IR 5.78; NMR 1.99 (s, 3 H, $OCOCH_3$), 3.62 (s, 3 H, CO_2CH_3), 4.2 (overlapping s and q, 7′(*E*)-H, OCH_2CH_3), 4.8 (overlapping m, 7′(*Z*)-H, 3′-H), 5.6 (br s, 1 H, 1″-H); GC/MS, two components in a 3:2 (**43**/**44**) ratio with identical fragmentations.

X-ray Analysis of 38. This compound crystallized as small monoclinic needles from *n*-hexane. The following crystallographic data were measured for these crystals: a = 5.378 (7) Å, b = 18.973 (18) Å, c = 14.182 (17) Å, β = 102.68(10)°, and space group $P2_1$ with 2 molecules in the unit cell.

Intensity data were collected by the stationary crystal–stationary counter method with Cu Kα radiation monochromatized by balanced nickel and cobalt filters on a GE XRD-6 diffractometer. A total of 1706 reflections were measured ($2\theta < 100°$) with 588 having intensities which were weak and considered unobserved. Corrections were applied to the data for α_1–α_2 splitting and Lorentz polarization effects.

All nonhydrogen atoms were located by a combination of tangent formula refinement[29] and Fourier methods. The structure was refined by the block diagonal least-squares method with anisotropic thermal parameters assigned to all the nonhydrogen atoms. The absolute configuration of the molecule was determined by statistical comparison of the converged structure factors for each enantiomorph. The refined R values were 0.087 and 0.092 for the correct and incorrect configurations, respectively.

(29) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

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Registry No. **1**, 71117-51-6; **2**, 71117-50-5; **3**, 71117-49-2; **4**, 80629-31-8; **5**, 67441-42-3; **6**, 80572-59-4; **7**, 69493-28-3; **8**, 80572-60-7; **9**, 80572-61-8; **10**, 80572-62-9; **11**, 67441-49-0; **12**, 80572-63-0; **13**, 67441-47-8; **14**, 68688-88-0; **15**, 67441-46-7; **15** bis(TMS), 80572-64-1; **16**, 67463-69-8; **16** bis(TMS), 80629-32-9; **17**, 71092-34-7; **18**, 80572-65-2; **19**, 80572-66-3; **20**, 80572-67-4; **21**, 71092-35-8; **22**, 80572-68-5; **23**, 80572-69-6; **23** di-2,4-DNP, 80572-70-9; **24**, 80572-71-0; **24** di-2,4-DNP, 80572-72-1; **25**, 41065-97-8; **25** 2,4-DNP, 14093-70-0; **26**, 80572-73-2; **27**, 71092-37-0; **28**, 1604-34-8; **29**, 38136-29-7; **30**, 32864-38-3; **31**, 80572-74-3; **32**, 57689-16-4; **33**, 80572-75-4; **34**, 80572-76-5; **35**, 80572-77-6; **36**, 67441-48-9; **37**, 80629-33-0; **38**, 80629-34-1; **39**, 80572-78-7; **40**, 80572-79-8; **41**, 80572-80-1; **42**, 80583-30-8; **43**/**44**, 80572-81-2; 5-chloro-2-pentanone ethylene ketal, 5978-08-5; triethyl phosphonoacetate, 867-13-0.

Supplementary Material Available: Tables III–V containing atomic coordinates, anisotropic thermal parameters, bond distances, and bond angles (3 pages). Ordering information is given on any current masthead page.

Observations on the Chemistry of α-Azido Esters. Efficient Synthesis of a Potently Sweet Homoserine–Dihydrochalcone Conjugate

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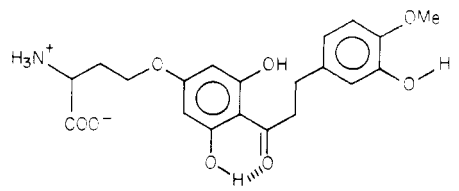
An efficient preparation of methyl 2-azido-4-bromobutyrate (**6**) has been developed. This reagent undergoes an alkylation reaction with the trihydroxyflavanone hesperetin (**2**) with complete regiospecificity to give only the 7-substitution product **3**. Hydrogenation of **3** in aqueous alkali yields the potent dihydrochalcone sweetener **1** in nearly quantitative yield. Azido ester **6** was found to undergo intramolecular alkylation to yield 1-(carbomethoxy)-1-azidocyclopropane (**9**) on treatment with base. This represents the *first* observation of base-promoted aliphatic azide alkylation. 4-[3-Azido-3-(carbomethoxy)propoxy]acetophenone (**8**), formed on alkylation of 4-hydroxyacetophenone (**7**) with **6**, undergoes oxidative nitrogen elimination on treatment with base to yield the unstable 4-[3-(carbomethoxy)-3-oxopropoxy]acetophenone (**11**). Keto ester **11** undergoes facile 1,2-elimination of **10** to yield **7**, thus explaining the fragmentation of **3** to **2**. Azido ester **6** alkylates **2**, a strongly acidic phenol [$(pK_a)_{rel}$ = 0.0], in high yield and **7**, a less acidic phenol [$(pK_a)_{rel}$ = 1.6], in poor yield, and fails to alkylate phenol, a weakly acidic phenol [$(pK_a)_{rel}$ = 3.0]. This result is explained in terms of the high basicity of the weak acid–phenol conjugate bases. Thus the more basic phenolate anions act as bases in promoting 1,3-elimination in **6** to yield **9**. This rationale is extended to explain the complete regiospecificity in the alkylation of **2**.

The interesting observations of Jarvis and Nicholas[1] on the base-promoted decomposition of α-azido nitriles and sulfones as well as related work by Rathke and Manis[2] on α-azido esters prompt us to report some observations of a related nature encountered in the development of a large-scale economical synthesis of the potent dihydrochalcone sweetener 1.[3] In order to apply the previously developed methodology for synthesis of 4-O-substituted hesperetin dihydrochalcones (**4**) outlined in Scheme I,[4] we required an inexpensive alkylating agent RX for the introduction of the homoserine side chain.



1

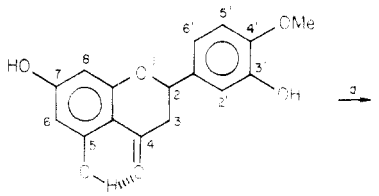
One possible candidate was methyl 2-azido-4-bromobutyrate (**6**). This compound was readily available from methyl 2,4-dibromobutyrate (**5**) by reaction with sodium azide in dimethylformamide (DMF). In earlier work we described an efficient synthesis of dibromide **5**.[5] The preparation of α-azido ester **6** is illustrated in Scheme II.

* Syva Company, 900 Arastradero Road, Palo Alto, CA 94303.

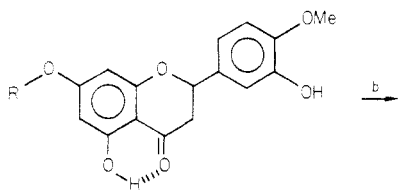
(1) Jarvis, B. J.; Nicholas, P. E. *J. Org. Chem.* **1979**, *44*, 2951–2952.
(2) Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952–4954.
(3) DuBois, G. E.; Crosby, G. A.; Lee, J. F.; Stephenson, R. A.; Wang, P. C. *J. Agric. Food Chem.* **1981**, *29*, 1269–1276.
(4) DuBois, G. E.; Crosby, G. A.; Saffron, P. *Synth. Commun.* **1977**, *7*, 49–56.
(5) DuBois, G. E.; Crosby, G. A.; Stephenson, R. A. *J. Med. Chem.* **1981**, *24*, 408–428.

0022-3263/82/1947-1319$01.25/0

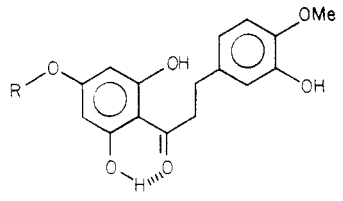
Scheme I[a]



2 (hesperetin)



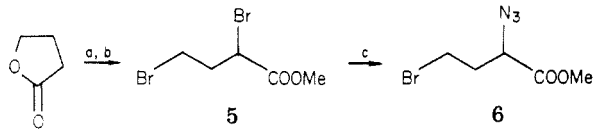
3 (R = $CH_2CH_2CHN_3COOCH_3$)



4

[a] (a) K_2CO_3/DMF/RX, (b) H_2/Pd-C/10% KOH.

Scheme II[a]



[a] (a) Br_2P, (b) CH_3OH, (c) NaN_3/DMF.

The synthesis of α-amino acids from α-azido carboxylic acid derivatives is a process that has been known for many years.[6]

Although the bromo azide **6** was always contaminated by small amounts (ca. 15%) of methyl 2,4-diazidobutyrate, this mixture proved satisfactory for alkylation studies. Treatment of hesperetin (**2**) with a slight excess of **6** in the presence of K_2CO_3 in DMF gave the 7-O-substituted derivative **3** as the only hesperetin-derived product. To our surprise, 3′-O-alkylation, which occurred to substantial extents with all alkylating agents employed in our earlier work,[4] was not detectable with **6**. Conversion of **3** to the sweet homoserine–dihydrochalcone conjugate **1** was then effected by dissolution in cold 10% KOH and low-pressure hydrogenation.

The yield of hesperetin alkylation product **3** was found to be unusually dependent on the time and temperature of the reaction. At 20 °C, a yield of 50% could be obtained on reaction workup after 24 h while longer reaction times resulted in much lower yields, even though the crude product appeared to contain **2** and **3** as the only flavanoid components. Interestingly, when pure **3** was treated under the reaction conditions, a mixture of **2** and **3** was obtained; clearly alkylation product **3** must be undergoing some type of fragmentation reaction to yield starting material **2**.

The hydrogenation of **3** in aqueous alkali also appeared at first to be a somewhat capricious reaction. Dissolution of **3** in 10% KOH at room temperature or above followed by low-pressure hydrogenation was found to give **1** as the major product but was contaminated by several other products which included hesperetin dihydrochalcone **4** (R = H). Dissolution of **3** in 10% KOH at ice-bath temperature, however, followed by hydrogenation as above, reproducibly gave **1** in nearly quantitative yield.

Table I. Alkylation of Hesperetin (2) with $XCH_2CH_2CH(N_3)COOMe$

$$2 \xrightarrow[XCH_2CH_2CH(N_3)COOMe]{\text{base/solvent}} 3$$

reaction[a]	base (mmol)	solvent	X	2/3 ratio[b]
1	K_2CO_3 (1)	DMF	Br	85:15
2	K_2CO_3 (0.5)	DMF	Br	90:10
3	K_2CO_3 (1)	DMF	I	72:28
4	K_2CO_3 (0.5)	DMF	I	82:18
5	Cs_2CO_3 (1)	DMF	Br	89:11
6	Cs_2CO_3 (1)	DMF	I	67:33
7	K_2CO_3 (1)	NMP	Br	80:20
8	K_2CO_3 (1)	Me_2SO	Br	84:16
9	$KHCO_3$ (1)	DMF	Br	92:8
10	K_2CO_3 (1)	acetone	I	98:2
11	K_2CO_3 (1)	NMP	I	51:49
12	Cs_2CO_3 (1)	NMP	I	64:36

[a] All reactions were run (18 h) on 0.25 mmol of **2** in 2.0 mL of solvent with 1.00 equiv of alkylating agent in a constant-temperature bath at 25 °C except for reaction 10 which was run at reflux temperature. [b] Hesperetin (**2**)/alkylation product **3** ratios were calculated from HPLC peak areas on a molar basis and are corrected for relative detector sensitivity.

In recognition of the potential utility of **1** as a nonnutritive sweetener, we sought to optimize the conditions for the hesperetin alkylation reaction. HPLC analysis of reaction aliquots showed hesperetin (**2**) and the desired alkylation product **3** as the only detectable components. The results of a study, in which the effects of base, solvent, and leaving group on the **2**/**3** ratio were quantitated after an 18-h reaction, are summarized in Table I. On inspection of these results it can be seen that K_2CO_3 base in *N*-methylpyrrolidone (NMP) solvent with the iodo alkylating agent (reaction 11) appears most promising. Further studies showed yield improvement with slightly elevated temperatures and excess reagents. Thus treatment of 10 mmol of **2** with 11 mmol each of K_2CO_3 and $ICH_2CH_2CH(N_3)COOMe$ in 40 mL of NMP at 35 °C resulted in an 85% yield of **3** as determined by HPLC.

Solvent has a quite marked effect on this reaction. NMP is clearly the preferred solvent while DMF and dimethyl sulfoxide (Me_2SO) are acceptable and acetone is unsatisfactory (cf. reactions 1, 7, 8, and 10 and also 3 and 11 of Table I).[7] Use of Cs_2CO_3 as the base, which on reaction with **2** should yield a phenolate anion more reactive than that obtained with K_2CO_3 as the base,[8] had no significant beneficial effect on the reaction in DMF (cf. reactions 1 vs. 5 and 3 vs. 6) and gave somewhat inferior results in NMP (cf. reaction 11 vs. 12).[9] It was believed that the apparent fragmentation of product **3** to starting material

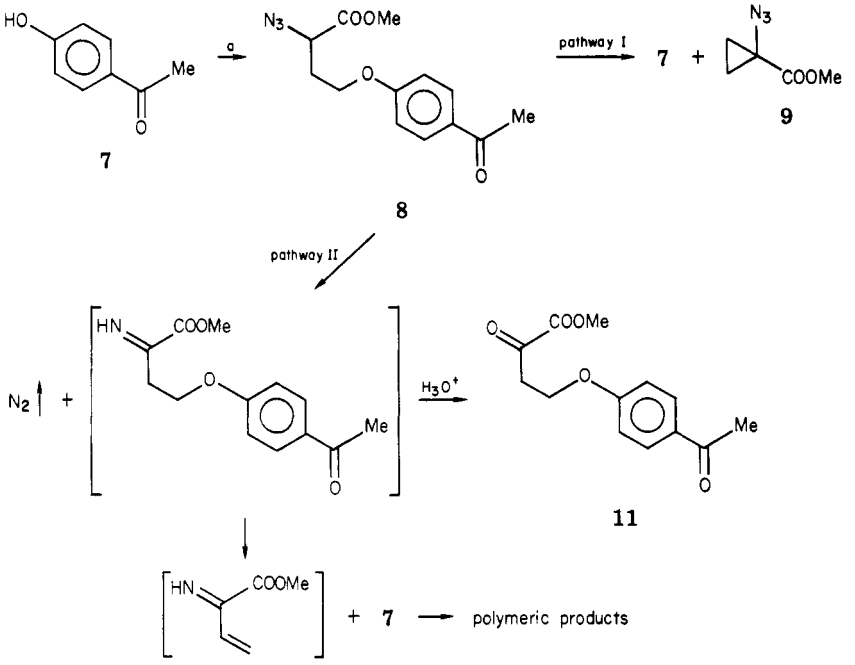
(6) Bertho, A.; Maier, J. *Justus Liebigs Ann. Chem.* **1932**, *498*, 50.

(7) Additionally, following a rigorous study of reaction kinetics, it was found that NMP was substantially more effective than DMF in promoting alkylation of malonic ester salts. See: Zaugg, H. E.; Horrom, B. W.; Borgwardt, S. *J. Am. Chem. Soc.* **1960**, *82*, 2895–2903.

(8) Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett.* **1976**, 3361–3364. Cesium phenolates, obtained in reactions of phenols with CsF, were observed to undergo reaction with dihalomethanes at a rate substantially higher than that for potassium phenolates obtained in reaction with KF.

(9) Although Cs_2CO_3 is reportedly significantly more soluble in organic solvents than K_2CO_3, this factor does not appear of benefit in hesperetin alkylation. See: Zaugg, H. E. *J. Org. Chem.* **1976**, *41*, 3419.

Scheme III[a]



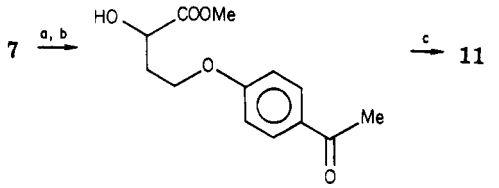
[a] (a) K_2CO_3/NMP/$BrCH_2CH_2CHN_3COOCH_3$.

was likely to be base promoted. Since use of 1 mol of a base such as K_2CO_3 actually introduces 2 equiv of base, the reaction was examined with 1 equiv of base (cf. reactions 2, 4, and 9). This was without beneficial effect.

In an effort to understand the complexities of alkylation of hesperetin (**2**) with bromoazide **6**, we elected to study this chemistry in a model system. Thus phenol was treated under the conditions found optimum for **2** alkylation. We were astonished to find no alkylation to have occurred; in fact, no conditions were found under which **6** would alkylate phenol. Subsequently, 4-hydroxyacetophenone (**7**) was treated under standard alkylation conditions. A 34% yield of the expected alkylation product **8** was obtained, while 54% of **7** was recovered. In addition, small amounts (each ca. 2% of crude product) of two unknown **7**-derived products were also isolated in impure form. TLC analysis of the crude product showed a significant amount of very polar, presumably polymeric, material. Interestingly, in an attempt to recover unused **6**, the chromatographic fraction in which it was expected was found to contain none. A new compound, cyclopropyl azide **9**, was isolated, however (Scheme III).

As was observed in the case of **3**, the alkylated acetophenone **8** also undergoes decomposition (54%; HPLC) to yield starting material **7** (24%) when treated under the reaction conditions. In view of the isolation of **9** in the preparation of **8**, it was unclear whether fragmentation of **8** to **7** was proceeding through a 1,3-elimination (pathway I, Scheme III) or via an oxidative N_2 elimination[2] followed by 1,2-elimination of **10** (pathway II, Scheme III). Examination of the NMR spectrum and HPLC chromatogram of the crude product showed no **9** to be detectable. TLC analysis showed the formation of a major more polar product in addition to **7**. NMR of the crude product suggested this product to be the α-keto ester **11**. Attempts to isolate **11** in pure form, via chromatography or recrystallization, from the crude product yielded only **7**. Structure **11** was assigned on the basis of comparison of TLC, HPLC, and NMR properties obtained from an authentic sample prepared as shown in Scheme IV.

Scheme IV[a]



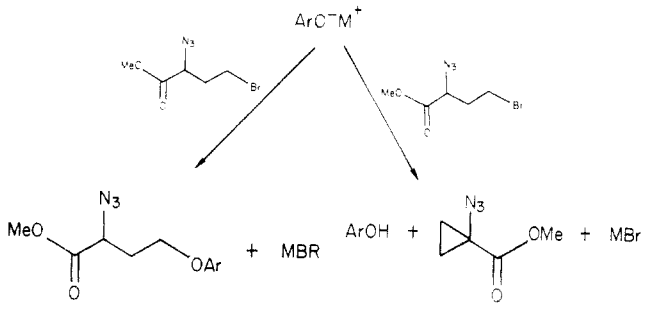
[a] (a) K_2CO_3/NMP/$BrCH_2CH_2CH(OAc)COOMe$, (b) MeOH/*p*-TsOH/Δ, (c) $C_5H_5NHCrO_3Cl/CH_2Cl_2$.

Therefore, it appears that the fragmentation of **8**, and by inference that of **3** also, proceeds essentially completely by the oxidative nitrogen elimination pathway. Thus it is likely that unduly long reaction times (**2** → **3**) allow significant amounts of fragmentation (**3** → **2** + **10**) to occur, thus resulting in consumption of alkylating agent **6** to yield the unsaturated imino ester **10**. Unfortunately, **10** likely participates in copolymerization reactions with **2** and **3** thus resulting in further yield reduction.

The absence of cyclopropyl azide **9** in the crude product from the **8**/K_2CO_3 reaction suggests it must be forming via alkylating agent **6** decomposition. In fact, treatment of **6** under the reaction conditions (K_2CO_3/NMP/20 °C/64 h) resulted in consumption of 58% (HPLC) of **6** to give a 47% yield of the base-stable cyclopropyl azide **9**. Apparently, if an alternative (e.g., alkylation) to oxidative N_2 elimination is possible for $R–C^-M^+(N_3)(COOR')$, such may occur. To our knowledge, the intramolecular alkylation which occurs in **6** represents the *first* observed base-promoted alkylation of an azide. The clean conversion of **6** to **9** suggests that metalated α-azido esters may undergo alkylation and thus provide a general route to novel α-amino acids.

The failure of phenol to undergo alkylation with **6** while **7** alkylates in modest yield and **2** in high yield merits comment. The propensity of these phenols to alkylate follows in an order reverse to that of acidity. The relative acidities in NMP [$(pK_a)_{rel}$] were determined by potentiometric titration by the method of Ritchie and Uschold.[10]

Scheme V



Thus hesperetin was found to be the strongest acid [$(pK_a)_{rel}$ = 0.0] with 4-hydroxyacetophenone somewhat less acidic [$(pK_a)_{rel}$ = 1.6] and phenol [$(pK_a)_{rel}$ = 3.0] much less acidic. The conjugate bases of the weaker acids are therefore correspondingly stronger bases and are quite likely involved in promotion of alkylating agent decomposition rather than nucleophilic displacement. Thus the phenolate anion partitions itself between two possible courses as illustrated in Scheme V. The relative proportions of products from these two pathways is dependent solely on the relative nucleophilic–basic properties of the phenolate anion. This rationale thus explains the failure of 3′-alkylation of **2** to occur. The corresponding phenolate anion doubtless does form but, rather than undergoing nucleophilic halide displacement in reaction with **6**, acts as a base in promoting decomposition of **6**. Alkylating agent **6** thus reacts with **2** with complete regiospecificity, a result which was completely unanticipated at the outset of this study on the basis of our earlier findings,[4] where substantial amounts of 3′,7-dialkylation products were invariably obtained. This allows for an easy isolation of the desired flavanone **3** and a much improved process for preparation of the potent nonnutritive sweetener **1**.

Experimental Section

All organic starting materials were purchased from Aldrich Chemical Co. except for hesperetin which was purchased from Sigma Chemical Co. All inorganic reagents were obtained from J. T. Baker Chemical Co. except for 5% palladium on carbon (Pd/C) hydrogenation catalyst (Englehard Minerals and Chemical Corp.) and pyridinium chlorochromate (Aldrich Chemical Co.). The solvents used were reagent grade and obtained from either J. T. Baker Chemical Co. or Fisher Scientific Co. The following solvents were additionally purified by distillation (from drying agent) and dried over activated (400 °C, 3 h) molecular sieves (Type 3 Å, J. T. Baker Chemical Co.): DMF (CaH_2), NMP (CaH_2), and CH_2Cl_2 (P_2O_5).

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 and proton magnetic resonance spectra (NMR) on either a Varian T-60A or a Varian XL-100 spectrometer and are reported as parts per million (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) with visualization with either UV light or iodine staining. Preparative radial chromatography was carried out on silica gel G (E. Merck) by using a Harrison Research, Chromatotron. Column chromatography was carried out on 60–200-mesh silica gel powder (J. T. Baker Chemical Co.).

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 μ-Bondapak C_{18} reverse-phase column (30 cm × 4 mm). 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 magnetic stirring. The standard workup of reactions employing DMF or NMP involved addition of H_2O, neutralization with 10% HCl, extraction (3×) of the mixture with an appropriate solvent (Et_2O, EtOAc, etc.), washing the combined extracts (6×) with H_2O, drying the combined extracts over $MgSO_4$, and concentration in vacuo.

Methyl 2-Azido-4-bromobutyrate (6). To a solution of 362 g (1.39 mol) of methyl 2,4-dibromobutyrate[5] in 600 mL of DMF was added 96.2 g (1.48 mol) of NaN_3 with stirring with an overhead stirrer at 5 °C. The cold heterogeneous reaction mixture was allowed to warm to ambient temperature over 4 h at which point a standard workup (Et_2O) yielded 288 g of a light yellow liquid. HPLC (50% MeOH in 0.03 M KH_2PO_4; 2.0 mL/min; 254 nm) showed all starting material (t_R = 9.4 min) to have been consumed to produce an 85:15 ratio of **6** (t_R = 7.7 min) to methyl 2,4-diazidobutyrate (**13**; t_R = 5.7 min). Short-path distillation yielded 275 g of a major fraction [bp 82–84 °C (1.00 mm)] which HPLC indicated to be an 80:20 ratio of **6**/**13**. TLC analysis (hexane/EtOAc, 90:10) showed fair separation of **6** and **13**, exhibiting R_f 0.27 and 0.41, respectively. An analytical sample was obtained from 505 mg of this material by preparative radial chromatography (hexane–EtOAc) followed by bulb-to-bulb distillation [90–100 °C (1.25 mm)], yielding 404 mg (80%) of **6** as a colorless liquid: IR (film) 4.72 (N_3), 5.73 (C=O) μm; NMR ($CDCl_3$) δ 2.28 (m, 2 H, $BrCCH_2$), 3.48 (t, 2 H, J = 6 Hz, $BrCH_2$), 3.80 (s, 3 H, OCH_3), 4.21 (AB q, 1 H, J = 8 Hz, J = 6 Hz, CHN). Anal. Calcd for $C_5H_8BrN_3O_2$: C, 27.04; H, 3.63; N, 18.92. Found: C, 26.96; H, 3.58; N, 18.87.

2,3′,6-Trihydroxy-4-(3-amino-3-carboxypropoxy)-4′-methoxydihydrochalcone (1). To a solution of 274 g of a **6**/**13** mixture (80:20) (0.99 mol of **6**) in 500 mL of acetone was added 297 g of NaI. The resultant mixture was stirred with an overhead stirrer at ambient temperature for 16 h. The acetone was then removed in vacuo after which a standard Et_2O–H_2O workup yielded 321 g of a light yellow liquid. HPLC analysis (50% MeOH in 0.03 M KH_2PO_4; 2.0 mL/min; 254 nm) showed all the **6** to be consumed to produce one product (t_R = 10.9 min), methyl 2-azido-4-iodobutyrate (**14**): NMR ($CDCl_3$) δ 2.30 (m, 2 H, $ICCH_2$), 3.20 (t, 2 H, J = 6 Hz, ICH_2), 3.80 (s, 3 H, OCH_3), 4.21 (m, 1 H, CHN).

Anhydrous hesperetin (151 g, 0.5 mol) was dissolved with overhead stirring at 35 °C in 700 mL of NMP in a 2-L three-necked flask. To this solution was then added 75 g (0.55 mol) of K_2CO_3 followed by a solution of 148 g (0.55 mol; 178 g of a 83:17 **14**/**13** mixture) of **14** in 50 mL of NMP. After the mixture was stirred at 35 °C for 30 h, a standard workup (EtOAc) yielded a crude product solution which was diluted in a volumetric flask with MeOH, and the yield of methyl 3′,5-dihydroxy-4′-methoxy-7-(3-azido-3-carboxypropoxy)flavanone (**3**) was determined by analytical HPLC (70% MeOH in 0.03 M KH_2PO_4; 2.0 mL/min; 286 nm; t_R = 5.5 min) to be 67%. Concentration of the EtOAc solution then yielded 254 g of crude product which TLC analysis ($CHCl_3$/MeOH, 95:5) showed to contain mainly **3** (R_f 0.58) along with a lesser amount of hesperetin (R_f 0.16). Column chromatography over 2.7 kg of silica gel eluted with $CHCl_3$–MeOH (98:2) yielded 121.6 g (55%) of **3** as an off-white solid. An analytical sample was obtained by recrystallization from $CHCl_3$–hexane: mp 123–126 °C; IR (KBr) 2.95–4.30 (OH), 4.70 (N_3), 5.76 (ester C=O), 6.11 (ketone C=O) μm; UV (MeOH) λ_{max} 286 nm (ϵ 19 850), 330 (3150); NMR ($CDCl_3$) δ 1.97–2.50 (m, 2 H, $ArOCCH_2CN_3$), 2.77–3.18 (m, 2 H, $ArCOCH_2$), 3.80 (s, 3 H, $COOCH_3$), 3.90 (s, 3 H, $Ar'OCH_3$), 4.10 (t, 2 H, J = 6 Hz, $ArOCH_2$), 4.02–4.22 (m, 1 H, CHN_3), 5.34 (AB q, 1 H, J = 10 Hz, J = 4 Hz, ArOCHAr′), 5.73 (s, 1 H, Ar′OH), 6.04 (s, 2 H, Ar aromatic H), 6.83–7.15 (m, 3 H, Ar′ aromatic H), 12.00 (s, 1 H, ArOH). Anal. Calcd for

(10) Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* **1967**, *89*, 1721–1725. pK_a values were determined by measurement of the potential at half-neutralization in a titration of the sample (0.05 M) vs. 1.00 M KOH/MeOH in NMP solvent. A combination glass/mercury electrode was used in conjunction with a Metrohm Model E436 titrator. The potentials measured were −201, −296, and −381 mV, for **2**, **7**, and phenol, respectively. pK_a values were then determined from the modified Nernst equation, $E = -0.059pK_a$, and placed on a relative scale where $(pK_a)_{rel}$ for hesperetin is defined as zero.

$C_{21}H_{21}N_3O_8$: C, 56.88; H, 4.77; N, 9.48. Found: C, 56.45; H, 4.68; N, 9.18.

Compound **3** (10 g, 22.6 mmol) was dissolved by addition in small portions, with stirring under an argon atmosphere, to 112 mL of ice-cold 10% KOH in a Parr hydrogenation bottle. One gram of 5% Pd/C was then added and the reaction mixture shaken on a Parr hydrogenation apparatus at 35 psi of hydrogen pressure for 6 h. The reaction mixture was then filtered through Celite and the pH adjusted to 6.0 by addition of 10% HCl with cooling in an ice bath. The precipitated product was filtered on a Büchner funnel to yield 8.70 g (95%) of **1** as a light tan powder, mp 181–185 °C dec (lit.[3] mp 182–184 °C).

Methyl 4-(3-Azido-3-carboxypropoxy)acetophenone (8). K_2CO_3 (1.38 g, 10 mmol) was added to a solution of 1.36 g (10 mmol) of 4-hydroxyacetophenone and 3.92 g of an 80:20 **6**/**13** mixture [3.14 g (14.2 mmol) of **6**] in 25 mL of NMP. The resultant reaction mixture was stirred vigorously at ambient temperature for 4 days after which a standard workup (Et_2O) yielded 3.80 g of a viscous oil. TLC analysis ($CHCl_3$/MeOH, 95:5) suggested approximately equal amounts of starting material (R_f 0.26) and product **8** (R_f 0.70) to be present. Preparative radial chromatography ($CHCl_3$/MeOH) resulted in recovery of 0.74 g (54%) of 4-hydroxyacetophenone and also yielded 2.90 g of a mixture of nonpolar products containing **8**. Further preparative radial chromatography (hexane/EtOAc) allowed isolation of 0.93 g (34%) of pure **8** as a colorless oil: TLC (hexane/EtOAc, 2:1): R_f 0.25; IR (film) 4.68 (N_3), 5.71 (ester C=O), 5.94 (ketone C=O) μm; NMR ($CDCl_3$) δ 2.00–2.60 (m, 2 H, $ArOCCH_2$), 2.53 (s, 3 H, $ArCOCH_3$), 3.84 (s, 3 H, $COOCH_3$), 4.18 (t, 2 H, J = 6 Hz, $ArOCH_2$), 4.24 (t, 1 H, J = 8 Hz, CH–N), 6.93 (d, 2 H, J = 9 Hz, C-3, C-5 Ar H), 7.96 (d, 2 H, J = 9 Hz, C-2, C-6 Ar H). Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.36; H, 5.36; N, 14.81. Recovered from the same chromatography was 36 mg (1.1%) of methyl 2-azido-4-bromobutyrate [TLC (hexane/EtOAc, 2:1) R_f 0.52] and 214 mg of 1-azido-1-(carbomethoxy)cyclopropane (**9**, R_f 0.63) as a volatile liquid. An analytical sample was obtained by preparative radial chromatography (hexane/EtOAc, 98:2) followed by bulb-to-bulb distillation [80–90 °C (5.0 mmHg)], IR (film) 4.71 (N_3), 5.75 (C=O) μm; NMR ($CDCl_3$) δ 1.20 (m, 2 H, *cis*-CH–CH), 1.43 (m, 2 H, *cis*-CH–CH), 3.78 (s, 3 H, OCH_3). Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00. Found: C, 42.18; H, 5.13.

Reaction of Methyl 2-Azido-4-bromobutyrate (6) with K_2CO_3/NMP. K_2CO_3 (138 mg, 1 mmol) was added to a solution of 219 mg (0.99 mmol) of pure azido ester **6** in 4 mL of NMP after which the resultant reaction mixture was stirred vigorously at ambient temperature for 64 h. Standard workup (Et_2O) then yielded 185 mg of a colorless liquid. NMR analysis ($CDCl_3$) of this crude product indicated it to be essentially a mixture of only starting material and 1-azido-1-(carbomethoxy)cyclopropane (**9**). Integration of the methoxy absorptions of **6** (3.82 ppm) and **9** (3.78 ppm) showed the ratio of **6**/**9** to be 52:48. HPLC analysis (50% MeOH in 0.03 M KH_2PO_4: 2.0 mL/min; 200 nm) showed peaks for **9** (t_R = 5.7 min; 68%) and for **6** (t_R = 7.9 min; 32%). Quantitative HPLC analysis for **6** using a standard solution showed 92 mg (42%) of **6** to have been recovered. Similarly, analysis for **9** indicated a yield of 47%.

Reaction of 4-[3-Azido-3-(carbomethoxy)propoxy]acetophenone (8) with K_2CO_3/NMP. K_2CO_3 (138 mg, 1 mmol) was added to a solution of 277 mg (1.00 mmol) of azido ester **8** in 4 mL of dry NMP. After 18 h of reaction at ambient temperature, TLC ($CHCl_3$/MeOH, 95:5) and HPLC (40% MeCN in 0.005 M KH_2PO_4; 2.0 mL/min; 254 nm) analyses suggested ca. half of **8** (R_f 0.63; t_R 10.5 min) to have been consumed to produce α-keto ester **11** (R_f 0.50; t_R = 5.3 min) as the major product and a minor amount of 4-hydroxyacetophenone (**7**; R_f 0.15; t_R = 2.4 min). A standard workup after 60 h, however, yielded 198 mg of a viscous oil which contained mainly **7** and **8**, only trace amounts of **11**, and many other products. Quantitative HPLC analysis indicated a 46% recovery of **8** and a 24% conversion to **7**.

This reaction was repeated. A standard workup (18 h reaction time) yielded a crude product which HPLC indicated to be a 10:67:23 ratio of **7**/**8**/**11**. The **11** detectable in this mixture was identical in all respects [TLC ($CHCl_3$/MeOH, hexane/EtOAc), HPLC, and NMR] with the product **11** obtained on oxidation of alcohol **12**.

4-[3-(Carbomethoxy)-3-hydroxypropoxy]acetophenone (12). 4-Hydroxyacetophenone (1.36 g, 10 mmol), 1.52 g (11.0 mmol) of K_2CO_3, and 2.63 g (11.0 mmol) of methyl 2-acetoxy-4-bromobutyrate[5] were reacted with vigorous stirring as a suspension–solution in 10 mL of DMF at ambient temperature (16 h), 50 °C (3 h), and finally 70 °C (2 h). A standard workup (Et_2O), which included washing (3×) the combined Et_2O extracts with ice-cold 5% KOH, yielded 2.70 g of a viscous yellow oil. Preparative radial chromatography (hexane–EtOAc) yielded 2.29 g (78%) of 4-[3-(carbomethoxy)-3-acetoxypropoxy]acetophenone (**15**) as a colorless oil. Acetate **15** was dissolved in 50 mL MeOH and refluxed with 50 mg of p-TsOH·H_2O for 24 h at which point TLC analysis ($CHCl_3$/MeOH, 95:5) showed all **15** (R_f 0.54) to have been consumed to give mainly **12** (R_f 0.32). The reaction mixture was then concentrated to dryness in vacuo after which the residue was partitioned between Et_2O and H_2O. The aqueous layer was washed with Et_2O (2×) after which the combined Et_2O extracts were dried ($MgSO_4$) and concentrated to yield 1.37 g of crude **12**. Preparative radial chromatography (hexane–EtOAc) yielded 1.19 g (61%) of pure **12** as a colorless oil which solidified on standing. Bulb-to-bulb distillation [190 °C (0.05 mm)] yielded an analytical sample: IR (film) 2.88 (OH), 5.81 (ester C=O), 5.99 (ketone C=O) μm; NMR ($CDCl_3$) δ 2.04–2.50 (m, 2 H, $ArOCCH_2$), 2.54 (s, 3 H, $ArCOCH_3$), 3.02 (d, 2 H, J = 5 Hz, OH), 3.82 (s, 3 H, $COOCH_3$), 4.24 (t, 2 H, J = 6 Hz, $ArOCH_2$), 4.30–4.67 (m, 1 H, ArOCCCH), 6.92 (d, 2 H, J = 8 Hz, C-3, C-5 Ar H), 7.96 (d, 2 H, J = 8 Hz, C-2, C-6 Ar H). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.94; H, 6.38.

4-[3-(Carbomethoxy)-3-oxopropoxy]acetophenone (11). Pyridinium chlorochromate (216 mg, 1 mmol) was added to a solution of 50 mg (0.20 mmol) of alcohol **12** in 4 mL of CH_2Cl_2. The resultant reaction mixture was stirred at ambient temperature for 24 h and was then poured into 25 mL of 1% HCl. This mixture was extracted with EtOAc (3 × 15 mL), the combined portions of which were washed with 5% NaCl (6 × 5 mL), dried ($MgSO_4$), and concentrated, yielding 50 mg of a colorless solid. TLC analysis ($CHCl_3$/MeOH, 95:5) indicated this product to be a mixture of approximately equal amounts of starting material (R_f 0.26) and product (R_f 0.43); a weak spot for 4-hydroxyacetophenone (R_f 0.10) was also observed. Recrystallization from hexane–EtOAc yielded 15 mg of pure white clusters: mp 94–96 °C; HPLC (40% MeCN in 0.005 M KH_2PO_4; 2.0 mL/min; 254 nm); t_R = 5.4 min; IR (KBr) 5.70 (aliphatic ketone C=O), 5.78 (ester C=O), 5.97 (aryl ketone C=O) μm; NMR ($CDCl_3$) δ 2.52 (s, 3 H, $ArCOCH_3$), 3.35 (t, 2 H, J = 6 Hz, $ArOCCH_2$), 3.90 (s, 3 H, $COOCH_3$), 4.40 (t, 2 H, J = 6 Hz, $ArOCH_2$), 6.92 (d, 2 H, J = 9 Hz, C-3, C-5 Ar H), 7.93 (d, 2 H, J = 9 Hz, C-2, C-6 Ar H). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 61.98; H, 5.74.

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