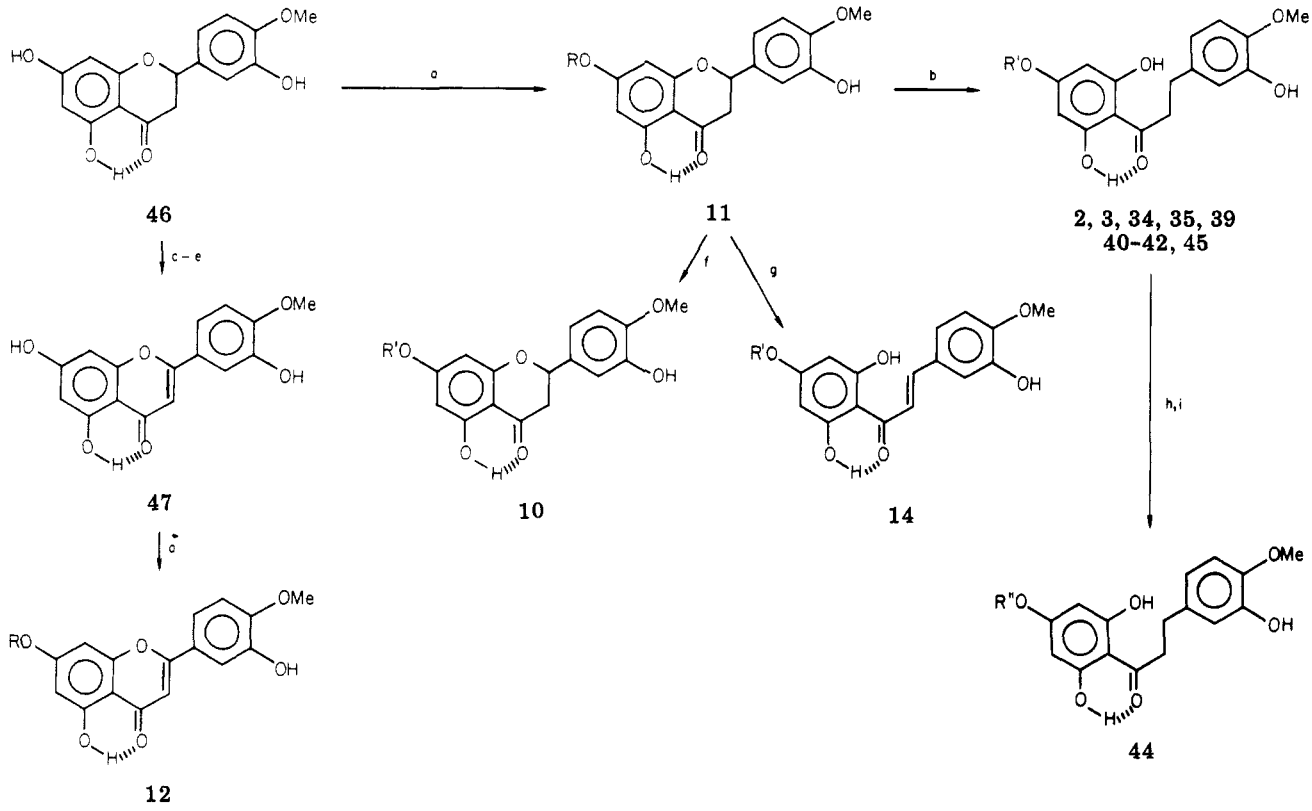


Figure 5. Proposed active conformation of sweet DHCs.

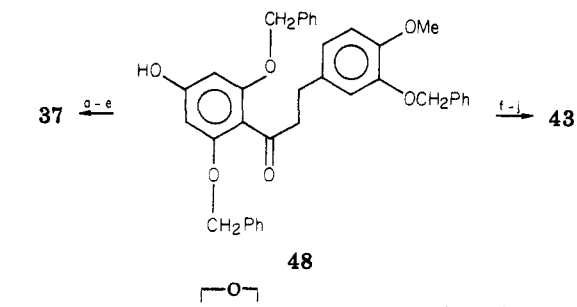
(17) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; p 79 and references cited therein.
(18) Crum, J. D.; Franks, J. A. *J. Heterocycl. Chem.* **1965**, *2*, 37.
(19) Bartoshuk, L.; Lee, C.-H.; Scarpellino, R. *Science* **1972**, *178*, 988–990.

Scheme I[a]



[a] a = K_2CO_3, RX, DMF; b = H_2; Pd/C, 10% KOH; c = Ac_2O, pyr; d = NBS, CCl_4, $(PhCOO)_2$; e = KOH, EtOH; f = $HClO_4$, H_2O, dioxane; g = 10% KOH; h = Et_3N, DMF, catechol sulfate; i = KOH, H_2O.

Scheme II[a]



[a] a = K_2CO_3, DMF, CH_2–$CHCH_2CHBrCOO$-t-C_4H_9; b = H_2SO_4, dioxane, H_2O; c = H_2, Pd/C, t-BuOH–CH_2Cl_2; d = KOH, H_2O; e = NaOH; f = K_2CO_3, DMF, $Br(CH_2)_3Br$; g = $P(OCH_3)_3$; h = $(CH_3)_3$-SiBr, CH_2Cl_2; i = H_2, Pd/C, CH_3OH; j = KOH.

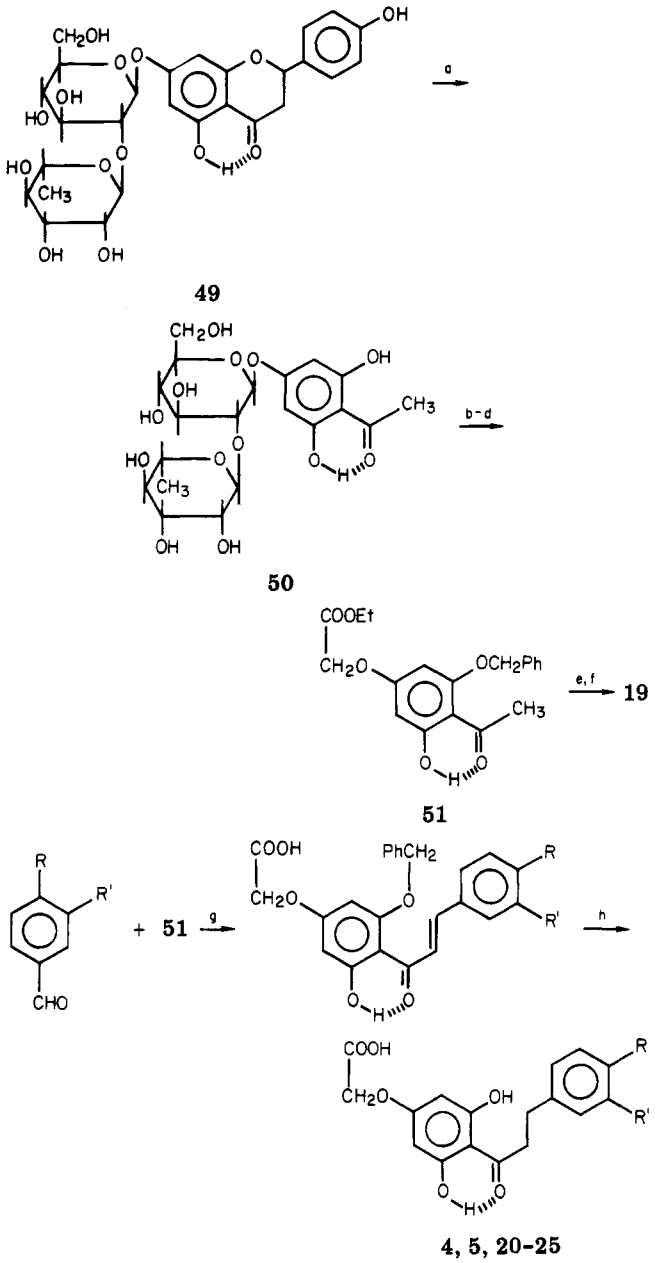
"folded" conformation, as required by a flavanone ring system, may yield a compound of ground-state energy close to a DHC's active conformation but with little effect on temporal properties. Thus, hypothesis B is not supported. It is interesting to note, however, that flavone **12**, a totally flat version of sweet flavanone **11**, is completely tasteless. Similar observations have been made by Yamato and co-workers[2s] on planar members of the isocoumarin family of sweeteners.

Flavanones, such as **9**–**11**, have two conformational options available to them, in which the aromatic moiety appended to the pyranone ring occupies either pseudoequatorial or pseudoaxial positions. The pseudoequatorial conformer yields a molecule with a generally planar topography, while the pseudoaxial conformer yields a wedge-shaped molecular topography. The observation that the planar flavone **12** is quite tasteless suggests that the active conformation of **9**–**11** is wedge shaped with the aromatic ring pseudoaxial to the pyranone ring. It is expedient to extend this rationalization to dihydrochalcones. Thus, the active conformation of DHC's would be expected to be a wedge-shaped version of the folded conformer shown in Figure 5, in which the $ArCOCH_2CH_2$ moiety is roughly planar and the Ar' is attached to the terminus at an oblique angle. We have previously predicted this to be the active conformation for sweet DHC's for other reasons.[2a] Hodge and Inglett[20] have suggested this type of active conformer for NHDHC by analogy with the topography of conformationally less flexible intensely sweet compounds, such as stevioside, osladin, and glycyrrhizic acid. Further support for the folded-wedge active conformation of DHC's is embodied in the observation that chalcones **13** and **14**, which likely exist in a planar conformation, are tasteless. Recently, however, Pfliegel and co-workers reported the synthesis of the "strongly sweet" chalcone **15**.[2m,n] The sweet taste of **15**, though found by us (sweet/bitter, 28:72) to be not nearly as clean as claimed, was observed by us and is difficult to reconcile in view of the tasteless natures of **13** and **14**.

Other compounds prepared include the tasteless deoxybenzoin **16**, which by comparison with the sweet DHC **3** suggests that the two aromatic rings must be connected by a minimum of three atoms. This result contrasts with that of Yamato and co-workers[2u,v] on 1,ω-diarylalkane phyllodulcin models where the 1,2-diarylethane has a greater potency (300× sucrose) than the 1,3-diarylpropane (1–10× sucrose). The glucose acetal of isovanillin **17**, attractive from a safety point of view since breakdown would likely yield only the common food constituents isovanillin and glucose, was, unfortunately, without sweet taste. The DHC-like variant, **18**, of the sweet-taste modifying agent[19] chlorogenic acid (**55**) was disappointingly tasteless also.

(20) Hodge, J. E.; Inglett, G. E. In "Symposium: Sweeteners"; Inglett, G. E., Ed.; Avi: Westport, CT, 1974; Chapter 20.

Scheme III[a]



[a] a = KOH, H_2O; b = K_2CO_3, $PhCH_2Cl$, DMF, c = H_2SO_4, EtOH, H_2O; d = K_2CO_3, $ClCH_2COOEt$, DMF; e = 10% KOH; f = H_2, Pd/C, EtOH, THF; g = 60% KOH, EtOH, THF; h = H_2, Pd/C, EtOH, THF.

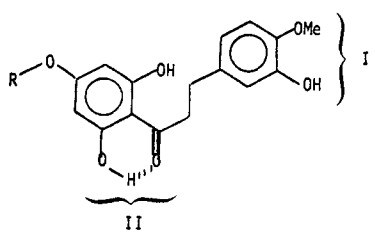
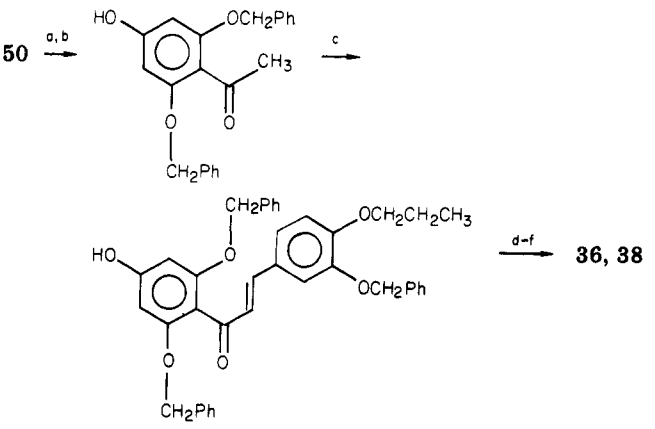


Figure 6. Proposed binding sites of sweet DHCs.

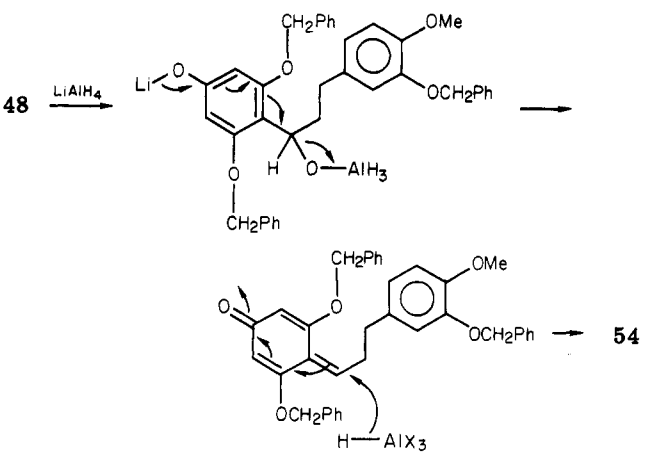
The concept that sweet DHC's may be involved in very strong receptor binding due to the interactions of two strong binding sites, as in a bidentate ligand (hypothesis C), was then studied. If two such centers exist, it seems most reasonable that they involve the groups shown in Figure 6. If sweet DHC's contain two binding centers, it

Scheme IV[a]



[a] a = K_2CO_3, $PhCH_2Cl$, DMF; b = H_2SO_4, EtOH, H_2O; c = 60% KOH, EtOH, THF, 3-$PhCH_2O$-4-PrO-C_6H_3CHO; d = K_2CO_3, RX' DMF; e = H_2, Pd/C, EtOH, THF; f = NaOH.

Scheme V

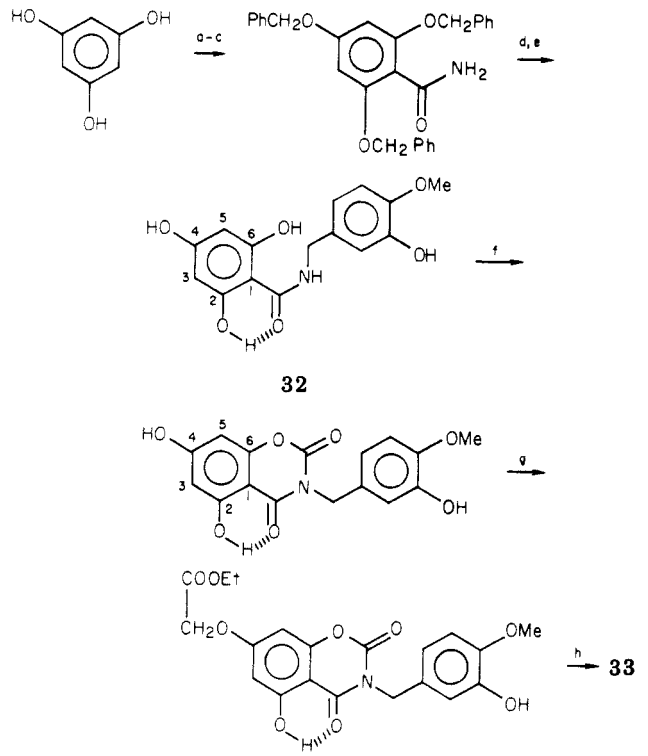


was of interest to determine the sensory properties of monodentate versions, since, if sweet, a lowered receptor association constant may result in decreased aftertaste. Disappointingly, however, both the phloroacetophenone derivative **19**, which contains binding site II of the sweet DHC **2**, and the dihydrocinnamic acid **6**, which contains binding site I, were without sweet taste.

A more subtle approach was then undertaken to moderate the binding ability of binding sites I and II by making various changes in the functionality involved. The functional requirements of binding site I appear to be quite rigid. Removal of the hydroxy–methoxy functionality eliminates all sweet taste (cf. **20**), while introducing a bond between the methoxy methyl and hydroxy oxygen functions (cf. **21**) has the same effect. Substitution of an amino group for the hydroxyl group (cf. **23**) also eliminates sweetness. Yamato and co-workers[25] noted that analogous amino substitution in sweet 1,2-diarylethanes causes a similar loss of sweetness. Thus, it appears that binding site I must contain a hydroxyl group capable of donating an acidic hydrogen in an intermolecular hydrogen bond. The strength of the competitive *intramolecular* interaction, as it exists in ortho-substituted phenols, has recently been studied in detail by Kollman and co-workers.[21] The availability of the acidic hydrogen atom for intermolecular binding with the receptor should depend on the strength

(21) Dietrich, S. W.; Jorgensen, E. C.; Kollman, P. A.; Rothenberg, S. *J. Am. Chem. Soc.* **1976**, *98*, 8310–8324.

Scheme VI[a]

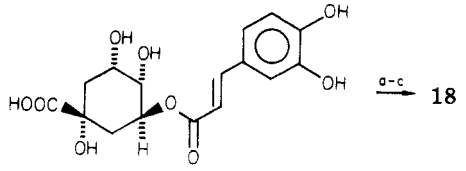


32

33

[a] a = K_2CO_3, $PhCH_2Cl$, DMF; b = $ClSO_2NCO$, Et_2O; c = KOH, THF, H_2O; d = NaH, 3-$PhCH_2O$-4-MeO-$C_6H_3CH_2Cl$, toluene; e = H_2, Pd/C, EtOAc; f = $PhCH_2OCOCl$, pyr; g = K_2CO_3, $ClCH_2COOEt$, DMF; h = KOH, H_2O.

Scheme VII[a]



55

[a] a = K_2CO_3, $PhCH_2Cl$, DMF; b = K_2CO_3, CH_3I, DMF; c = H_2, Pd/C, THF.

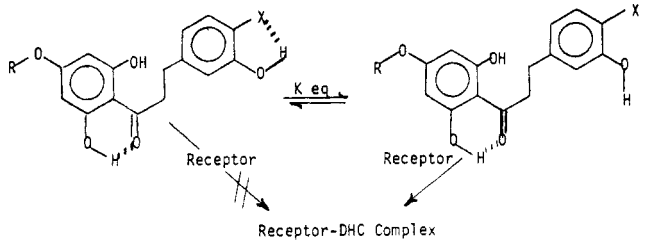


Figure 7. Intra- vs. intermolecular binding of C-4′ substituted DHCs.

of the intramolecular bond, as illustrated in Figure 7. Thus, when the nature of X favors intramolecular H bonding, the DHC may be less capable of strong receptor interaction such that overall receptor binding be decreased with concomitant reduction in sweet taste linger. Unfortunately, in the case of the aminomethyl isostere (**25**) of sweet DHC **2**, sweet taste is eliminated entirely. The intramolecular bond may be of such strength as to render the hydroxyl hydrogen unavailable for intermolecular interaction. Modification of binding site I so as to either eliminate (cf. **5**, X = H) or reduce (cf. **24**, X = Cl) intramolecular binding results in either dramatic reduction, in

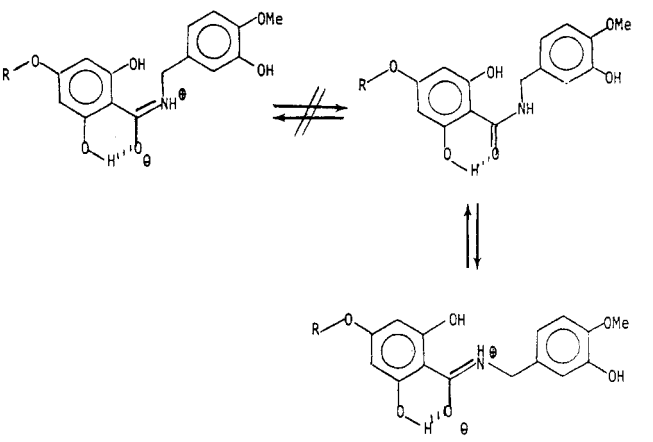


Figure 8. Amide resonance in **32** and **33**.

the case of **5**, or in elimination, as in the case of **24**, of sweetness. Kollman's results,[21] where the hydrogen bond strength in 2-chlorophenol (1.62 kcal/mol) is found to be less than in 2-methoxyphenol (2.00 kcal/mol), indicate that the acidic hydroxyl of chloro analogue **24** should be more available for intermolecular hydrogen bonding than in the sweet methoxy compound **2**. Thus, it appears that binding site I must contain, in addition to an acidic hydroxyl, a very special type of hydrogen-accepting moiety apparently satisfied only by an alkoxy group. These substituents may be considered as an A-H/B system of the type proposed by Shallenberger[22] as necessary for sweet taste. Thus, it appears that the taste of DHC's is optimal with the natural methoxy–hydroxy functionality of binding site I. The observation of similar effects in 1,2-diarylethanes, flavanones, and simple DHC's has recently been reviewed by Yamato and Hashigaki.[2x]

The effects of modification of binding site II were also studied in the hope that weakening of this binding center would result in diminished aftertaste without elimination of sweetness. Substitution of the keto oxygen of binding site II with an imine NH (cf. **27**), which presumably would increase the strength of the intramolecular H bond, surprisingly eliminated all taste. Similarly, the oxime **26**, which was evaluated as a mixture of syn and anti isomers, was completely lacking in sweet taste. A lesser increase in the strength of the intramolecular H bond of binding site II is embodied in amides **32** and **33**, which are to be compared with the intensely sweet DHC's **3** and **2**, respectively. The tasteless natures of **32** and **33** seem quite remarkable but may be a result of their existence, due to amide resonance, exclusively in the "elongated" conformation, as shown in Figure 8, rather than the "folded" conformation of Figure 5. Analogously, the amide analogues of the intensely sweet dihydroisocoumarins were found by Yamato and co-workers to be tasteless.[2r]

If the intramolecular H bonding is completely removed through saturation of the carbonyl moiety, as in **28** and **29**, which may be compared with **3** and **2**, respectively, all sweet taste is lost. Thus, the carbonyl functionality has major importance for sweetness. An interesting intermediate in the preparation of imine **27** was the isoxazole **30**. This compound, which lacks H-bonding functionality at binding site II, surprisingly had a moderate-intensity, clean, sweet taste. Apparently, binding site II is acting via dispersion, charge transfer, or other types of bonding rather than H bonding. The sulfopropyl-substituted isoxazole **31** was quite similar to the carboxymethyl derivative **30**,

(22) Shallenberger, R. S.; Acree, T. E. *Nature (London)* **1967**, *216*, 480.

but, disappointingly, neither compound showed diminished sweet taste linger, as indicated by aftertaste response.

In summary, with respect to testing hypothesis C, all attempts to modify binding site I, so as to weaken receptor interaction with this center, resulted in loss of all sweetness. Similar strategy applied to binding site II resulted in the discovery of other functionality which allowed retention of sweet taste but which had no effect on lingering aftertaste. Thus, no evidence has been obtained to support hypothesis C.

The fourth hypothesis, which suggests that non-sucrose-like taste properties of NHDHC may be due to hydrophobic forces which cause slow diffusion of the compound to and from the receptor, was probed through the sensory analysis of DHC's **34–45**. If this hypothesis were valid, modifications which affect increase in gross hydrophilic character should result in improved taste-timing properties. In view of the recognized insensitivity of the A-ring C-4 hydroxyl substituent on sensory properties, this center was the obvious choice as the site of modification. First prepared were dicarboxylic acids **34** and **35**, which may be viewed as analogues resulting from substituting COONa and CH_2CH_2COONa, respectively, for a hydrogen atom of compound **2**. Surprisingly, both compounds were totally tasteless. These observations suggested that an upper limit may exist for gross hydrophilicity for DHCs and was surpassed by both **34** and **35**. Thus, the somewhat less hydrophilic dihydroxy acid **37**, which may be viewed as a $CH_2CHOHCH_2OH$-substituted derivative of **2**, was prepared. It also proved totally tasteless. Apparently, the dihydroxypropyl side chain still imparts too great a hydrophilicity increase for receptor interaction. It has been known for some time that the 4′-*O*-*n*-Pr analogue of NHDHC is intensely sweet.[2b] This suggested that the excessive hydrophilicity increase obtained on CH_2CH_2C-OONa and $CH_2CHOHCH_2OH$ substitution in **35** and **37** may be offset by substitution of *n*-Pr for Me in the B ring. Thus, DHC's **36** and **38** were prepared. Much to our surprise, both were totally tasteless. Interestingly, a slight increase of hydrophilicity as embodied in DHC **39**, which may be viewed as DHC **2** containing a $CH_2CH_2CH_2OH$ substituent, does not eliminate sweet taste, although the intensity is reduced by an order of magnitude. DHC **45**, which illustrates the effect of a moderate hydrophilicity increase of the previously described[2i] intensely sweet carboxypropyl-DHC, was found to be cleanly and intensely sweet (440 ± 70× sucrose) but to have a strong lingering aftertaste. It was not evaluated by the TI method. Amino DHC's **41** and **42** illustrate the effect of a positively charged hydrophilic group. Both compounds are bittersweet at acidic pH, thus suggesting that a negatively charged or neutral side chain is optimal for clean sweetness.

DHC's **40**, **43**, and **44** were all found to be cleanly and intensely sweet. The keto acid **40** illustrates the result of a modest hydrophilicity increase of the earlier described, intensely sweet carboxypropyl-DHC,[2i] and **43** and **44** illustrate the result of substitution of the phosphomethyl (CH_2PO_3HK) and sulfamo ($NHSO_3K$) moieties for the sulfomethyl group of the previously described,[2a] intensely sweet sulfopropyl-DHC. Aftertaste responses for all three compounds suggest no improvement in lingering sweetness effects. Nevertheless, these three compounds, along with sucrose, saccharin, NHDHC, DHC **2**, and MAG, were evaluated by the earlier discussed TI method. The taste appearance and extinction times thus determined are summarized in Tables II and III, respectively. Inspection of these data shows sucrose and saccharin both to exhibit rapid appearance times of 5 s with relatively short extinction times of 24 and 42 s, respectively.[23] The dihydrochalcones show significantly longer appearance times, ranging from 7 to 11 s with extinction times tightly grouped between 56 and 68 s. All of these compounds show a statistically significant longer extinction time than sucrose but cannot be distinguished from each other. The data on MAG are quite remarkable with respect to the length of the appearance (23 s) and extinction (133 s) times and thus clearly show the DHC class of sweeteners to have temporal properties intermediate between sucrose and MAG.

A survey of the foregoing discussion leads to the conclusion that none of the four hypotheses proposed as a rationale for the lingering sweet aftertaste of DHC's is supported by the results of our study. How then can the non-sucrose-like temporal properties of dihydrochalcones be understood? Recently, Boudreau[24] has suggested that two types of sweet taste sensation exist, $sweet_1$ and $sweet_2$, which result from stimulation of sensory cells found on the fungiform papillae (tongue anterior) and circumvallate papillae (tongue posterior), respectively. He further states that DHC's are active stimuli for $sweet_2$ sensation, while sucrose and sweet amino acids are active stimuli for $sweet_1$ sensation. In our experience, the sweet taste of DHC's is noted at first on the tongue anterior, with a subsequent stronger and longer lasting sweetness on the tongue posterior. Thus, sweet DHC's may be giving both $sweet_1$ and $sweet_2$ sensations, which arise by interaction with two different receptor systems. The problem of reducing sweet aftertaste of a DHC may therefore be one of reducing the ability of the molecule to interact with the $sweet_2$ receptor while not affecting its binding with the $sweet_1$ receptor.

The postulation of multiple receptors for the sensation of sweet taste is not new. Faurion and co-workers[25] have presented evidence for the existence of four receptor systems. In addition, Beets[26] has comprehensively presented some excellent intuitive arguments for multiple receptors. Shallenberger[22] and Birch,[10a] on the other hand, cling to the "one receptor" concept of sweet taste perception. In our view, the argument over one vs. multiple sweet taste receptors is largely a matter of semantics. Intuitively, it is most difficult to accept receptor binding of sweet compounds, as divergent in structure as sucrose, chloroform, dulcin, NHDHC, aspartame, monellin, etc., which involves interaction with precisely the same receptor site functionality. We prefer to visualize sweet taste receptors as groups of identical *dynamic* sites on taste cell membrane-bound proteins. These receptors are capable of presenting a variety of protein side chain functionalities to prospective tastant molecules. Interaction with the correct combination of substituents may then induce a protein conformational change, followed by taste cell depolarization and initiation of sweet taste response. Such

(23) These results may be contrasted with those of ref 10a where an AT of ca. 1–2 s and ET of ca. 15 s were determined for 10% sucrose. The data from ref 11a suggests somewhat higher values (AT ≃ 12 s, ET ≃ 33 s), which is doubtlessly due, at least partially, to the higher concentration (0.32 M) of sucrose employed. The disparity between these literature results and our data can be rationalized by the differences in sensory methods used.

(24) Boudreau, J. C.; Oravec, J.; Hoang, N. K.; White, T. D. In "Food Taste Chemistry"; Boudreau, J. C., Ed.; American Chemical Society: Washington, D.C., 1979; Chapter 1, p 14.

(25) Faurion, A.; Saito, S.; MacLeod, P. In "Olfaction and Taste"; LeMagnen, J.; MacLeod, P., Ed.; Information Retrieval: London, 1977; Volume VI, p 60.

(26) Beets, M. G. J. "Structure-Activity Relationships in Human Chemoreception"; Applied Science: London, 1978, Chapter 3.

a general receptor site would contain the binding functionality to accommodate most, if not all, of the structurally quite divergent sweet compounds. Dihydrochalcones and other sweeteners with lingering sweet aftertaste, such as MAG, may be exceptional, however, since the major portion of their sensation seems to derive from a region of the tongue not particularly sensitive to other sweeteners.

Very recently, Birch and co-workers[10a] have proposed an "orderly queue" hypothesis to rationalize the peculiar temporal properties of sweet compounds with strong lingering effects. In essence, they suggest the formation of an "orderly queue" of tastant molecules at the receptor site, such that the rate of passage through the queue is responsible for temporal effects. Sweeteners such as sucrose are said to form and pass through queues quickly, while strong lingering aftertaste sweeteners such as thaumatin do so relatively slowly, thus leading to the observed temporal effects. At present, the arguments for the "orderly queue" hypothesis do not seem compelling. Accordingly, we favor a rationalization of temporal effects by invoking a second receptor site for sweeteners with lingering aftertaste, as suggested earlier by Boudreau.[24]

Conclusions

As a result of the studies of this and earlier papers, the following conclusions concerning the SAR of dihydrochalcone sweeteners may be drawn: (1) The A ring 2,6-dihydroxy ketone moiety, though not essential for weak to moderate potency sweet taste, is required in entirety for high sweetness potency (cf. **30**, **31**, and mono- and norhydroxy analogues cited in ref 2a and 2i). (2) The unit, $-CO(CH_2)_n-$, bridging the gap between the two aromatic rings results in optimal sweetness potency with $n = 2$. Substitution of the $-(CH_2)_2-$ subunit with either hydrophobic or hydrophilic substituents eliminates all sweet taste (cf. **16**, ref 2x for methyl- and ref 2z for hydroxy-substituted compounds). (3) The B-ring methoxy–hydroxy functionality is essential for clean, sweet taste (cf. **4**, **5**, **20–25**, **36**, **38**, and other compounds discussed in ref 1c). (4) The A-ring C-4 hydroxy moiety may be substituted with an apparently limitless number of hydrophilic side chains without loss of sweet taste, so long as the net molecular hydrophobe–hydrophile balance remains within a narrow range (cf. **1**, **2**, **3**, **39**, **40**, **43–45**, and the many compounds cited in ref 2).

Experimental Section

Synthetic Procedures. All organic starting materials and reactants were obtained from Aldrich Chemical Co., except for hesperetin, naringin, and chlorogenic acid which were obtained from Sigma Chemical Co. All inorganic reagents were obtained from J. T. Baker Chemical Co., except for $LiAlH_4$ (Alfa Chemical Co), 5% palladium on carbon (Pd/C) hydrogenation catalyst (Engelhard Minerals & Chemicals Corp.), Amberlyst 15 ion-exchange resin (Mallinckrodt Chemical Works), and anhydrous HCl (Matheson Gas Corp.). Solvents used were reagent grade and obtained from either J. T. Baker Chemical Co. or Fisher Scientific Co. The following reaction solvents and reagents were additionally purified by distillation from (drying agent) THF ($LiAlH_4$), DME ($LiAlH_4$), dioxane ($LiAlH_4$), Et_2O ($LiAlH_4$), DMF (CaH_2), Me_2SO (CaH_2), pyridine (BaO), Et_3N (P_2O_5), and CH_2Cl_2(P_2O_5), and stored over activated (400 °C, 3 h) molecular sieves (type 3Å, J. T. Baker Chemical Co.).

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 infrared spectrometer, ultraviolet–visible (UV–vis) spectra on a Cary Model 119 spectrometer, and proton magnetic resonance spectra (NMR) on a Varian T-60A spectrometer and are reported as parts per million (ppm, δ) relative to tetramethylsilane. Combustion analyses were performed by the Microanalytical Laboratory, Stanford University, Stanford, CA.

Analytical thin-layer chromatography (TLC) was carried out on prelayered silica gel F-254 plates (E. Merck, Darmstadt, Germany), visualizing with either UV light or iodine staining. Preparative thick-layer chromatography was carried out on 20 × 20 cm plates of 2-mm thickness prepared of silica gel PF-254 (E. Merck). Preparative radial chromatography was carried out on silica gel G (E. Merck) using a Harrison Research (Palo Alto, CA) chromatotron. Column chromatography was carried out on 60–200 mesh silica gel powder (J. T. Baker Chemical Co.). Vapor phase chromatography was carried out on a Varian Associates Aerograph Model 920.

High-pressure liquid chromatography (HPLC) was performed on a Waters Associates Instrument equipped with a Model 660 solvent programmer and two Model 6000A pumps. Analytical work was carried out on a μBondapak C-18 reverse-phase column (30 cm × 4 mm) eluting with a linear program (15 min, 2 mL/min) of 10 to 100% CH_3OH in 0.03 M KH_2PO_4 buffer. Preparative work was done on a Porasil-B C-18 reverse-phase column ($^3/_8$ in. × 4 ft.), which was eluted with a linear program (60 min, 8 mL/min) of 10–100% CH_3OH in distilled H_2O. The detector employed was a Schoeffel Model SF 770 spectroflow monitor equipped with a Model GM770 monochromator.

Unless otherwise indicated, all reactions were carried out under an inert atmosphere of argon at ambient temperature with vigorous stirring, magnetic for homogeneous and overhead for nonhomogeneous reactions, and all reagents employed were anhydrous. Standard workup of reactions employing H_2O-immiscible solvents (e.g., Et_2O, CH_2Cl_2, toluene, etc.) involved addition of H_2O neutralization with aqueous acid or base, extraction of the mixture with an appropriate organic solvent (Et_2O, $CHCl_3$, EtOAc, etc.), drying the combined extracts over $MgSO_4$, and concentration in vacuo. Standard workup of reactions employing H_2O-miscible solvents (e.g., THF, DME, CH_3OH, etc.) involved dilution with H_2O, neutralization with aqueous acid or base, and concentration in vacuo. The residue was extracted into an appropriate solvent (Et_2O, $CHCl_3$, EtOAc, etc.), the combined extracts of which were dried over $MgSO_4$ and concentrated in vacuo. Standard workup of reactions employing DMF and Me_2SO solvents involved dilution with H_2O, neutralization, extraction of the mixture with an appropriate solvent (Et_2O, EtOAc, etc.), washing the combined extracts with H_2O (6 times), drying over $MgSO_4$, and concentration in vacuo. Standard workup of reactions employing pyridine involved pouring the reaction mixture into 5 volumes of 10% HCl and extraction of the product into an appropriate solvent (Et_2O, EtOAc, etc.), the combined portions of which were washed with 10% HCl (4 times), dried over $MgSO_4$, and concentrated in vacuo. Hydrogenation reactions were carried out on a Parr hydrogenation apparatus. Standard workup involved filtration through Celite and neutralization with 10% HCl, if the solvent was aqueous base, followed by product isolation either by filtration or, if an oil, by extraction with EtOAc. If the solvent was organic, it was simply removed in vacuo to yield the product.

Carboxylic acids were converted to sodium salts by potentiometric titration, as CH_3OH or THF–H_2O solutions, with 0.200 N NaOH using a Brinkmann Metrohm Herisau Potentiograph E576. The resultant solution was concentrated to dryness in vacuo, after which the residue was dissolved in distilled H_2O (10 mL/0.1 g). This solution was filtered through a 0.45-μm type HA Millipore filter and lyophilized to give the sodium salt as a flocculent solid, which was stored under argon at 0 °C.

Caution: 1,3-Propane sultone has been shown to be a potent carcinogen in animals![27] Reactions employing it should be handled with extreme caution.

The syntheses of compounds **2**,[28] **3**,[2a] **6**,[29] **8**,[30,31] **34**,[28] and **35**[28]

(27) (a) Druckey, H.; Kruse, H.; and Preussmann, R. *Naturwissenschaften* **1968**, *55*, 449. (b) Doak, S. M. A.; Simpson, B. J. E.; Hunt, P. F.; and Stevenson, D. E. *Toxicology* **1976**, *6*, 139. (c) Ulland, B.; Finkelstein, M.; Weisburger, E. K.; Rice, J. M.; Weisburger, J. H. *Nature (London)* **1971**, *230*, 460.

(28) DuBois, G. E.; Crosby, G. A.; Saffron, P. *Synth. Commun.* **1977**, *7*, 49–56.

(29) Moore, M. B.; Wright, H. B.; Vernsten, M.; Freifelder, M.; Richards, R. K. *J. Am. Chem. Soc.* **1954**, *76*, 3656–3662.

have been previously described, while congener 7 was obtained from Aldrich Chemical Co.

2,3′,4′,6-Tetrahydroxy-4-(carboxymethoxy)dihydrochalcone Sodium Salt (4). A mixture of 6.9 g (50 mmol) of 3,4-dihydroxybenzaldehyde, 27.6 g (200 mmol) of K_2CO_3, 25.2 g (200 mmol) of $PhCH_2Cl$, and 100 mL of DMF was reacted for 18 h. Standard workup and recrystallization (hexane–EtOAc) yielded 13.0 g (82%) of 3,4-(dibenzyloxy)benzaldehyde (**56**) as amber clusters.

A solution of 150.7 g (0.244 mol) of naringin in 1370 mL of 10% KOH was refluxed for 4 h. After cooling to 10–15 °C, the reaction mixture was acidified to pH 5.5 and filtered. Recrystallization of the filter cake from H_2O yielded 79.5 g (64%) of 2,6-dihydroxy-4-(β-neohesperidosyloxy)acetophenone (**50**) as colorless clusters. A mixture of 102.6 g (0.2 mol) of **50**, 76 g (0.6 mol) of $PhCH_2Cl$, 82.9 g (0.6 mol) of K_2CO_3, and 650 mL of DMF was reacted for 7 days. After addition of 600 mL of H_2O, the reaction mixture was acidified to pH 5.5 with 10% HCl and concentrated in vacuo at a temperature <60 °C. The crude oily 2-hydroxy-4-β-neohesperidosyloxy-6-(benzyloxy)acetophenone thus obtained was dissolved in a mixture of 1250 mL of EtOH and 620 mL of 3% H_2SO_4. The resultant solution was refluxed for 46 h, after which standard workup and recrystallization (EtOH–H_2O) yielded 21.96 g (42%) of 2,4-dihydroxy-6-(benzyloxy)acetophenone (**57**) as colorless needles: mp 140–144.5 °C; IR (KBr) 2.90 (OH), 6.05 (C=O) μm; NMR (acetone-d_6) δ 2.50 (s, 3 H, $ArCOCH_3$), 5.17 (s, 2 H, $ArOCH_2Ph$), 5.95 (d, 1 H, J = 2 Hz, ArH), 6.12 (d, 1 H, J = 2 Hz, ArH), 7.42 (s, 5 H, PhH). Anal. ($C_{15}H_{14}O_4$) C, H.

A mixture of 10 g (38.8 mmol) of **57**, 9.5 g (77.5 mmol) of ethyl chloroacetate, 5.9 g (42.7 mmol) of K_2CO_3, and 75 mL of DMF was reacted for 24 h, after which standard workup and recrystallization (EtOH) yielded 10.3 g (76%) of 2-hydroxy-4-(carbethoxymethoxy)-6-(benzyloxy)acetophenone (**51**) as colorless clusters: mp 90–92 °C; IR (KBr) 2.85 (OH), 5.70 (ester C=O), 6.15 (ketone C=O) μm; NMR (acetone-d_6) δ 1.27 (t, 3 H, J = 7 Hz, $COOCCH_3$), 2.52 (s, 3 H, $ArCOCH_3$), 4.25 (q, 2 H, J = 7 Hz, $COOCH_2C$), 4.95 (s, 2 H, $ArOCH_2COO$), 5.23 (s, 2 H, $ArOCH_2Ph$), 6.03 (d, 1 H, J = 3 Hz, ArH), 6.27 (d, 1 H, J = 3 Hz, ArH), 7.50 (s, 5 H, PhH), 13.91 (s, 1 H, ArOH). Anal. ($C_{19}H_{20}O_6$) C, H.

To a solution of 1.44 g (4.54 mmol) of aldehyde **56** and 784 mg (2.27 mmol) of acetophenone **51** in 16 mL of EtOH–THF (1:1) was added 2.8 mL of warm 60% KOH. After 18 h, standard workup and recrystallization (EtOH) yielded 1.23 g (85%) of 2-hydroxy-3′,4′,6-tris(benzyloxy)-4-(carboxymethoxy)chalcone (**58**) as yellow needles: mp 187.5–188 °C; IR (KBr) 2.9–4.2 (OH), 5.70 (carboxylic acid C=O), 6.14 (ketone C=O) μm; UV (CH_3OH) λ_{max} 372 nm (ε 29 600); NMR (acetone-d_6) δ 4.80 (s, 2 H, $ArOCH_2COO$), 5.15 (s, 6 H, $PhCH_2O$), 6.08 (d, 1 H, J = 2 Hz, ArH), 6.32 (d, 1 H, J = 2 Hz, ArH). Anal. ($C_{38}H_{32}O_8$) C, H.

Hydrogenation of 1.12 g (1.79 mmol) of **58** over 1.1 g of Pd/C at 3 atm for 18 h as a solution in 70 mL of THF–EtOH (4:3), followed by standard workup and recrystallization (EtOH–H_2O), yielded 434 mg (70%) of **4** (H) as a flocculent white solid: mp 230–232 °C dec; IR (KBr) 2.95–4.25 (OH), 5.74 (carboxylic acid C=O), 6.32 (ketone C=O) μm; UV (CH_3OH) λ_{max} 285 nm (ε 22 920); NMR (acetone-d_6) δ 2.83 (t, 2 H, J = 8 Hz, $ArCOCCH_2Ar'$), 3.36 (t, 2 H, J = 8 Hz, $ArCOCH_2$), 4.70 (s, 2 H, $ArOCH_2COO$), 6.00 (s, 2 H, ArH). Anal. ($C_{17}H_{16}O_8 \cdot 0.25H_2O$) C, H.

A 334-mg sample of **4** (H) was titrated with NaOH by the general procedure to give 358 mg of **4** as a flocculent white solid.

2,3′,6-Trihydroxy-4-(carboxymethoxy)dihydrochalcone Sodium Salt (5). To a solution of 1.96 g (5.7 mmol) of acetophenone **51** and 1.39 g (11.4 mmol) of 3-hydroxybenzaldehyde in 30 mL of EtOH–THF (2:1) was added 8 mL of warm 60% KOH. After 18 h, standard workup and recrystallization (EtOH) yielded 1.67 g (72%) of 2,3′-dihydroxy-6-(benzyloxy)-4-(carboxymethoxy)chalcone (**59**) as orange needles: mp 208–209 °C; IR (KBr) 2.9–4.2 (OH), 5.78 (carboxylic acid C=O), 6.20 (ketone C=O) μm; UV (EtOH) λ_{max} 348 nm (ε 25 400); NMR (acetone-d_6) δ 4.80 (s, 2 H, $ArOCH_2COO$), 5.22 (s, 2 H, $ArOCH_2Ph$), 6.09 (d, 1 H, J = 2 Hz, ArH), 6.35 (d, 1 H, J = 2 Hz, ArH). Anal. ($C_{24}H_{20}O_7$) C, H.

Hydrogenation of 1.00 g (2.97 mmol) of **59** over 1 g of Pd/C catalyst at 3 atm for 18 h as a solution in 40 mL of THF–EtOH (25:15), followed by standard workup and recrystallization (EtOH–H_2O), yielded 0.80 g (81%) of **5** (H) as a white powder: mp 210–212 °C dec; IR (KBr) 2.9–4.2 (OH), 5.74 (carboxylic acid C=O), 6.13 (ketone C=O) μm; UV (CH_3OH) λ_{max} 284 nm (ε 19 880); NMR (acetone-d_6) δ 2.8–3.4 (m 4 H, $ArCOCH_2CH_2Ar'$), 4.72 (s, 2 H, $ArOCH_2COO$), 6.05 (s, 2 H, ArH). Anal. ($C_{17}H_{16}O_7$) C, H.

A 467-mg sample of **5** (H) was titrated with NaOH by the general procedure to give 517 mg of **5** as a flocculent white solid.

3′,5-Dihydroxy-4′-methoxyflavanone (9). A mixture of 100 mL of DMF, 1.52 g (10 mmol) of 2,6-dihydroxyacetophenone, 4.14 g (30 mmol) K_2CO_3, and 3.8 g (30 mmol) of $PhCH_2Cl$ was reacted at 65 °C for 15 h, followed by 3 h at 100 °C. Standard workup, followed by concentration in vacuo (0.1 mm, 70 °C) to remove excess $PhCH_2Cl$, yielded 3.32 g (99%) of 2,6-bis(benzyloxy)-acetophenone (**60**) as a colorless oil, which solidified on standing. A mixture of 3.32 g (10 mmol) of **60** and 2.42 g (10 mmol) of 3-(benzyloxy)-4-methoxybenzaldehyde was dissolved in 10 mL of EtOH, after which 15 mL of warm 60% KOH was added in one portion. After 4 days, standard workup, followed by recrystallization (EtOH–EtOAc), yielded 4.31 g (77%) of 2,3′,6-tris(benzyloxy)-4′-methoxychalcone (**61**) as a yellow solid: mp 124–126 °C; IR (KBr) 6.15, 6.28 (C=O) μm; UV (CH_3OH) λ_{max} 251 nm (ε 11 800), 341 (18 900); NMR ($CDCl_3$) δ 3.88 (s, 3 H, $Ar'OCH_3$), 5.08 (s, 4 H, $ArOCH_2Ph$), 5.10 (s, 2 H, $Ar'OCH_2Ph$), 6.47–7.50 (m, 23 H, ArH, Ar'H, $ArCOCHCHAr'$). Anal. ($C_{37}H_{32}O_5$) C, H.

A solution of 2.8 g (5 mmol) of **61** in 125 mL of glacial HOAc was treated with 12.5 mL of 47% HI at 45 °C. After 3 h, standard workup, followed by silica gel column chromatography (hexane–EtOAc) and recrystallization (hexane–EtOAc), yielded 233 mg (16%) of **9** as an off-white powder: mp 130–135 °C (lit.[2w] mp 136 °C); IR (KBr) 3.00 (OH), 6.11 (C=O) μm; UV (H_2O) λ_{max} 275 nm (ε 11 900); NMR ($CDCl_3$) δ 2.66–3.10 (m, 2 H, $ArCOCH_2$), 3.88 (s, 3 H, $Ar'OCH_3$), 5.27 (AB q, 1 H, J = 11 and 4 Hz, $ArCOCCHAr'$), 6.31–7.68 (m, 6 H, ArH, Ar'H), 11.08 (s, 1 H, ArOH). Anal. ($C_{16}H_{14}O_5$) C, H.

3′,5-Dihydroxy-4′-methoxy-7-(carboxymethoxy)flavanone Sodium Salt (10). Five milliliters of H_2O and 0.5 mL of 70% $HClO_4$ were added to a solution of 1.30 g (3.33 mmol) of 3′,5-dihydroxy-4′-methoxy-7-(carbethoxymethoxy)flavanone in 10 mL of dioxane. After refluxing for 2 h, the reaction mixture was allowed to slowly cool overnight. Filtration then yielded 871 mg (72%) of 3′,5-dihydroxy-4′-methoxy-7-(carboxymethoxy)flavanone [**10** (H)] as colorless granular crystals: mp 193–195.5 °C; IR (KBr) 2.5–4.3 (OH), 5.75 (carboxyl C=O), 6.12 (ketone C=O) μm; UV (MeOH) λ_{max} 237 nm (ε 23 600), 286 (20 000); NMR (acetone-d_6) δ 2.75–3.32 (m, 2 H, $ArCOCH_2$), 3.86 (s, 3 H, $Ar'OCH_3$), 4.76 (s, 2 H, $ArOCH_2COO$), 5.42 (AB q, 1 H, J = 11 and 3 Hz, $ArOCHAr'$), 12.03 (s, 1 H, ArOH). Anal. ($C_{18}H_{16}O_8 \cdot 0.5H_2O$) H; C: calcd, 58.53; found, 58.08. Titration of 400 mg of **10** (H) according to the general procedure yielded 381 mg of **10** as a flocculent solid.

3′,5-Dihydroxy-4′-methoxy-7-(sulfopropoxy)flavanone Potassium Salt (11). Congener **11**, an intermediate in the reported[2a] preparation of **53**, is obtained after recrystallization (H_2O) as pure white clusters: mp 249–256 °C dec; IR (KBr) 2.90 (OH), 6.22 (C=O), 9.1 (S=O), 11.3 (S=O) μm; UV (MeOH) λ_{max} 288 nm (ε 26 500), 334 (4100); NMR (D_2O) δ 1.65–3.10 (m, 6 H, $OCCH_2CH_2S$, $ArCOCH_2$), 3.77 (s, 3 H, $Ar'OCH_3$), 5.80 (br s, 1 H, ArH), 5.97 (br s, 1 H, ArH), 6.53–7.03 (m, 3 H, Ar'H). Anal. ($C_{19}H_{19}KO_9S \cdot H_2O$) C, H.

3′,5-Dihydroxy-4′-methoxy-7-(sulfopropoxy)flavone Potassium Salt (12). To a solution of 15.6 g (50 mmol) of hesperetin in 120 mL of pyridine was added 30.6 g (0.3 mol) of Ac_2O dropwise over 10 min at 0 °C. After warming to ambient temperature over 5 h, 0.15 mol of additional Ac_2O was added and reaction continued for 18 h. Standard workup, followed by trituration of the solid product with ether, yielded 21.4 g (100%) of 3′,5,7-triacetoxy-4′-methoxyflavanone (**62**) as a white solid. Five milligrams of benzoyl peroxide was reacted with 1.00 g (2.34 mmol) of **62** and 0.83 g (4.65 mmol) of *N*-bromosuccinimide in 50 mL of CCl_4

(30) Koo, J.; Fish, M. S.; Walker, G. N.; Blake, J. In "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 327.
(31) Dombrow, M.; Linnel, W. H. *J. Pharm. Pharmacol.* **1952**, *4*, 118–119.

according to the procedure of Looker and Holm.[32] Workup and recrystallization (EtOH) yielded 0.60 g (60%) of 3',5,7-triacetoxy-4'-methoxyflavone (**63**) as yellow clusters. One-hundred milliliters of 5% KOH was added to a solution of 4.26 g (10.0 mmol) of **63** in 150 mL of EtOH–dioxane (2:1). After 2 h, standard workup followed by recrystallization (EtOH–H_2O) yielded 2.87 g (96%) of 3',5,7-trihydroxy-4'-methoxyflavone (**47**) as a granular yellow solid. A mixture of 7 mL of DMF, 300 mg (1 mmol) of **47**, 152 mg (1.1 mmol) of K_2CO_3, and 244 mg of 1,3-propane sultone was reacted for 24 h, after which it was diluted with 10 mL of H_2O, neutralized with dilute HCl, and concentrated in vacuo to yield a yellow solid. Preparative HPLC of this crude product yielded 276 mg (65%) of **12** as a yellow flocculent solid: mp 285–290 °C dec; IR (KBr) 2.7–4.0 (OH), 6.02, 6.20 (C=O), 9.65 (S=O) μm; UV (MeOH) λ_{max} 253 nm (ε 20500), 269 (19300), 345 (22100); NMR (D_2O) δ 2.03 (br m, 2 H, $ArOCCH_2$), 2.93 (br m, 2 H, $ArOCCCH_2S$), 3.60 (s, 3 H, $Ar'OCH_3$), 4.00 (br m, 2 H, $ArOCH_2$), 5.70 (br s, 2 H, ArH), 6.33 (br m, 4 H, Ar'H, ArCOCH). Anal. ($C_{19}H_{17}KO_9S \cdot H_2O$) C, H.

2,3'-Dihydroxy-4-(carboxymethoxy)-4'-methoxychalcone Sodium Salt (13). Fifteen milliliters of warm 60% KOH was added in one portion to a solution of 1.52 g (10 mmol) of 2,4-dihydroxyacetophenone and 1.52 g (10 mmol) of 3-hydroxy-4-methoxybenzaldehyde in 10 mL of EtOH. After 30 min, 20 mL of additional EtOH was added and reaction continued for 15 h. The reaction mixture was then poured into 100 mL of ice-cold 10% HCl, after which the precipitate was filtered and recrystallized (EtOH–H_2O) to yield 1.16 g (41%) of 2,3',4-trihydroxy-4'-methoxychalcone (**64**) as a yellow solid. A solution–suspension of 0.86 g (3 mmol) of **64**, 0.46 g (3.3 mmol) of K_2CO_3, and 0.40 g (3.3 mmol) of ethyl chloroacetate in 20 mL of DMF was reacted at 20 °C for 15 h, followed by 8 h at 35 °C. Standard workup, followed by product isolation via thick-layer chromatography, yielded 0.288 g (25%) of 2,3'-dihydroxy-4-(carbethoxymethoxy)-4'-methoxychalcone (**65**) as yellow clusters. Ten milliliters of 5% KOH was added to 186 mg (0.5 mmol) of **65**. After 1 h, standard workup and recrystallization (EtOH–H_2O) yielded 103 mg (60%) of 2,3'-dihydroxy-4-(carboxymethoxy)-4'-methoxychalcone [**13** (H)] as orange granular crystals: mp 215–217 °C; IR (KBr) 3.06–4.2 (OH), 5.68 (carboxyl C=O), 6.12 (ketone C=O) μm; UV (MeOH) λ_{max} 242 nm (ε 9500), 258 (11400), 310 (12700), 377 (33500); NMR (acetone-d_6) δ 3.91 (s, 3 H, $Ar'OCH_3$), 4.83 (s, 2 H, $ArOCH_2$), 6.40–7.90 (m, 8 H, ArH, Ar'H, $ArCOCHCHAr'$). Anal. ($C_{18}H_{16}O_7 \cdot 0.25H_2O$) C, H. Titration of a 52-mg sample of **13**(H) to the sodium salt by the general procedure yielded 55 mg of **13** as an orange flocculent solid.

2,3',6-Trihydroxy-4-(carboxymethoxy)-4'-methoxychalcone Sodium Salt (14). Three millimoles (1.16 g) of 3',5-dihydroxy-7-(carbethoxymethoxy)-4'-methoxyflavanone was dissolved in 100 mL of 5% KOH. After 3 h, TLC analysis (PhH–MeOH–HOAc, 4.5:1.6:0.8) indicated that the reaction mixture consisted of ca. a 4:1 mixture of chalcone **14** (H) (R_f 0.56) and flavanone **10** (H) (R_f 0.73). This ratio was not significantly altered after an additional 27 h. The hydrolysis mixture was then cooled to 0 °C and poured into 100 mL of ice-cold 10% HCl. The precipitate was filtered, dissolved in cold EtOAc, dried over $MgSO_4$, and concentrated in vacuo at ca. 0 °C. Recrystallization of the residue (EtOAc–hexane–dioxane) yielded 433 mg (40%) of TLC pure **14** (H) as orange clusters: mp 196–198 °C dec; IR (KBr) 2.6–4.3 (OH), 5.77 (carboxylic acid C=O), 6.19 (ketone C=O) μm; NMR (acetone-d_6) δ 3.90 (s, 3 H, Ar'OMe), 4.73 (s, 2 H, $ArOCH_2$), 6.06 (s, 2 H, ArH), 7.11 (d, 1 H, J = 11 Hz, Ar'CH=), 7.88 (d, 1 H, J = 11 Hz, ArCOCH=). Anal. ($C_{18}H_{16}O_8 \cdot 0.75H_2O$) C, H. Titration of a 350-mg sample of **14**(H) to the sodium salt by the general procedure yielded 383 mg of **14** as a flocculent yellow solid.

HPLC analysis of an aqueous solution of **14** immediately after preparation showed only one component having t_R = 12.0 min. HPLC analysis of a second aliquot from this solution after 10.0 min, while monitoring at 300 nm [ε (**14**) at 300 nm = 4.22×10^3; ε (**10**) at 300 nm = 4.48×10^3], indicated that the solution contained a 63:37 mixture of **14** and **10** (t_R = 10.8 min). Thus, 37% cyclization of chalcone **14** to flavanone **10** occurs within 10 min at ambient temperature.

2,3'-Dihydroxy-4-(sulfopropoxy)-4'-methoxychalcone Potassium Salt (15). This compound was prepared by a modification of the procedure described by Pfliegel and co-workers.[2m] Twenty-five milliliters of DMF was added to a mixture of 1.25 g (10 mmol) of 2,4-dihydroxyacetophenone, 1.32 g (12.5 mmol) of Na_2CO_3, and 1.53 g (12.5 mmol) of 1,3-propane sultone. The resultant mixture was reacted for 8 days, after which it was concentrated to dryness in vacuo. The residue was dissolved in 50 mL of H_2O. The resultant solution was acidified to pH 1 with 10% HCl and extracted with EtOAc (3 × 25 mL). The aqueous solution was then neutralized with 5% KOH and concentrated in vacuo until crystallization began. After this mixture was cooled in an ice bath for several hours, filtration and drying in vacuo yielded 1.61 g (54%) of 2-hydroxy-4-(sulfopropoxy)acetophenone, potassium salt (**66**), as a light tan solid. To a solution of 1.61 g (5.15 mmol) of **66** and 0.79 g (5.2 mmol) of 3-hydroxy-4-methoxybenzaldehyde in 10 mL of EtOH–H_2O (1:1) was added 15 mL of warm 60% KOH in one portion. After 18 h, 10 mL of H_2O was added and stirring continued. After 42 h, 5.2 mmol of additional 3-hydroxy-4-methoxybenzaldehyde was added and stirring continued for another 24 h, after which the reaction mixture was neutralized with 10% HCl and extracted with EtOAc (3 × 25 mL). The aqueous solution was concentrated to dryness in vacuo, after which the residue was recrystallized (H_2O) to yield 1.44 g (63%) of **15** as tiny yellow needles: mp 259–262 °C (lit.[2m] mp 273–276 °C); IR (KBr) 2.89 (OH), 6.13 (C=O) μm; UV (H_2O) λ_{max} 258 nm (ε 9840), 376 (30700); NMR (Me_2SO-d_6) δ 3.30 (m, 2 H, CH_2S), 3.83 (s, 3 H, $Ar'OCH_3$), 4.13 (t, 2 H, J = 6 Hz, $ArOCH_2$), 7.70 (s, 2 H, CH=CH). Anal. ($C_{19}H_{19}KO_8S \cdot H_2O$) C, H.

3-Hydroxy-4-methoxybenzyl 2,4,6-Trihydroxyphenyl Ketone (16). Conversion of 3-(benzyloxy)-4-methoxybenzaldehyde to 3-(benzyloxy)-4-methoxybenzylcyanide (**69**)[35] was affected in 47% overall yield by (1) $LiAlH_4$ reduction to 3-(benzyloxy)-4-methoxybenzyl alcohol (**67**),[33] (2) HCl/ether chloride exchange[34] to 3-(benzyloxy)-4-methoxybenzyl chloride (**68**),[33] and (3) NaCN/Me_2SO cyanide displacement.

According to the general method of Gulati and co-workers,[36] a solution of 3.00 g (24 mmol) of phloroglucinol and 3.00 g (11.8 mmol) of **69** in 450 mL of Et_2O was reacted with anhydrous HCl in the presence of 0.80 g of anhydrous $ZnCl_2$. Standard workup, followed by silica gel column chromatography (CH_2Cl_2–CH_3OH), yielded 2.10 g (61%) of **16** as a white solid. Recrystallization from hexane–EtOAc yielded colorless clusters: mp 208.5–213 °C dec (lit.[35] mp 105 °C resolidifying and mp 196–199 °C); IR (KBr) 3.00 (OH), 6.18 (C=O) μm; UV (H_2O–CH_3OH, 3:1) λ_{max} 224 nm (ε 20300), 287 (20100); NMR (acetone-d_6) δ (s, 3 H, $Ar'OCH_3$), 4.28 (s, 2 H, $ArCOCH_2Ar'$), 5.90 (s, 2 H, ArH). Anal. ($C_{15}H_{14}O_6$) C, H.

2-(3-Hydroxy-4-methoxyphenyl)-6,7α,8β-trihydroxy-1,3,5-trioxatetrahydronaphthalene (17; Mixture of Four Diastereomers). According to the general procedure of Dick and Hodge,[2y] a mixture of 1-*O*-benzylglucopyranose epimers[37] (4.8 g, 17.8 mmol) was condensed with 4.82 g (16.6 mmol) of 3-(benzyloxy)-4-methoxybenzaldehyde dimethyl acetal[2y] as a solution in benzene–dioxane in the presence of *p*-TsOH catalyst. Recrystallization of the crude product from hexane–Et_2O–EtOAc (52:43:5) yielded 4.4 g (54%) of 2-[3-(benzyloxy)-4-methoxyphenyl]-6-(benzyloxy)-7α,8β-dihydroxy-1,3,5-trioxatetetrahydronaphthalene (**70**) as colorless needles: mp 162.5–165 °C; IR (KBr) 3.04 (OH) μm; NMR ($CDCl_3$) δ 3.87 (s, 3 H, $ArOCH_3$), 4.13–4.60 (m, 1 H, PhCOCHO), 4.60 (d, 1 H, J = 12 Hz, $PhCH_AOCO$), 4.97 (d, 1 H, J = 12 Hz, $PhCH_BOCO$), 5.13 (s, 2 H, $PhCH_2OAr$), 5.45 (s, 1 H, $ArCHO_2$), 6.77–7.20 (m, 3 H, ArH), 7.27–7.63 (m, 10 H, PhH). Anal. ($C_{28}H_{30}O_8$) C, H.

Hydrogenation of **70** (3.5 g, 7.08 mmol) over 1 g of Pd/C as a solution in 240 mL of THF–CH_3OH–H_2O (100:40:100) at 3 atm

(32) Looker, J. H.; Holm, M. J. *J. Org. Chem.* **1959**, *24*, 567–568.
(33) Bersch, H. W. *Arch. Pharm. (Weinheim, Ger.)* **1939**, *277*, 271–286.
(34) Shriner, R. L.; Hull, C. J. *J. Org. Chem.* **1945**, *10*, 230.
(35) Wong, E. *Tetrahedron Lett.* **1963**, 159–161.
(36) Gulati, K. C.; Seth, S. R.; Venkataraman, K. In "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 522.
(37) (a) Whistler, R. L.; Wolfram, M. L. *Methods Carbohydr. Chem.* **1972**, *6*, 476. (b) Whistler, R. L.; Wolfram, M. L. *Ibid.* **1962**, *2*, 216–217.

for 24 h after standard workup and lyophilization yielded 2.04 g (92%) of **17** as a flocculent white solid: mp 155–165 °C dec; IR (KBr) 3.12 (OH) μm; UV (CH_3OH) λ_{max} 227 nm (ε 7310), 276 (3290); NMR (acetone-d_6) δ 3.84 (s, 3 H, $ArOCH_3$), 5.47 (s, 1 H, $ArCHO_2$), 7.00 (m, 3 H, ArH). Anal. ($C_{14}H_{18}O_8 \cdot 0.5H_2O$) C, H.

1α,3β,4β-Trihydroxy-5α-[[3-(3-hydroxy-4-methoxyphenyl)propanoyl]oxy]cyclohexane-β-carboxylic Acid (18). A mixture of 1.06 g (3 mmol) of chlorogenic acid, 0.415 g (3 mmol) of K_2CO_3, 0.399 g (3.15 mmol) of $PhCH_2Cl$, and 10 mL of DMF was reacted for 6 days. Standard workup, followed by chromatography over 50 g of silica gel ($CHCl_3$–CH_3OH), yielded 0.50 g (38%) of benzyl chlorogenate (**71**) as a white solid. Treatment of 0.50 g (1.13 mmol) of **71** with 166 mg (1.2 mmol) of K_2CO_3 and 224 mg (1.2 mmol) of methyl *p*-toluenesulfonate in 10 mL of DMF for 18 h, followed by standard workup and product isolation by thick-layer silica gel chromatography ($CHCl_3$–CH_3OH), yielded 219 mg (42%) of benzyl 1α,3β,4β-trihydroxy-5α-[[3-(3-hydroxy-4-methoxyphenyl)propenoyl]oxy]cyclohexane-β-carboxylate (**72**) as a colorless oil: IR (film) 3.12 (OH), 5.76 (benzyl ester C=O), 5.86 (unsaturated ester C=O) μm; UV (EtOH) λ_{max} 243 nm (ε 11 500), 295 (14 400), 326 (17 300); NMR ($CDCl_3$) δ 3.82 (s, 3 H, $ArOCH_3$), 5.19 (s, 2 H, $PhCH_2$), 6.20 (d, 1 H, J = 16 Hz, COCH=), 7.56 (d, 1 H, J = 16 Hz, COC=CHAr). Anal. ($C_{24}H_{26}O_9$) C, H. Diester **72** (205 mg, 0.447 mmol) was then hydrogenated at 1 atm over 200 mg of Pd/C catalyst as a solution in 10 mL of THF. After 4 days, standard workup, followed by recrystallization (H_2O), yielded 65 mg (38%) of **18** as colorless clusters: mp 175–176 °C; IR (KBr) 2.8–4.4 (OH), 5.88 (carboxylic acid and ester C=O) μm; NMR (CD_3OD) 2.65 (t, 2 H, J = 5 Hz, $COCH_2CAr$), 2.82 (t, 2 H, J = 5 Hz, $ArCH_2$), 3.80 (s, 3 H, $ArOCH_3$). Anal. ($C_{17}H_{22}O_9$) C, H.

2,6-Dihydroxy-4-(carboxymethoxy)acetophenone Sodium Salt (19). A solution of 3.00 g (8.72 mmol) of acetophenone **51** in 15 mL of THF was added slowly to 75 mL of 5% KOH at 0 °C. After 2 h, standard workup gave 2.83 g of 2-hydroxy-4-(carboxymethoxy)-6-(benzyloxy)acetophenone (**73**) as a white solid. Hydrogenation of 2.83 g (8.95 mmol) of **73** as a solution in 80 mL of EtOH–THF (1:1) at 3 atm for 6 h, followed by standard workup and recrystallization (EtOH–H_2O), yielded 1.44 g (78%) of 2,6-dihydroxy-4-(carboxymethoxy)acetophenone [**19** (H)] as white needles: mp 232–233.5 °C; IR (KBr) 2.95–4.7 (OH), 5.72 (carboxylic acid C=O), 6.17 (ketone C=O) μm; UV (CH_3OH) λ_{max} 283 nm (ε 17 910); NMR (acetone-d_6) δ 2.63 (s, 3 H, $ArCOCH_3$), 4.73 (s, 2 H, $ArOCH_2$), 6.02 (s, 2 H, ArH). Anal. ($C_{10}H_{10}O_6$) C, H. Conversion of a 492-mg sample of **19** (H) to the sodium salt by the general method yielded 541 mg of **19** as a flocculent white solid.

2,6-Dihydroxy-4-(carboxymethoxy)dihydrochalcone Sodium Salt (20). To a solution of 2.58 g (7.5 mmol) of acetophenone **51** and 1.59 g (15 mmol) benzaldehyde in 84 mL of EtOH–THF (1:1) was rapidly added 7.5 mL of 60% KOH. After 24 h, standard workup and recrystallization (EtOAc–hexane) yielded 1.89 g (62%) of 2-hydroxy-4-(carboxymethoxy)-6-(benzyloxy)chalcone (**74**) as yellow needles: mp 181–182.5 °C; IR (KBr) 2.84–4.23 (OH), 5.73 (carboxylic acid C=O), 6.17 (ketone C=O) μm; UV (CH_3OH) λ_{max} 342 nm (ε 25 300); NMR (acetone-d_6) δ 4.76 (s, 2 H, $ArOCH_2COO$), 5.18 (s, 2 H, $ArOCH_2Ph$), 6.08 (d, 1 H, J = 3 Hz, ArH), 6.30 (d, 1 H, J = 3 Hz, ArH).

Hydrogenation of 1.56 g (3.85 mmol) of **74** over 1.5 g of Pd/C catalyst as a solution in 80 mL of EtOH–THF (1:1) at 3 atm for 2.25 h, followed by standard workup and recrystallization (EtOH–H_2O), yielded 0.87 g (72%) of **20** (H) as long colorless needles: mp 180–182 °C; IR (KBr) 2.84–4.22 (OH), 5.74 (carboxylic acid C=O), 6.14 (ketone C=O) μm; UV (CH_3OH) λ_{max} 284 nm (ε 18 300); NMR (acetone-d_6) δ 2.91 (t, 2 H, J = 8 Hz, $ArCOCCH_2Ar'$), 3.30 (t, 2 H, J = 8 Hz, $ArCOCH_2$), 4.70 (s, 2 H, $ArOCH_2COO$), 6.00 (s, 2 H, ArH). Anal. ($C_{17}H_{16}O_6 \cdot 0.5H_2O$), C, H.

Titration of 488 mg of **20** (H) with NaOH according to the general procedure yielded 517 mg (99%) of **20** as a flocculent solid.

2,6-Dihydroxy-3′,4′-(methylenedioxy)-4-(carboxymethoxy)dihydrochalcone Sodium Salt (21). Three grams (8.73 mmol) of acetophenone **51** and 2.61 g (17.4 mmol) of piperonal were dissolved in 100 mL of DME with rapid stirring, after which 10 mL of 60% KOH was added rapidly. After 24 h, 5 mL of H_2O was added and stirring continued for 56 h, after which standard workup and recrystallization (95% EtOH) yielded 1.81 g (49%) of 2-hydroxy-3′,4′-(methylenedioxy)-4-(carboxymethoxy)-6-(benzyloxy)chalcone (**75**) as yellow needles: mp 195–197 °C; IR (KBr) 2.7–4.3 (OH), 5.76 (carboxylic acid C=O), 6.18 (ketone C=O) μm; UV-vis (CH_3OH) λ_{max} 372 nm (ε 30 860); NMR (acetone-d_6) δ 4.86 (s, 2 H, $ArOCH_2COO$), 5.26 (s, 2 H, $ArOCH_2Ph$), 6.06 (s, 2 H, OCH_2O), 6.13 (d, 1 H, J = 2 Hz, ArH), 6.36 (d, 1 H, J = 2 Hz, ArH). Anal. ($C_{25}H_{20}O_8$) C, H. Hydrogenation of 1.59 g (3.80 mmol) of **75** over 0.5 g of Pd/C catalyst as a solution in 104 mL of a 1:1 EtOH–THF mixture at 3 atm for 1 h, followed by standard workup and recrystallization (EtOH–H_2O), yielded 1.12 g (86%) of **21** (H) as a tan powder: mp 222–223 °C dec; IR (KBr) 2.9–4.25 (OH), 5.71 (carboxylic acid C=O), 6.15 (ketone C=O) μm; UV (CH_3OH) λ_{max} 285 nm (ε 22 760); NMR (acetone-d_6) δ 2.90 (t, 2 H, J = 8 Hz, $ArCOCCH_2Ar'$), 3.40 (t, 2 H, J = 8 Hz, $ArCOCH_2$), 4.66 (s, 2 H, $ArOCH_2COO$), 5.86 (s, 2 H, OCH_2O), 5.98 (s, 2 H, ArH). Anal. ($C_{18}H_{16}O_8$) C, H. Conversion of a 499-mg sample of **21** (H) to the sodium salt by the general method yielded 549 mg of **21** as a flocculent white solid.

2,3′,6-Trihydroxy-4-(carboxymethoxy)-4′-*n*-propoxydihydrochalcone Sodium Salt (22). To a solution of 1.26 g (7.0 mmol) of 3-hydroxy-4-*n*-propoxybenzaldehyde (**76**)[38] and 1.2 g (3.5 mmol) of acetophenone **51** in 40 mL of EtOH–THF (1:1) was rapidly added 4.5 mL of warm 60% KOH. After 18 h, standard workup and recrystallization (EtOH) yielded 743 mg (45%) of 2,3′-dihydroxy-4-(carboxymethoxy)-4′-propoxy-6-(benzyloxy)-chalcone (**77**) as orange needles: mp 192–194 °C; IR (KBr) 2.9–4.2 (OH), 5.74 (carboxylic acid C=O), 6.18 (ketone C=O) μm; UV-vis (CH_3OH) λ_{max} 377 nm (ε 28 860); NMR (acetone-d_6) δ 1.03 (t, 3 H, J = 7 Hz, $Ar'OCCCH_3$), 1.76 (h, 2 H, J = 7 Hz, $Ar'OCCH_2$), 4.07 (t, 2 H, J = 7 Hz, $Ar'OCH_2$), 4.81 (s, 2 H, $ArOCH_2COO$), 5.25 (s, 2 H, $ArOCH_2Ph$), 6.10 (d, 1 H, J = 3 Hz, ArH), 6.33 (d, 1 H, J = 3 Hz, ArH). Anal. ($C_{27}H_{26}O_8$) C, H. Hydrogenation of 707 mg (1.48 mmol) of **77** over 700 mg of Pd/C catalyst as a solution in 30 mL of EtOH–THF (1:1) at 3 atm for 18 h, followed by standard workup and recrystallization (EtOH–H_2O), yielded 407 mg (70%) of **22** (H) as colorless needles: mp 180.5–182 °C; IR (KBr) 2.92–4.2 (OH), 5.72 (carboxyl C=O), 6.15 (ketone C=O) μm; UV (CH_3OH) λ_{max} 287 nm (ε 21 830); NMR (acetone-d_6) δ 0.98 (t, 3 H, J = 6 Hz, $Ar'OCCCH_3$), 1.75 (h, 2 H, J = 6 Hz, $Ar'OCCH_2$), 2.80 (t, 2 H, J = 6 Hz, $ArCOCCH_2Ar'$), 3.30 (t, 2 H, J = 6 Hz, $ArCOCH_2$), 3.96 (t, 2 H, J = 6 Hz, $Ar'OCH_2$), 4.75 (s, 2 H, $ArOCH_2COO$), 6.06 (s, 2 H, ArH). Anal. ($C_{20}H_{22}O_8 \cdot 1.5H_2O$) H; C: calcd, 57.54; found, 56.95.

Titration of 363 mg (0.93 mmol) of this carboxylic acid to the first end point according to the general method yielded 356 mg (93%) of the sodium salt **22**.

2,6-Dihydroxy-3′-amino-4-(carboxymethoxy)-4′-methoxydihydrochalcone Sodium Salt (23). To a solution of 3.15 g (17.4 mmol) of 3-nitro-4-methoxybenzaldehyde (**78**)[39] and 3.00 g (8.7 mmol) of acetophenone **51** in 80 mL of EtOH–DME (1:1) was added 10 mL of warm 60% KOH. After 24 h, 1.58 g of additional **78** was added, and stirring continued for 24 h, after which standard workup and recrystallization (EtOAc–MeCN–hexane) yielded 1.73 g of a yellow solid. HPLC and NMR analysis indicated the product to be a ca. 1:2 mixture of the expected 2-hydroxy-3′-nitro-4-(carboxymethoxy)-4′-methoxy-6-(benzyloxy)chalcone (**79**) and its 4′-ethoxy analogue. Treatment of this mixture with a solution of 5.2 g (0.13 mol) of K in 50 mL of CH_3OH at 35–40 °C for 14 days, followed by standard workup and recrystallization (CH_3OH–H_2O–acetone), yielded 1.10 g (26%) of **79** as a yellow powder: mp 215–216 °C dec; IR (KBr) 2.9–4.15 (OH), 5.70 (carboxylic acid C=O), 6.16 (ketone C=O) μm; NMR (acetone-d_6) δ 4.04 (s, 3 H, $Ar'OCH_3$), 4.80 (s, 2 H, $ArOCH_2COO$), 5.23 (s, 2 H, $ArOCH_2Ph$), 6.12 (d, 1 H, J = 2 Hz, ArH), 6.38 (d, 1 H, J = 2 Hz, ArH). Hydrogenation of 814 mg (1.7 mmol) of **79** over 0.4 g of Pd/C catalyst as a solution in 210 mL of THF–CH_3OH (2:1) at 2 atm for 1 h, followed by standard workup and trituration with H_2O–MeOH, yielded 377 mg (59%) of **23** (H) as an off-white powder: mp 200–208 °C dec; IR (KBr) 2.9–4.35 (OH), 5.80

(38) Beke, D.; Szántay, C. *Acta Chim. Acad. Sci. Hung.* **1958**, *14*, 325–332.
(39) Berlin, A. Y.; Sherlin, S. M.; Serebrennikova, T. A. *Zh. Obshch. Khim.* **1949**, *19*, 759–768.

(carboxylic acid C=O), 6.14 (ketone C=O) μm; UV (CH_3OH) λ_{max} 285 (ε 21 140); NMR (Me_2SO-d_6) δ 2.77 (t, 2 H, J = 7 Hz, $ArCOCCH_2Ar'$), 3.23 (t, 2 H, J = 7 Hz, $ArCOCH_2$), 3.72 (s, 3 H, $Ar'OCH_3$), 4.67 (s, 2 H, $ArOCH_2COO$), 5.95 (s, 2 H, ArH). Anal. ($C_{18}H_{19}NO_7 \cdot 0.75H_2O$) C, H.

Conversion of a 253-mg sample of **23** (H) to the sodium salt by the general procedure yielded 263 mg of **23** as a flocculent off-white solid.

2,3′,6-Trihydroxy-4-(carboxymethoxy)-4′-chlorodihydrochalcone Sodium Salt (24). According to the three-step procedure of Faith and co-workers,[40] 3-hydroxy-4-chlorobenzaldehyde (**80**) was prepared from 3-nitro-4-chlorobenzaldehyde in 49% overall yield. To a solution of 2.13 g (13.5 mmol) of **80** and 3.00 g (8.73 mmol) of acetophenone **51** in 100 mL of DME was added 10 mL of warm 60% KOH. After 5 days, standard workup and recrystallization (EtOH–H_2O), 1.98 g (50%) of 2,3′-dihydroxy-4-(carboxymethoxy)-4′-chloro-6-(benzyloxy)chalcone (**81**) was obtained as yellow needles: mp 180–181 °C; IR (KBr) 2.9–4.2 (OH), 5.74 (carboxylic acid C=O), 6.19 (ketone C=O) μm; UV (CH_3OH) λ_{max} 350 nm (ε 23 550); NMR (acetone-d_6) δ 4.81 (s, 2 H, $ArOCH_2COO$), 5.26 (s, 2 H, $ArOCH_2Ph$), 6.15 (d, 1 H, J = 2 Hz, ArH), 6.36 (d, 1 H, J = 2 Hz, ArH). Anal. ($C_{24}H_{19}ClO_7 \cdot 1.5H_2O$) C, H. Hydrogenation of 682 mg (1.5 mmol) of **81** over 205 mg of Pd/C at 1 atm for 3 h as a solution in 45 mL of EtOAc yielded, after standard workup and recrystallization (EtOH–H_2O), 499 mg (91%) of **24** (H) as a tan powder: mp 207–208.5 °C dec; IR (KBr) 2.9–4.2 (OH), 5.73 (carboxylic acid C=O), 6.13 (ketone C=O) μm; UV (CH_3OH) λ_{max} 285 nm (ε 20 560); NMR (acetone-d_6) δ 2.90 (t, 2 H, J = 8 Hz, $ArCOCCH_2Ar'$), 3.40 (t, 2 H, J = 8 Hz, $ArCOCH_2$), 4.70 (s, 2 H, $ArOCH_2COO$), 6.00 (s, 2 H, ArH). Anal. ($C_{17}H_{15}ClO_7$) C, H. Conversion of a 302-mg sample of **24** (H) to the sodium salt by the general procedure yielded 297 mg of **24** as a white flocculent solid.

2,3′,6-Trihydroxy-4-(carboxymethoxy)-4′-(methylamino)-dihydrochalcone (25). To a solution of 3.75 g (10.9 mmol) of acetophenone **51** and 5.05 g (28.5 mmol) of *N*-methyl-5-formyl-2-benzoxazolinone (**83**)[41] in 90 mL of DMF was added 10.9 mL of warm 60% KOH. After 72 h, standard workup and recrystallization (H_2O) yielded 2.13 g (44%) of 2,3′-dihydroxy-4-(carboxymethoxy)-4′-(methylamino)-6-(benzyloxy)chalcone (**84**) as yellow plates: mp 199–203 °C; IR (KBr) 3.1–4.3 (OH), 6.20 (C=O) μm; UV-vis (H_2O) λ_{max} 282 nm (ε 8000), 325 (8800), 425 (19 000); NMR (Me_2SO-d_6) δ 2.90 (s, 3 H, NCH_3), 4.30 (s, 2 H, $ArOCH_2COO$), 5.20 (s, 2 H, $ArOCH_2Ph$). Anal. ($C_{25}H_{23}NO_7 \cdot 2H_2O$) C, H. Hydrogenation of 1.12 g (2.5 mmol) of **84** over 0.5 g Pd/C catalyst at 3 atm for 18 h, followed by standard workup and recrystallization (H_2O), yielded 0.453 g (50%) of **25** as a light orange powder: mp 203–204 °C dec; IR (KBr) 3.1–4.32 (OH), 6.15, 6.22 (carboxylic acid and ketone C=O); UV (H_2O) λ_{max} 288 nm (ε 4650); NMR (Me_2SO-d_6) δ 2.66 (s, 3 H, NCH_3), 2.70 (t, 2 H, J = 8 Hz, $ArCOCCH_2Ar'$), 3.20 (t, 2 H, J = 8 Hz, $ArCOCH_2$), 4.65 (s, 2 H, $ArOCH_2COO$), 5.93 (s, 2 H, ArH). Anal. ($C_{18}H_{19}NO_7 \cdot 0.5H_2O$) C, H.

2,3′,6-Trihydroxy-4-(carboxymethoxy)-4′-methoxydihydrochalcone Oxime (26). A mixture of 1.44 g (2.5 mmol) of 2,3′,6-tris(benzyloxy)-4-hydroxy-4′-methoxydihydrochalcone (**48**), 0.69 g (5 mmol) of K_2CO_3, 0.61 g (5 mmol) of ethyl chloroacetate, and 30 mL of DMF was reacted at 40 °C for 4 h, followed by 65 °C for 15 h. Standard workup yielded 1.65 g (100%) of 2,3′,6-tris(benzyloxy)-4-(carbethoxymethoxy)-4′-methoxydihydrochalcone (**85**) as a white solid. Twenty-five milliliters of 5% KOH was added to a solution of 1.65 g (2.5 mmol) of **85** in 50 mL of CH_3OH. After 2 days, standard workup yielded 1.55 g (98%) of 2,3′,6-tris(benzyloxy)-4-(carboxymethoxy)-4′-methoxydihydrochalcone (**86**) as a white solid. A solution of 1.58 g (2.5 mmol) of **86**, 0.87 g (12.5 mmol) of $NH_2OH \cdot HCl$, and 1.33 g (16.2 mmol) of NaOAc in 37.5 mL of EtOH–H_2O (2:1) was heated to reflux for 17 h. Standard workup yielded 1.59 g (98%) of 2,3′,6-tris(benzyloxy)-4-(carboxymethoxy)-4′-methoxydihydrochalcone oxime (**87**) as a light tan solid. Hydrogenation of 1.62 g (2.5 mmol) of **87** over 1.5 g of Pd/C at 1 atm for 14.5 h as a solution in 50 mL of MeOH, followed by standard workup and recrystallization (H_2O), yielded 561 mg (61%) of **26** as light tan clusters: mp 195–196 °C; IR (KBr) 2.5–4.5 (OH), 5.79 (carboxylic acid C=O), 6.21 (C=N) μm; UV (H_2O) λ_{max} 277 nm (ε 5160); NMR (acetone-d_6) 3.79 (s, 3 H, $Ar'OCH_3$), 4.60 (s, 2 H, $ArOCH_2$), 6.02 (s, 2 H, ArH). Anal. ($C_{18}H_{19}NO_8 \cdot 1.25H_2O$) C, H, N. HPLC analysis indicated the crude oxime product to be a 75:25 mixture of syn and anti epimers, having t_R = 8.8 and 9.3 min, respectively. The recrystallized product is the pure t_R = 9.3 min isomer believed to have the syn configuration.

1-[2,6-Dihydroxy-4-(carboxymethoxy)phenyl]-3-[3-hydroxy-4-methoxyphenyl]propan-1-imine (27). Hydrogenation of 1.08 g (3 mmol) of the isoxazole **30** (H) over 0.54 g of Pd/C at 1.5 atm for 30 min as a solution in 60 mL of CH_3OH–H_2O (2:1), followed by catalyst filtration and solvent removal in vacuo at ca. 0 °C, gave 0.96 g (89%) of **27** as a hydrolytically unstable green solid. HPLC analysis indicated this product to be a 96:4 mixture of imine **27** (t_R = 9.4 min) and ketone **2** (t_R = 11.7 min). An aqueous solution of this constitution allowed to stand at ambient temperature for 15 h showed exclusively t_R = 11.7 min material. Efforts to obtain an analytical sample by recrystallization and preparative HPLC were uniformly unsuccessful.

1-(2,4,6-Trihydroxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)propane (28). To a suspension of 1.90 g (50 mmol) of $LiAlH_4$ in 100 mL of DME was added 2.88 g (5 mmol) of 2,3′,6-tris(benzyloxy)-4-hydroxy-4′-methoxydihydrochalcone (**48**) as a dry solid. The resultant reaction mixture was refluxed for 2.5 h, after which it was allowed to cool and excess $LiAlH_4$ was decomposed by cautious addition of EtOAc. One hundred milliliters of 10% HCl was then added, and the mixture was extracted with ether (3 × 75 mL), the combined portions of which were dried over $MgSO_4$ and concentrated in vacuo to give 2.81 g (100%) of 1-[2,6-bis(benzyloxy)-4-hydroxyphenyl]-3-[3-(benzyloxy)-4-methoxyphenyl]propane (**88**) as a tan solid. Recrystallization (hexane–EtOAc) yielded 2.37 g (85%) of **88** as light tan needles: mp 114–116 °C; IR (KBr) 2.90 (OH) μm; NMR ($CDCl_3$) δ 1.50–2.08 (m, 2 H, $ArCCH_2CAr'$), 2.33–2.90 (m, 4 H, $ArCH_2CCH_2Ar'$), 3.76 (s, 3 H, $Ar'OCH_3$), 4.93 (s, 4 H, $PhCH_2O$), 4.97 (s, 2 H, $PhCH_2O$), 6.03 (s, 2 H, ArH). Anal. ($C_{37}H_{36}O_5$) H; C: calcd, 79.26; found, 78.80.

Hydrogenation of a 1.12-g (2 mmol) sample of **88** over 0.56 g of Pd/C at 3 atm for 6 h as a solution in 40 mL of EtOH–THF (1:1), followed by standard workup and recrystallization (CH_2Cl_2–CH_3OH), yielded 0.55 g (95%) of **28** as off-white granular crystals: mp 163–164 °C; IR (KBr) 3.10 (OH) μm; UV (MeOH) λ_{max} 279 nm (ε 2560); NMR (acetone-d_6) δ 1.50–2.08 (m, 2 H, $ArCCH_2CAr'$), 2.40–3.53 (m, 8 H, $ArCH_2CCH_2Ar'$, OH), 3.77 (s, 3 H, $Ar'OCH_3$), 5.98 (s, 2 H, ArH), 6.57–6.95 (m, 3 H, Ar′H). Anal. ($C_{16}H_{18}O_5 \cdot H_2O$) C, H.

1-[2,6-Dihydroxy-4-(carboxymethoxy)phenyl]-3-(3-hydroxy-4-methoxyphenyl)propane Sodium Salt (29). A mixture of 1.68 g (3 mmol) of **88**, 0.55 g (4 mmol) of K_2CO_3, 0.74 g (6 mmol) of ethyl chloroacetate, and 30 mL of DMF was reacted at 40 °C for 22 h. Standard workup yielded 1.94 g (100%) of 1-[2,6-bis(benzyloxy)-4-(carbethoxymethoxy)phenyl]-3-(3-hydroxy-4-methoxyphenyl)propane (**89**) as a light yellow solid. Hydrogenation of this sample of **89** over 1 g of Pd/C as a solution in 150 mL of EtOAc–EtOH (2:1) at 4 atm for 22 h, followed by standard workup, yielded 1.13 g (100%) of 1-[2,6-dihydroxy-4-(carbethoxymethoxy)phenyl]-3-(3-hydroxy-4-methoxyphenyl)-propane (**90**) as a light tan solid. Ester **90** (1.13 g, 3 mmol) was dissolved in 50 mL of 5% KOH. After standing for 18 h, standard workup and recrystallization (H_2O–CH_3OH) yielded 0.798 g (77%) of **29** (H) as light tan granular crystals: mp 190–192 °C; IR (KBr) 2.5–4.3 (OH), 5.76 (C=O) μm; UV (MeOH) λ_{max} 278 nm (ε 3170); NMR (acetone-d_6) δ 1.66–197 (m, 2 H, $ArCCH_2CAr'$), 2.36–2.90 (m, 4 H, $ArCH_2CCH_2Ar'$), 3.80 (s, 3 H, $Ar'OCH_3$), 4.51 (s, 2 H, $ArOCH_2$), 6.03 (s, 2 H, ArH). Anal. ($C_{18}H_{20}O_7$) C, H. Titration of a 234-mg sample of **29** (H) to the sodium salt by the general procedure yielded 256 mg of **29** as a flocculent white solid. Anal. ($C_{18}H_{19}NaO_7 \cdot H_2O$) C, H.

3-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-4-hydroxy-6-(carboxymethoxy)-1,2-benzisoxazole Sodium Salt (30). A solution of 3.62 g (10 mmol) of 2,3′,6-trihydroxy-4-(carboxymethoxy)-4′-methoxydihydrochalcone [(2 (H)], 1.74 g (25 mmol)

(40) Faith, H. E.; Bahler, M. E.; Florestano, H. J. *J. Am. Chem. Soc.* **1955**, *77*, 543.

(41) Bonte, J. P.; Lesieur, D.; Lespagnol, C.; Plat, M.; Cazin, J. C.; Cazin, M. *Eur. J. Med. Chem. Chim. Ther.* **1974**, *9*, 491–496.

of NH_2OH·HCl, and 2.87 g (35 mmol) of NaOAc in 60 mL of EtOH–H_2O (2:1) was refluxed for 48 h. After cooling in ice for 2 h, filtration yielded 2.84 g (68%) of **30** as tiny light tan crystals: mp >200 °C dec; IR (KBr) 2.5–4.5 (OH), 6.20 (carboxylate anion C=O, C=N) μm; UV (H_2O) λ_{max} 259 nm (ε 10 200); NMR (Me_2SO-d_6) δ 3.74 (s, 3 H, Ar'OCH_3), 4.28 (s, 2 H, ArOCH_2). Anal. ($C_{18}H_{17}NNaO_7$·1.5H_2O) C, H.

3-[2-(3-Hydroxy-4-methoxyphenyl)ethyl]-4-hydroxy-6-(sulfopropoxy)-1,2-benzisoxazole Potassium Salt (31). A solution of 4.64 g (10 mmol) of 2,3',6-trihydroxy-4-(sulfopropoxy)-4'-methoxydihydrochalcone potassium salt, 1.74 g (25 mmol) of NH_2OH·HCl, and 3.43 g (35 mmol) of KOAc in 50 mL of H_2O was refluxed for 5 h. After the solution cooled overnight, the crystals were filtered and recrystallized from H_2O to give 2.91 g (63%) of **31** as light tan needles: mp 285–290 °C dec; IR (KBr) 2.87 (OH), 6.15 (C=N) μm; UV (H_2O) λ_{max} 259 nm (ε 12 900); NMR (Me_2SO-d_6) δ 3.71 (s, 3 H, Ar'OCH_3), 4.07 (t, 2 H, J = 6 Hz, ArOCH_2). Anal. ($C_{19}H_{20}KNO_8S$) C, H, N.

***N*-(3-Hydroxy-4-methoxybenzyl)-2,4,6-trihydroxybenzamide (32).** To a solution of 4.00 g (10 mmol) of 1,3,5-tris(benzyloxy)benzene (**91**)[42] in 100 mL of Et_2O–CH_2Cl_2 (9:1) was added 1.42 g (10 mmol) of chlorosulfonyl isocyanate dropwise over 2–3 min at 0 °C. After 4 h, the precipitated product was filtered, washed with Et_2O, and dried in vacuo to yield 3.94 g (73%) of *N*-(chlorosulfonyl)-2,4,6-tris(benzyloxy)benzamide (**92**) as light pink crystals: IR (KBr) 5.92 (C=O), 7.26 (S=O), 8.50 (S=O) μm; NMR (acetone-d_6) δ 3.67 (br s, 1 H, NH), 5.17 (s, 6 H, OCH_2Ph), 6.46 (s, 2 H, ArH), 7.23–7.60 (m, 15 H, PhH).

According to the procedure of Effenberger and co-workers,[43] 3.32 g (6.14 mmol) of **92** was dissolved in 50 mL of THF, diluted with 25 mL of H_2O, and then treated with 25 mL of 20% KOH. After 1 h, standard workup yielded 2.72 g (100%) of 2,4,6-tris(benzyloxy)benzamide (**93**) as a white solid: NMR ($CDCl_3$) δ 5.00 (s, 2 H, C-4 OCH_2Ph), 5.07 (s, 4 H, C-2, C-6 OCH_2Ph), 5.80 (br s, 2 H, NH_2), 6.26 (s, 2 H, ArH), 7.36 (s, 15 H, PhH).

To a suspension of 2.67 g (6 mmol) of **93** in 100 mL of toluene was added 159 mg (6.6 mmol) of NaH. The reaction mixture was refluxed until H_2 evolution was complete and then allowed to cool to ambient temperature. As a dry solid, 1.74 g (6.6 mmol) of chloride **68** was added in one portion, after which the resultant reaction mixture was refluxed for 26 h. Standard workup, followed by chromatography over 500 g of silica gel (hexane–EtOAc), yielded 2.05 g (51%) of *N*-[3-(benzyloxy)-4-methoxybenzyl]-2,4,6-tris(benzyloxy)benzamide (**94**) as a light yellow solid. Recrystallization (CH_2Cl_2–hexane) yielded white clusters: mp 152–153 °C; IR (KBr) 2.94 (NH), 6.12 (C=O) μm; NMR ($CDCl_3$) δ 3.80 (s, 3 H, Ar'OCH_3), 4.47 (d, 2 H, J = 5 Hz, N-CH_2), 4.95 (s, 4 H, Ar'OCH_2Ph, Ar 4-OCH_2Ph), 5.04 [s, 4 H, Ar 2,6-OCH_2Ph], 6.00 (t, 1 H, J = 5 Hz, NH), 6.23 (s, 2 H, ArH). Anal. ($C_{43}H_{39}NO_6$) C, H. Hydrogenation of a 0.84-g (1.26 mmol) sample of **94** over 0.4 g of Pd/C at 1 atm for 15 h as a solution in 50 mL of EtOAc yielded, after standard workup and recrystallization (CH_3OH–H_2O), 314 mg (81%) of **32** as light pink clusters: mp 212–213 °C; IR (KBr) 2.98 (OH, NH), 6.30 (C=O) μm; UV (EtOH) λ_{max} 265 nm (ε 18 900), 300 (3320); NMR (acetone-d_6) δ 3.48 (br s, 1 H, NH), 3.82 (s, 3 H, OCH_3), 4.49 (d, 2 H, J = 6 Hz, Ar'CH_2N), 5.94 (s, 2 H, ArH), 6.77–7.00 (m, 3 H, Ar'H). Anal. ($C_{15}H_{15}NO_6$·0.5H_2O) C, H.

***N*-(3-Hydroxy-4-methoxybenzyl)-2,6-dihydroxy-4-(carboxymethoxy)benzamide (33).** According to the method of Crum and Franks,[18] 563 mg (3.3 mmol) of benzyl chloroformate was added dropwise to a solution of 200 mg (0.66 mmol) of **32** in 5 mL of pyridine while at 0 °C. After 2 h, 3.3 mmol of additional benzyl chloroformate was added, after which the reaction mixture was allowed to warm to ambient temperature over 6 h. The reaction mixture was then refluxed for 8 h, after which standard workup and radial chromatography ($CHCl_3$–CH_3OH) yielded 209 mg (96%) of *N*-(3-hydroxy-4-methoxybenzyl)-5,7-dihydroxy-3,4-dihydro-2*H*-1,3-benzoxazine-2,4-dione (**95**) as a colorless solid: IR (THF) 5.65 (urethane C=O), 6.02 (imide C=O) μm; NMR (acetone-d_6) δ 3.83 (s, 3 H, Ar'OCH_3), 5.00 (s, 2 H, ArCH_2N), 6.01 (d, 1 H, J = 2 Hz, ArH), 6.06 (d, 1 H, J = 2 Hz, ArH), 6.77–7.10 (m, 3 H, Ar'H).

Benzoxazinedione **95** (209 mg, 0.63 mmol) was reacted with 97 mg (0.7 mmol) of K_2CO_3 and 154 mg (1.26 mmol) ethyl chloroacetate in 5 mL of DMF for 24 h. Standard workup, followed by preparative radial chromatography ($CHCl_3$–MeOH), yielded 94 mg (36%) of *N*-(3-hydroxy-4-methoxybenzyl)-5-hydroxy-7-(carbethoxymethoxy)-3,4-dihydro-2*H*-1,3-benzoxazine-2,4-dione (**96**) as white clusters: IR ($CHCl_3$) 2.83 (OH), 2.93 (OH), 5.70 (ester C=O, urethane C=O), 6.01 (imide C=O) μm; NMR ($CDCl_3$) δ 1.29 (t, 3 H, J = 7 Hz, $COOCCH_3$), 3.83 (s, 3 H, Ar'OCH_3), 4.28 (q, 2 H, J = 7 Hz, $COOCH_2$), 4.65 (s, 2 H, ArOCH_2COO), 5.02 (s, 2 H, Ar'CH_2N), 5.74 (s, 1 H, Ar'OH), 6.27 (s, 2 H, ArH), 10.89 (s, 1 H, ArOH).

Three milliliters of 10% KOH was added to 94 mg (0.22 mmol) of **96**. After 5 h, standard workup and recrystallization (CH_3OH–H_2O) yielded 58 mg (71%) of the carboxylic acid **33** as light pink needles: mp 178–180 °C; IR (KBr) 2.99–4.22 (OH), 5.79 (carboxyl C=O), 6.12 (ketone C=O) μm; UV (EtOH) λ_{max} 265 nm (ε 21 480); NMR (acetone-d_6) δ 3.2–4.6 (br m, 5 H, OH, NH), 3.8 (s, 3 H, OCH_3), 4.40–4.60 (m, 2 H, Ar'CH_2N), 4.66 (s, 2 H, $ArOCH_2$), 6.03 (s, 2 H, ArH), 6.90 (br s, 3 H, Ar'H). Anal. ($C_{17}H_{17}NO_8$·H_2O) C, H, N.

2,3',6-Trihydroxy-4-(1,3-dicarboxypropoxy)-4'-propoxydihydrochalcone (36). Dimethyl 2-bromoglutarate (**97**)[45] was prepared by methanolysis of 2-bromoglutaryl chloride.[44]

A mixture of 22.5 g (0.044 mol) of 2,6-dihydroxy-4-β-(neohesperidosyloxy)acetophenone (**50**), 60.8 g (0.44 mol) of K_2CO_3, and 55.8 g (0.44 mol) of $PhCH_2Cl$ in 250 mL of DMF was reacted at ambient temperature for 21 h and then 80 °C for 6 h. Standard workup then yielded 48.1 g of 2,6-bis(benzyloxy)-4-β-(neohesperidosyloxy)acetophenone (**98**) as a viscous oil. This oil was dissolved in 300 mL of EtOH and diluted with 150 mL of 3% H_2SO_4, and the resultant solution was refluxed for 22 h. Standard workup yielded 22.1 g of an oily solid, which on trituration with Et_2O yielded 2.69 g of 2,4-dihydroxy-6-(benzyloxy)acetophenone (**57**) as colorless needles. The residue was chromatographed over 400 g of grade 3 basic alumina ($CHCl_3$–CH_3OH) to give 2.49 g of additional **57** in an early fraction, followed by a later fraction of 2,6-bis(benzyloxy)-4-hydroxyacetophenone (**99**) as an impure oil. Dibenzyl ether **99** was obtained in pure form following chromatography over 800 g of silica gel (hexane–EtOAc) and recrystallization (Et_2O–hexane) to give 3.80 g (25%; two steps) of **99** as colorless clusters: mp 122–123 °C; IR (KBr) 3.00 (OH), 6.00 (C=O) μm; UV (EtOH) λ_{max} 276 nm (ε 5100); NMR ($CDCl_3$) δ 2.47 (s, 3 H, $COCH_3$), 4.84 (s, 4 H, $PhCH_2O$), 6.07 (s, 2 H, ArH), 7.30 (s, 10 H, PhH). Anal. ($C_{22}H_{20}O_4$) C, H.

A mixture of 1.8 g (10 mmol) of 3-hydroxy-4-propoxybenzaldehyde (**76**), 1.52 g (11 mmol) of K_2CO_3, and 1.58 g (12.5 mmol) of $PhCH_2Cl$ in 50 mL of DMF was reacted for 70 h. Standard workup and sublimation in vacuo yielded 1.59 g (59%) of 3-(benzyloxy)-4-propoxybenzaldehyde (**100**) as colorless clusters: mp 60.5–62 °C; IR (KBr) 5.92 (C=O) μm; NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7 Hz, $ArOCCCH_3$), 1.86 (h, 2 H, J = 7 Hz, $ArOCCH_2C$), 4.04 (t, 2 H, J = 6 Hz, $ArOCH_2CC$), 5.18 (s, 2 H, $PhCH_2O$), 6.80–7.62 (m, 8 H, ArH, PhH), 9.75 (s, 1 H, ArCHO). Anal. ($C_{17}H_{18}O_3$) C, H.

Eighteen milliliters of warm 60% KOH was added in one portion to a solution of 1.05 g (3 mmol) of **99** and 0.89 g (3.3 mmol) of **100** in 12 mL of EtOH. After 1 h, 0.7 mmol of additional **100** was added in 2 mL of EtOH. After 3 days, standard workup, chromatography over grade 3 basic alumina ($CHCl_3$–CH_3OH), and preparative radial chromatography on silica gel yielded 1.37 g (76%) of 2,3',6-tris(benzyloxy)-4-hydroxy-4'-propoxychalcone (**101**) as a yellow oil: IR (film) 3.04 (OH), 6.27 (C=O) μm; NMR ($CDCl_3$) δ 1.04 (t, 3 H, J = 7 Hz, Ar'$OCCCH_3$), 1.85 (h, 2 H, J = 7 Hz, Ar'$OCCH_2C$), 4.00 (t, 2 H, J = 7 Hz, Ar'OCH_2CC), 4.76 (s, 4 H, $ArOCH_2Ph$), 5.04 (s, 2 H, Ar'OCH_2Ph), 6.10 (s, 2 H, ArH). Anal. ($C_{39}H_{36}O_6$) C, H.

Ten milliliters of DMF was added to a mixture of 1.37 g (2.29 mmol) of **101**, 0.634 g (4.58 mmol) of K_2CO_3, and 1.09 g (4.58

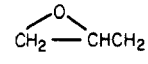
(42) Harris, C. M.; Roberson, J. S.; Harris, T. M. *J. Am. Chem. Soc.* **1976**, *98*, 5380–5386.
(43) Effenberger, F.; Gleiter, R.; Heider, L.; Niess, R. *Chem. Ber.* **1968**, *101*, 502.
(44) Bertho, A.; Schmidt, I.; Strecker, E. *Justus Liebigs Ann. Chem.* **1962**, *651*, 185.
(45) Teichmann, B. *Acta Chim. Acad. Sci. Hung.* **1964**, *41*, 331–336.

mmol) of **97**. After 15 h, standard workup and preparative silica gel radial chromatography (hexane–EtOAc) yielded 1.40 g (81%) of 2,3′,6-tris(benzyloxy)-4-(1,3-dicarbomethoxypropoxy)-4′-propoxychalcone (**102**) as a yellow oil: IR (film) 5.74 (ester C=O), 6.08 (ketone C=O) μm; NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz, Ar′OCCCH$_3$), 1.80 (h, 2 H, J = 7 Hz, Ar′OCCH$_2$C), 3.63 (s, 6 H, COOCH$_3$), 3.96 (t, 2 H, J = 7 Hz, Ar′OCH$_2$CC), 4.71 (t, 1 H, J = 5 Hz, ArOCH), 5.02 (s, 4 H, ArOCH$_2$Ph), 5.07 (s, 2 H, Ar′OCH$_2$Ph), 6.23 (s, 2 H, ArH). Anal. ($C_{46}H_{46}O_{10}$) C, H.

Hydrogenation of 1.40 g (1.85 mmol) of **102** over 0.5 g of Pd/C at 1 atm for 4 h as a solution in 50 mL of MeOH–THF (1:1), followed by standard workup and preparative silica gel radial chromatography ($CHCl_3$–CH_3OH), yielded 801 mg (88%) of 2,3′,6-trihydroxy-4-(1,3-dicarbomethoxypropoxy)-4′-propoxydihydrochalcone (**103**) as a colorless oil: IR (film) 2.95 (OH), 5.76 (ester C=O), 6.16 (ketone C=O) μm; NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz, Ar′OCCCH$_3$), 1.79 (h, 2 H, J = 7 Hz, Ar′OCCH$_2$C), 2.87 (t, 2 H, J = 8 Hz, ArCOCCH$_2$Ar′), 3.35 (t, 2 H, J = 8 Hz, ArCOCH$_2$CAr′), 3.67 (s, 3 H, ArOCCCCOOCH$_3$), 3.74 (s, 3 H, ArOCCOOCH$_3$), 3.96 (t, 2 H, J = 7 Hz, Ar′OCH$_2$CC), 4.72 (t, 1 H, J = 6 Hz, ArOCH), 5.90 (s, 3 H, ArH, Ar′OH), 10.86 (s, 1 H, ArOH). Anal. ($C_{25}H_{30}O_{10}$) C, H.

Fifty milliliters of 10% KOH was added to 801 mg (1.63 mmol) of **103**, after which the resultant solution was stirred for 16 h. Standard workup and recrystallization (CH_2Cl_2–acetone) yielded 585 mg (79%) of **36** as light tan clusters: mp 153–154 °C; IR (KBr) 2.8–4.7 (OH), 5.82 (carboxylic acid C=O), 6.23 (ketone C=O) μm; UV (MeOH) λ_{max} 285 nm (ε 20 370); NMR (acetone-d_6) δ 1.05 (t, 3 H, J = 6 Hz, Ar′OCCCH$_3$), 1.80 (h, 2 H, J = 6 Hz, Ar′OCCH$_2$C), 2.82 (t, 2 H, J = 6 Hz, Ar′CH$_2$), 3.46 (t, 2 H, J = 6 Hz, ArCOCH$_2$), 3.96 (t, 2 H, J = 6 Hz, Ar′OCH$_2$CC), 4.90 (t, 1 H, J = 6 Hz, ArOCH), 6.05 (s, 2 H, ArH). Anal. ($C_{23}H_{26}O_{10}\cdot 3H_2O$) C, H.

2,3′,6-Trihydroxy-4-(1-carboxy-3,4-dihydroxybutoxy)-4′-methoxydihydrochalcone Sodium Salt (37). According to the method of Stotter and Hill,[46] 6.49 g (28%) of *tert*-butyl 2-bromo-4-pentenoate (**104**) was obtained in three steps from *tert*-butyl acetoacetate. To a solution of 6.25 g (26.6 mmol) of **104** in 100 mL of CH_2Cl_2 was added 5.05 g (29.3 mmol) of *m*-chloroperbenzoic acid. After 14 h, standard workup, silica gel column chromatography (hexane–EtOAc), followed by bulb to bulb distillation (120 °C (0.1 mm)), yielded 3.95 g (59%) of *tert*-butyl 2-bromo-4,5-epoxypentanoate (**105**) as a colorless liquid: IR (film) 5.77 (C=O) μm; NMR ($CDCl_3$) δ 1.50 [s, 9 H, $(CH_3)_3C$], 2.00–3.33 (m, 5 H, i), 4.14–4.53 (m, 1 H, CHBr). Anal. ($C_9H_{14}BrO_3$)



i

C, H.

A mixture of 553 mg (2.2 mmol) of **105**, 1.15 g (2 mmol) of **48**, and 304 mg (2.2 mmol) of K_2CO_3 in 10 mL of DMF was reacted at ambient temperature. After 38 h, 0.8 mmol each of K_2CO_3 and **105** were added and stirring continued for 48 h. Standard workup, followed by preparative silica gel ($CHCl_3$) radial chromatography, yielded 1.49 g (100%) of 2,3′,6-tris(benzyloxy)-4-[1-(carbo-*tert*-butoxy)-3,4-epoxybutoxy]-4′-methoxydihydrochalcone (**106**) as a colorless oil: IR (film) 5.75 (ester C=O), 5.87 (ketone C=O) μm; NMR ($CDCl_3$) δ 1.44, 1.48 [s, 9 H, $(CH_3)_3C$ for two diastereoisomers], 1.93–3.26 (m, 9 H, ArCOCH$_2$CH$_2$Ar′, i) 3.81 (s, 3 H, Ar′OCH$_3$), 5.00 (s, 6 H, PhCH$_2$O), 4.36–4.90 (m, 1 H, ArOCHCOO), 6.20 (s, 1 H, ArH), 6.22 (s, 1 H, ArH), 6.63–6.88 (m, 3 H, Ar′H), 7.37 (s, 15 H, PhH).

Epoxy ester **106** (1.49 g, 2 mmol) was dissolved in 44 mL of 11:1) dioxane–H_2O, after which 1 mL of 50% H_2SO_4 was added. After 40 h, the reaction mixture was neutralized with 10% KOH, concentrated in vacuo at ambient temperature, worked up by standard methods, and purified by preparative silica gel radial chromatography ($CHCl_3$–CH_3OH) to give 1.01 g (67%) of 2,3′,6-tris(benzyloxy)-4-[1-(carbo-*tert*-butoxy)-3,4-dihydroxybutoxy]-4′-methoxydihydrochalcone (**107**) as a colorless oil: IR ($CHCl_3$) 2.87 (OH), 5.74 (ester C=O), 5.90 (ketone (C=O) μm; NMR ($CDCl_3$) δ 1.44 [br s, 9 H, $(CH_3)_3CO$], 1.83–2.33 (m, 2 H, ArOCCH$_2$), 2.80–3.13 (m, 4 H, ArCOCH$_2$CH$_2$Ar′), 3.37–3.83 (m, 3 H, ArOCCCHCH$_2$), 3.83 (s, 3 H, Ar′OCH$_3$), 4.60–4.95 (m, 1 H, ArOCHCOO), 5.00 (s, 6 H, PhCH$_2$O), 6.24 (d, 1 H, J = 2 Hz, ArH), 6.28 (d, 1 H, J = 2 Hz, ArH), 6.60–6.80 (m, 3 H, Ar′H), 7.33 (br s, 15 H, PhH).

Tribenzyl ether **107** (664 mg, 0.87 mmol) was then hydrogenated over 0.35 g of Pd/C at 3.5 atm for 19 h as a solution in 50 mL of (1:1) *t*-BuOH–CH_2Cl_2. Standard workup, followed by preparative silica gel radial chromatography (CH_2Cl_2–CH_3OH), yielded 318 mg (74%) of 2,3′,6-trihydroxy-4-[1-(carbo-*tert*-butoxy)-3,4-dihydroxybutoxy]-4′-methoxydihydrochalcone (**108**) as a colorless foam: IR (film) 2.95 (OH), 5.74 (ester C=O), 6.16 (ketone C=O) μm; NMR ($CDCl_3$) δ 1.46 [s, 9 H, $(CH_3)_3CO$], 2.87 (t, 2 H, J = 7 Hz, ArCOCCH$_2$Ar′), 3.40 (t, 2 H, J = 7 Hz, ArCOCH$_2$CAr′), 3.85 (s, 3 H, Ar′OCH$_3$), 4.84 (m, 1 H, ArOCH), 6.00 (s, 2 H, ArH), 11.60 (s, 1 H, ArOH). TLC analysis ($CHCl_3$–CH_3OH, 90:10) with multiple elution showed the presence of two diastereomers in comparable amounts. *tert*-Butyl ester (**108**; 318 mg, 0.65 mmol) was dissolved with stirring in 25 mL of 10% KOH. After 3 days, the solution was cooled to 0 °C, acidified to pH 3.7 (turbidity) with 10% HCl, saturated with NaCl, and extracted with ice-cold EtOAc (3 × 25 mL). The extracts were kept cold while drying over $MgSO_4$ and then concentrated in vacuo at 0 °C to yield 282 mg (100%) of **37** (H) as a viscous oil. HPLC analysis indicated this product to be a 71:29 mixture of diastereomers having t_R = 10.8 and 11.1 min, respectively. Without purification, **37** (H) (282 mg) was titrated to the sodium salt by the general method to yield 176 mg of **37** as an off-white flocculent solid: mp 137–140 °C dec; IR (KBr) 2.7–4.3 (OH), 6.15 (carboxylate anion and ketone C=O) μm; UV (H_2O) λ_{max} 285 nm (ε 12 620); NMR (Me_2SO-d_6) 2.87 (t, 2 H, J = 7 Hz, ArCOCCH$_2$Ar′), 3.40 (t, 2 H, J = 7 Hz, ArCOCH$_2$CAr′), 3.61 (s, 3 H, Ar′OMe), 4.84 (m, 1 H, ArOCH), 5.80 (s, 2 H, ArH). Anal. ($C_{21}H_{23}NaO_{10}\cdot H_2O$) C, H.

2,3′,6-Trihydroxy-4-(1-carboxy-3,4-dihydroxybutoxy)-4′-propoxydihydrochalcone Sodium Salt (38). Ten milliliters of DMF was added to a mixture of 559 mg (0.93 mmol) of chalcone **101**, 161 mg (1.16 mmol) of K_2CO_3, and 292 mg (1.16 mmol) of **105**. After 48 h, standard workup, followed by preparative silica gel radial chromatography ($CHCl_3$), yielded 642 mg (89%) of 2,3′,6-tris(benzyloxy)-4-[1-(carbo-*tert*-butoxy)-3,4-epoxybutoxy]-4′-propoxychalcone (**109**) as a viscous yellow oil. Epoxy ester **109** (642 mg, 0.83 mmol) was dissolved in 22 mL (11:1) of dioxane–H_2O and treated with 0.5 mL of 50% H_2SO_4. After 30 h, standard workup, followed by preparative silica gel radial chromatography (hexane–EtOAc) yielded 394 mg (60%) of 2,3′,6-tris(benzyloxy)-4-[1-(carbo-*tert*-butoxy)-3,4-dihydroxybutoxy]-4′-propoxydihydrochalcone (**110**) as a viscous oil: IR ($CHCl_3$) 2.92 (OH), 5.78 (ester C=O), 6.16 (ketone C=O) μm; NMR ($CDCl_3$) δ 1.04 (t, 3 H, J = 7 Hz, Ar′OCCCH$_3$), 1.37, 138 [s, 9 H, $(CH_3)_3CO$ for two diastereomers], 1.67–2.24 (m, 4 H, Ar′OCCH$_2$C, ArOCCH$_2$), 3.34–3.87 (m, 3 H, ArOCCCHCH$_2$), 4.00 (t, 2 H, J = 7 Hz, Ar′OCH$_2$CC), 5.00 (s, 4 H, ArOCH$_2$Ph), 5.04 (s, 2 H, Ar′OCH$_2$Ph), 6.16–7.60 (m, 22 H, PhH, ArH, Ar′H, ArCOCHCHAr′).

Tribenzyl ether **110** (394 mg, 0.5 mmol) was hydrogenated over 200 mg of Pd/C at 3 atm for 4 h as a solution in 50 mL of 1:1 *t*-BuOH–CH_2Cl_2. Standard workup, followed by preparative radial chromatography on silica gel ($CHCl_3$–CH_3OH), yielded 163 mg (63%) of 2,3′,6-trihydroxy-4-[1-(carbo-*tert*-butoxy)-3,4-dihydroxybutoxy]-4′-propoxydihydrochalcone (**111**) as a colorless foam: IR ($CHCl_3$) 2.93 (OH), 5.78 (ester C=O), 6.15 (ketone C=O) μm; NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 6 Hz, Ar′OCCCH$_3$), 1.40 [s, 9 H, $(CH_3)_3C$], 1.80 (h, 2 H, J = 6 Hz, Ar′OCCH$_2$C), 2.83 (t, 2 H, J = 6 Hz, ArCOCCH$_2$Ar′), 3.32 (t, 2 H, J = 6 Hz, ArCOCH$_2$CAr′), 3.93 (t, 2 H, J = 6 Hz, Ar′OCH$_2$CC), 4.56 (m, 1 H, ArOCH), 5.92 (s, 2 H, ArH), 11.26 (s, 1 H, ArOH). *tert*-Butyl ester 111 (163 mg, 0.31 mmol) was dissolved in 5 mL of 10% KOH and stirred vigorously for 15 h. The solution was then cooled to 0 °C, acidified to pH 1.8 with 10% HCl, saturated with NaCl, and extracted with ice-cold EtOAc (3 × 15 mL). The combined cold extracts were dried over $MgSO_4$ and concentrated in vacuo at 0 °C to give 145 mg (100%) of **38** (H) as a light yellow foam. HPLC analysis shows two peaks in a ratio of 60:40 for the two possible diastereomers having t_R = 12.7 and 13.0 min, respectively. Without purification, **38** (H) (145 mg) was titrated to the sodium salt according to the general procedure to yield 112 mg of **38** as

(46) Stotter, P. L.; Hill, K. A. *Tetrahedron Lett.* **1972**, 4067.

a flocculent off-white solid: IR (KBr) 2.7–4.4 (OH), 6.22 (carboxylate anion C=O, ketone C=O) μm; UV (H_2O) λ_{max} 286 nm (ε 17300); NMR (Me_2SO-d_6) δ 0.96 (t, 3 H, J = 7 Hz, Ar'OCCCH$_3$), 3.87 (t, 2 H, J = 7 Hz, Ar'OCH$_2$CC), 4.36 (m, 1 H, ArOCH), 5.80 (s, 2 H, ArH).

2,3',6-Trihydroxy-4-(1-carboxy-4-hydroxybutoxy)-4'-methoxydihydrochalcone Sodium Salt (39). Twenty-five milliliters of DMF was added to a mixture of 3.02 g (10 mmol) of hesperetin, 1.52 g (11 mmol) of K_2CO_3, and 3.30 g (20 mmol) of 2-bromobutyrolactone. The resultant mixture reacted for 14 h, after which standard workup, followed by column chromatography over 215 g of silica gel ($CHCl_3$–CH_3OH), yielded 1.37 g (35%) of 3',5-dihydroxy-4'-methoxy-7-(2-butyrolactonoxy)-flavanone (**112**) as a light yellow oil.

Flavanone **112** (773 mg, 2 mmol) was hydrogenated over 0.4 g of Pd/C at 3.5 atm for 2 h as a solution in 25 mL of 10% KOH. Standard workup, followed by recrystallization (CH_2Cl_2–Et-OAc–acetone), yielded 550 mg (68%) of **39** (H) as white clusters: mp 165–165.5 °C; IR (KBr) 2.8–4.4 (OH), 5.83 (carboxyl C=O), 6.18 (ketone C=O) μm; UV (EtOH) λ_{max} 224 nm (ε 24780), 290 (26500); NMR (acetone-d_6) δ 2.90 (t, 2 H, J = 7 Hz, ArCOCCH$_2$Ar'), 3.42 (t, 2 H J = 7 Hz, ArCOCH$_2$CAr'), 3.77 (t, 2 H, J = 6 Hz, OCH$_2$CCOAr), 3.80 (s, 3 H, Ar'OCH$_3$), 4.97 (t, 1 H, J = 6 Hz, ArOCH), 6.02 (s, 2 H, ArH). Anal. ($C_{20}H_{22}O_9 \cdot 0.25H_2O$) C, H.

The carboxylic acid (436 mg) was titrated to the sodium salt by the general procedure to give 452 mg of **39** as a flocculent white solid.

2,3',6-Trihydroxy-4-(2-oxo-3-carboxypropoxy)-4'-methoxydihydrochalcone Sodium Salt (40). Two grams of amberlyst 15 ion exchange resin was added to a solution of 8.23 g (0.05 mol) of ethyl 4-chloroacetoacetate in 25 mL of methyl orthoformate. After the solution stirred overnight, the resin was filtered, and excess ortho ester was removed in vacuo. The residue was then heated slowly over 1 h to 190 °C, after which it was allowed to cool and then short path distilled to yield 7.37 g (83%) of ethyl 3-methoxy-4-chlorocrotonate (**113**) as a colorless liquid: bp 145–148 °C (40 mm) [lit.[47] bp 98–99 °C (8 mm)]; VPC (6 ft 5% SF96 on 60–80 mesh chromosorb G; 160 °C; 60 cm^3/min He flow) t_R = 1.9 min; NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7 Hz, COOCCH$_3$), 3.73 (s, 3 H, OCH$_3$), 4.20 (q, COOCH$_2$C, J = 7 Hz, COOCH$_2$C), 4.67 (s, 2 H, ClCH$_2$), 5.17 (s, 1 H, CH).

Fifteen grams (0.1 mol) of NaI was added to a solution of 3.58 g (0.02 mol) of **113** in 150 mL of acetone. After the solution stirred vigorously for 20 h in a flask protected from light, standard workup yielded 5.38 g (100%) of ethyl 3-methoxy-4-iodocrotonate (**114**) as an amber liquid: VPC (6 ft 5% SF96 on 60–80 mesh chromosorb G; 160 °C; 60 cm^3/min He flow) t_R = 4.0 min; NMR ($CDCl_3$) δ 1.31 (t, 3 H, J = 7 Hz, COOCCH$_3$), 3.73 (s, 3 H, OCH$_3$), 4.24 (q, 2 H, J = 7 Hz, COOCH$_2$C), 4.48 (s, 2 H, CH$_2$I), 5.13 (s, 1 H, CH).

One-hundred milliliters of DMF was added to a mixture of 6.04 g (20 mmol) of hesperetin, 3.04 g (22 mmol) of K_2CO_3, and 5.40 g (20 mmol) of **114**. The resultant mixture was stirred at 0 °C for 16 h in a flask protected from light, followed by 5 days at ambient temperature, after which standard workup yielded 9.92 g of crude 3',5-dihydroxy-4'-methoxy-7-[(2-methoxy-3-carbethoxyprop-2-enyloxy]flavanone (**115**) as a dark oil. Without purification, crude **115** was dissolved in 95 mL of CH_3OH and treated with 5 mL of 50% H_2SO_4 at reflux for 2.5 h. Standard workup, followed by column chromatography over 775 g of silica gel ($CHCl_3$–CH_3OH) and recrystallization (hexane–EtOAc), yielded 1.82 g (20%) of 3,5-dihydroxy-4'-methoxy-7-(2-oxo-3-carbomethoxypropoxy)flavanone (**116**) as tiny clusters: mp 114–118 °C; IR (KBr) 2.90 (OH), 5.72 (ester C=O), 5.82 (ketone C=O), 6.11 (ketone C=O) μm; UV (MeOH) λ_{max} 286 nm (ε 21500); NMR (acetone-d_6) δ 2.45–3.26 (br m, 2 H, ArCOCH$_2$), 3.70 (s, 3 H, COOCH$_3$), 3.86 (s, 3 H, Ar'OCH$_3$), 4.60 (s, 2 H, ArOCH$_2$), 5.00 (s, 2 H, ArOCCOCH$_2$), 5.33–5.63 (m, 1 H, Ar'CHO), 6.06 (s, 2 H, ArH), 7.02 (m, 3 H, Ar'H). Anal. ($C_{21}H_{20}O_9$) C, H.

Flavanone **116** (833 mg, 2.0 mmol) was hydrogenated over 0.4 g Pd/C at 1 atm for 48 h as a solution in 85 mL of 10% KOH. Standard workup, followed by recrystallization (H_2O–CH_3OH), yielded 519 mg (64%) of **40** (H) as light tan needles: mp 227–228 °C dec; IR (KBr) 3.0–4.4 (OH), 5.80 (carboxylic acid C=O), 5.85 (aliphatic ketone C=O), 6.19 (aromatic ketone C=O) μm; UV (MeOH) λ_{max} 224 nm (ε 22600), 285 (23500); NMR (acetone-d_6) δ 2.84 (t, 2 H, J = 7 Hz, ArCOCCH$_2$Ar'), 3.37 (t, 2 H, J = 7 Hz, ArCOCH$_2$CAr'), 3.80 (s, 3 H, Ar'OMe), 4.65 (s, 2 H, ArOCH$_2$), 6.04 (s, 2 H, ArH). Anal. ($C_{20}H_{20}O_9$) C, H. A 189-mg sample of **40** (H) was titrated to the sodium salt by the general method to yield 200 mg of **40** as a flocculent white solid.

2,3',6-Trihydroxy-4-(2-aminoethoxy)-4'-methoxydihydrochalcone (41). To an ice-cold solution of 20.5 g (0.1 mol) of 2-bromoethylammonium bromide in 140 mL of H_2O was added 15.2 g (0.089 mol) of benzyl chloroformate in one portion, followed immediately by 18.5 g (0.22 mol) of $NaHCO_3$. The resultant reaction mixture was allowed to warm to ambient temperature while stirring overnight, after which standard workup and column chromatography over 400 g of silica gel ($CHCl_3$–CH_3OH) yielded 20.4 g (99%) of benzyl 2-bromoethylcarbamate (**117**) as an oil, which solidified on standing: mp 43–46.5 °C; IR (KBr) 3.00 (NH), 5.94 (C=O) μm; NMR ($CDCl_3$) δ 3.27–3.77 (m, 4 H, BrCH$_2$CH$_2$N), 5.09 (s, 2 H, PhCH$_2$O), 5.16–5.57 (br s, 1 H, NH), 7.33 (s, 5 H, PhH). Anal. ($C_{10}H_{12}BrNO_2$) C, H, N.

A mixture of 6.04 g (20 mmol) of hesperetin, 3.04 g (22 mmol) of K_2CO_3, and 5.68 g (22 mmol) of **117** in 150 mL of DMF was reacted at ambient temperature for 24 h, 30 °C for 24 h, and 40 °C for 8 h. Eight millimoles of additional **117** was then added and stirring at 40 °C continued for 18 h. Standard workup, followed by column chromatography over 500 g of silica gel ($CHCl_3$–CH_3OH) and recrystallization (hexane–EtOAc), yielded 5.30 g (55%) of 3',5-dihydroxy-4'-methoxy-7-[2-[*N*-(carbobenzyloxy)amino]ethoxy]flavanone (**118**) as white clusters: mp 129–131 °C; IR (KBr) 3.19 (OH, NH), 5.92 (urethane C=O), 6.12 (ketone C=O) μm; UV (EtOH) λ_{max} 286 nm (ε 21500); NMR (acetone-d_6) δ 2.87 (m, 2 H, ArCOCH$_2$), 3.56 (m, 2 H, ArOCCH$_2$N), 3.86 (s, 3 H, OCH$_3$), 4.14 (t, 2 H, J = 6 Hz, ArOCH$_2$), 5.07 (s, 2 H, PhCH$_2$O), 5.43 (q, 1 H, J = 11 and 3 Hz, ArCOCCHAr'), 6.04 (s, 2 H, ArH), 7.31 (s, 5 H, PhH), 7.64 (s, 1 H, NH). Anal. ($C_{26}H_{25}NO_8$) C, H. Hydrogenation of **118** (4.84 g, 10.1 mmol) over 2 g of Pd/C at 3 atm for 12 h as a solution in 200 mL of 10% KOH, followed by filtration through Celite, acidification to pH 5.5 with 10% HCl, and concentration in vacuo, yielded a mixture of dihydrochalcone **41** and salt. This mixture was triturated with cold water, and the product was filtered. It was then recrystallized (H_2O) to yield 2.52 g (72%) of pure **41** as tiny tan clusters: mp 241–245 °C dec; IR (KBr) 3.15 (OH, NH), 6.18 (C=O) μm; UV (H_2O) λ_{max} 285 nm (ε 2010); NMR (Me_2SO-d_6) δ 3.72 (s, 3 H, OCH$_3$), 4.17 (t, 2 H, J = 5 Hz, ArOCH$_2$), 6.07 (s, 2 H, ArH). Anal. ($C_{18}H_{21}NO_6 \cdot 2H_2O$) C, H.

2,3',6-Trihydroxy-4-(3-aminopropoxy)-4'-methoxydihydrochalcone (42). To an ice-cold solution of 6.67 g (30 mmol) of 3-bromopropylammonium bromide in 40 mL of H_2O was added 4.10 g (24 mmol) of benzyl chloroformate in one portion, followed immediately by 5.55 g (66 mmol) of $NaHCO_3$. The resultant reaction mixture was allowed to warm to ambient temperature over 3 h, after which standard workup and column chromatography over 200 g of silica gel ($CHCl_3$–CH_3OH) yielded 4.88 g (75%) of benzyl 3-bromopropylcarbamate (**119**) as a colorless oil: IR (film) 2.96 (NH), 5.78 (C=O), 5.86 (C=O) μm; NMR ($CDCl_3$) δ 1.96 (p, 2 H, J = 7 Hz, BrCCH$_2$), 3.24 (q, 2 H, J = 7 Hz, NCH$_2$), 3.36 (t, 2 H, J = 5 Hz, BrCH$_2$), 5.07 (s, 2 H, PhCH$_2$O), 5.08 (br s, 1 H, NH), 7.30 (s, 5 H, PhH). Anal. ($C_{11}H_{14}BrNO_2$) C, H.

A mixture of 598 mg (2.2 mmol) of **119**, 604 mg (2.0 mmol) of hesperetin, 304 mg (2.2 mmol) of K_2CO_3, and 15 mL of DMF was reacted at 30 °C for 24 h, after which standard workup and silica gel thick-layer chromatography yielded 524 mg (53%) of 3',5-dihydroxy-4'-methoxy-7-[[*N*-(carbobenzyloxy)amino]propoxy]-flavanone (**120**) as a yellow foam: NMR ($CDCl_3$) δ 1.93 (p, 2 H, J = 6 Hz, ArOCCH$_2$CN, 2.76–3.07 (m, 2 H, ArCOCH$_2$), 3.33 (q, 2 H, J = 6 Hz, CH$_2$N), 3.92 (s, 3 H, Ar'OCH$_3$), 4.00 (t, 2 H, J = 6 Hz, ArOCH$_2$), 5.10 (s, 2 H, PhCH$_2$O), 5.30 (AB q, 1 H, J = 10 and 4 Hz, ArCOCCHAr'), 5.88 (s, 1 H, Ar'OH), 6.03 (s, 2 H, ArH), 6.80–7.09 (m, 3 H, Ar'H), 7.36 (s, 5 H, PhH), 12.00 (s, 1 H, ArOH).

Hydrogenation of **120** (247 mg, 0.5 mmol) over 145 mg of Pd/C at 3 atm for 6 h as a solution in 20 mL of 5% KOH, followed by filtration through Celite, acidification to pH 1 with 10% HCl, and concentration in vacuo, yielded a dihydrochalcone **42**/salt mixture.

(47) Bankowska, Z. *Rocz. Chem.* **1966**, *40*, 587–595.

Extraction with hot EtOH yielded 255 mg of a white solid, which on recrystallization from H_2O yielded 99 mg (55%) of **42** as a white powder: mp 228–235 °C dec; IR (KBr) 2.5–4.0 (OH, NH), 6.17 (C=O) μm; UV (MeOH) λ_{max} 227 nm (ε 19300), 284 (19860); NMR (CD_3OD) δ 2.12 (p, 2 H, J = 7 Hz, $ArOCCH_2CN$), 2.43–3.53 (m, 6 H, CH_2N, $ArCOCH_2CH_2Ar'$), 3.86 (s, 3 H, $Ar'OCH_3$), 4.17 (t, 2 H, J = 7 Hz, $ArOCH_2$), 6.00 (s, 2 H, ArH), 6.53–6.98 (m, 3 H, Ar'H). Anal. ($C_{19}H_{23}NO_6$·HCl·0.25H_2O) C, H.

2,3′,6-Trihydroxy-4-(3-phosphopropoxy)-4′-methoxydihydrochalcone Potassium Salt (43). A mixture of 2.87 g (5 mmol) of 2,3′,6-tris(benzyloxy)-4-hydroxy-4′-methoxydihydrochalcone (**48**), 1.38 g (10 mmol) of K_2CO_3, and 70.1 g (50 mmol) of 1,3-dibromopropane in 75 mL of DMF was reacted for 48 h, after which standard workup yielded 2.91 g (84%) of 2,3′,6-tris(benzyloxy)-4-(3-bromopropoxy)-4′-methoxydihydrochalcone (**121**) as a white solid. Bromide **121** (2.91 g, 4.18 mmol) was dissolved in 50 mL of $P(OCH_3)_3$ and refluxed for 39 h. After all solvent was removed in vacuo, standard workup, followed by column chromatography over 200 g of silica gel ($CHCl_3$–CH_3OH), yielded 1.93 g (64%) of 2,3′,6-tris(benzyloxy)-4-(dimethyl-3-phosphopropoxy)-4′-methoxydihydrochalcone (**122**) as an oil, which crystallized on standing. Crystallization from hexane–EtOAc yielded colorless clusters: mp 92–95.5 °C; IR (film) 5.88 (C=O) μm; UV (MeOH) λ_{max} 278 nm (ε 7600); NMR ($CDCl_3$) δ 2.90 (m, 4 H, $ArCOCH_2CH_2Ar'$), 3.64 [s, 6 H, $PO(OCH_3)_2$], 3.77 (s, 3 H, $Ar'OCH_3$), 3.94 (t, 2 H, J = 6 Hz, $ArOCH_2$), 5.03 (s, 6 H, $PhCH_2O$), 6.17 (s, 2 H, ArH), 7.37 (s, 15 H, PhH). Anal. ($C_{42}H_{45}O_9P$) C, H.

To a solution of 725 mg (1 mmol) of **122** in 10 mL of CH_2Cl_2 was added 337 mg (2.2 mmol) of Me_3SiBr while stirring at 0 °C. After 30 min, 2.2 mmol of additional Me_3SiBr was added and stirring continued at 0 °C for 2 h, at which point the hydrolysis reaction was quenched by the addition of 60 mL of THF–H_2O–EtOH (5:1:6). The crude tribenzylphosphonic acid was then hydrogenated over 300 mg of Pd/C at 3 atm for 15 h. The reaction mixture was then filtered through Celite and concentrated in vacuo to give a tan solid. The solid product was dissolved in 25 mL of 5% KOH and washed with Et_2O, after which the pH was adjusted to 5.0 by the addition of 10% HCl. After the solution was left standing overnight, filtration yielded 316 mg of an impure crystalline product. Preparative HPLC of this sample then yielded 217 mg (51%) of **43** as a flocculent white solid: mp 138–150 dec; IR (KBr) 2.96–4.22 (OH), 6.17 (C=O) μm; UV (MeOH) λ_{max} 225 nm (ε 18800), 287 (23100); NMR (CD_3OD) δ 2.83 (t, 2 H, J = 6 Hz, $ArCOCCH_2Ar'$), 3.30 (t, 2 H, J = 6 Hz, $ArCOCH_2$), 3.80 (s, 3 H, $Ar'OCH_3$), 4.05 (t, 2 H, J = 6 Hz, $ArOCH_2$), 5.95 (s, 2 H, ArH). Anal. ($C_{19}H_{22}KO_9P$·1.5H_2O) C, H.

2,3′,6-Trihydroxy-4-(2-sulfamoethoxy)-4′-methoxydihydrochalcone Potassium Salt (44). A solution of 541 mg (3.14 mmol) of catechol sulfate in 1.5 mL of CH_2Cl_2 was added dropwise to a solution of 991 mg (2.85 mmol) of amine **41** and 318 mg (3.14 mmol) of Et_3N in 15 mL of DMF while at 0 °C. After the solution warmed to ambient temperature over 16 h, standard workup and recrystallization ($CHCl_3$) yielded 1.14 g (77%) of 2-hydroxyphenyl *N*-(2,3′,6-trihydroxy-4-ethoxy-4′-methoxydihydrochalcone)-sulfamate (**123**) as light tan clusters: mp 78–80 °C; IR (KBr) 2.93 (OH, NH), 6.17 (C=O) μm; UV (EtOH) λ_{max} 283 nm (ε 21900); NMR (acetone-d_6) δ 2.86 (t, 2 H, J = 7 Hz, $ArCOCCH_2Ar'$), 3.36 (t, 2 H, J = 7 Hz, $ArCOCH_2$), 3.63 (t, 2 H, J = 6 Hz, CH_2N), 3.82 (s, 3 H, OCH_3), 4.14 (t, 2 H, J = 6 Hz, $ArOCH_2$), 5.97 (s, 2 H, ArH). Anal. ($C_{24}H_{25}NO_{10}S$·H_2O) C, H. One-hundred milliliters of 0.2 M KOH was added to 5.2 g (10 mmol) of **123**, after which the resulting solution was refluxed for 1 h. The reaction mixture was then neutralized by the addition of 10% HCl, concentrated in vacuo to dryness, and triturated with Et_2O. Quantitative HPLC analysis of the residue, with a standard solution of **44**, indicated a yield of 4.66 g (100%). Recrystallization (H_2O) yielded 4.15 g (89%) of **44** as off-white flakes: mp 176–180 °C IR (KBr) 2.95 (OH), 3.03 (NH), 6.17 (C=O) μm; UV (H_2O) λ_{max} 282 nm (ε 20200); NMR (Me_2SO-d_6) δ 2.97 (t, 2 H, J = 6 Hz, $ArCOCCH_2Ar'$), 3.16 (t, 2 H, J = 6 Hz, $ArCOCH_2$), 3.54 (t, 2 H, J = 5 Hz, NCH_2), 3.70 (s, 3 H, OCH_3), 4.03 (t, 2 H, J = 5 Hz, $ArOCH_2$), 5.96 (s, 2 H, ArH). Anal. ($C_{18}H_{20}KNO_9S$·0.5H_2O) C, H, N, S.

2,3′,6-Trihydroxy-4-(3-carboxy-3-hydroxypropoxy)-4′-methoxydihydrochalcone Sodium Salt (45). According to the method of Price and Judge,[48] 25.8 g (0.3 mol) of butyrolactone was reacted with 101 g (0.63 mol) of Br_2 in the presence of 3.25 g (0.105 mol) of red phosphorus to give 2,4-dibromobutyryl bromide. Methanolysis by treatment with 50 mL of CH_3OH at reflux for 14 h, followed by standard workup and fractional distillation (20-cm Vigreux column), yielded 72.8 g (93%) of methyl 2,4-dibromobutyrate (**124**) as a colorless liquid: bp 107–108 °C (9 mm); IR (film) 5.76 (C=O) μm; NMR ($CDCl_3$) δ 2.53 (q, 2 H, J = 6.5 Hz, $BrCCH_2$), 3.56 (t, 2 H, J = 6.5 Hz, $BrCH_2$), 3.82 (s, 3 H, OCH_3), 4.53 (t, 1 H, J = 6.5 Hz, CHBr).

A mixture of 13.0 g (50 mmol) of **124**, 4.92 g (60 mmol) of NaOAc, and 250 mL of DMF was stirred at ambient temperature for 18 h and then at 50 °C for 1 h, after which standard workup, followed by distillation, yielded 9.24 g (77%) of methyl 2-acetoxy-4-bromobutyrate (**125**) as a colorless liquid: bp 70–72 °C (0.1 mm); IR (film) 5.66 (C=O), 5.72 (C=O) μm; NMR ($CDCl_3$) δ 2.15 (s, 3 H, CH_3COO), 2.40 (q, 2 H, J = 7 Hz, $BrCCH_2$), 3.48 (t, 2 H, J = 7 Hz, $BrCH_2$), 3.76 (s, 3 H, OCH_3), 5.20 (t, 1 H, J = 7 Hz, CHCOO). Anal. ($C_7H_{11}BrO_4$) C, H, Br.

A mixture of 3.02 g (10 mmol) of hesperetin, 2.63 g (11 mmol) of **125**, 1.52 g (11 mmol) of K_2CO_3, and 50 mL of DMF was reacted for 3 days. Standard workup, followed by silica gel column chromatography ($CHCl_3$–CH_3OH), yielded 3.50 g (76%) of 3′,5-dihydroxy-4′-methoxy-7-(3-acetoxy-3-carbomethoxypropoxy)-flavanone (**126**) as a light yellow oil. Hydrogenation of a 3.50-g (7.6 mmol) sample of **126** over 0.5 g of Pd/C at 3 atm for 18 h as a solution in 55 mL of 5% KOH, followed by standard workup and recrystallization (H_2O–CH_3OH), yielded 1.13 g (36%) of **45** (H) as off-white clusters: mp 140–144 °C; IR (KBr) 2.9–4.2 (OH), 5.82 (carboxylic acid C=O), 6.20 (ketone C=O) μm; UV (H_2O) λ_{max} 287 nm (ε 21040); NMR (acetone-d_6) δ 2.87 (t, 2 H, J = 7 Hz, $ArCOCCH_2Ar'$), 3.37 (t, 2 H, J = 7 Hz, $ArCOCH_2$), 3.80 (s, 3 H, $Ar'OCH_3$), 4.17 (t, 2 H, J = 6 Hz, $ArOCH_2$), 4.12–4.62 (m, 1 H, ArOCCCHCOO), 6.00 (s, 2 H, ArH). Anal. ($C_{20}H_{22}O_9$) C, H.

Conversion of a 150-mg sample of **45** (H) to the sodium salt by the general procedure yielded 158 mg of **45** as a light pink flocculent solid.

Acknowledgment. We thank Ms. M. Swartz and Ms. J. Lee for sensory analytical work and Tragon Corp. for assistance in the design of sensory experiments. We also thank Mr. S. de Keczer for assistance with the computer analysis, Dr. R. Phillips and Mr. C. T. Seitz for analytical studies, and Dr. J. Brown, Mr. P. Dietrich, Mr. C. Smith, and Ms. F. Enderlin for biological safety studies. In addition, we are indebted to Dr. N. Weinshenker for useful comments concerning this manuscript and to Ms. B. Henderson and Ms. E. Plowman for their diligent efforts in assembling the latter. Finally, we are very grateful to the National Institute of Dental Research (Contract 1-DE-62479) for the funding of this research in its entirety.

Supplementary Material Available: Time–intensity data for sucrose, saccharin, **2**, **40**, **43**, **44**, NHDHC, and MAG, as well as perceived intensity vs. time plots for **2**, **40**, **43**, **44**, NHDHC, and MAG, are presented (9 pages). Ordering information is given on any current masthead page.

(48) Price, C. C.; Judge, J. M. In "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 255.