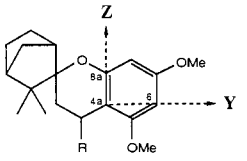
Temperatures were read from the instrument panel and were constant within ±0.2 °C during each experiment. All spectra were plotted at 1500 Hz/50 cm. Chemical shifts of the hydrogens of the geminal methyl groups for each diastereomer at −21 and 70 °C are given in Figure 3.

For predictions of paramagnetic shielding or deshielding of hydrogens in the geminal methyl groups in XT_1, XT_2, NT_1, and NT_2 (data presented in Table III), the Cartesian coordinates of the mol file were transposed into cylindrical coordinates. The cylindrical z axis is normal to the plane of the aromatic ring with its origin at the center of the ring. The p axis is in the plane of the aromatic ring with its origin at the center of the ring. The molecule was first oriented with one carbon of the aromatic ring at the origin (e.g., atom 4a), a vicinal carbon of the aromatic ring on the positive Cartesian z axis (e.g., atom 8a), and a third carbon of the aromatic ring on the positive Cartesian y axis (e.g., atom 6), using the ALIGN command in the ORIENT subprogram of Chemlab-II. The Cartesian x axis is thus normal to the aromatic



ring, and the cylindrical z coordinate will correspond to the Cartesian x coordinate of any atom in the molecule thus oriented. The y and z Cartesian coordinates for the center of the aromatic ring are then $y/2$ and $z/2$ for the ring atoms located on the y and z axes respectively (e.g., atoms 6 and 8a). The cylindrical p coordinate for any atom whose Cartesian coordinates are x_n,y_n, z_n is then computed from the relationship $p = [(y_n - y/2)^2 + (z_n - z/2)^2]^{1/2}$.

Equilibration of Dihydropyranones *endo*-2 and *exo*-2. Ketone *endo*-**2** (0.130 g, 0.41 mmol) and anhydrous potassium carbonate (1.2 g) in 90% ethanol (59 mL) were heated at reflux under nitrogen. After 1.0, 6.0, 25.0, 49.0, 73.0, 121.0, 170.0, and 219.0 h, aliquots (2–3 mL) were removed from the reaction mixture and diluted with methylene chloride (10 mL). These were washed with water, dried ($MgSO_4$), and stripped of volatiles under reduced pressure to yield samples for subsequent ^1H NMR ($CDCl_3$) analysis. The isomeric ratio was determined by integration of an expanded plot of the region (490–805 Hz). After 219 h, 9% of the α,β-unsaturated ketone **3** was present as determined by comparison of integral peak areas of the signal at δ 6.66 (1 H, s) for the vinyl hydrogen of **3** to that of the resonances for the hydrogens of the methylene α to the carbonyl group for *exo*-**2** at δ 2.70 (H, d, J = 16.2 Hz) and 2.72 (H, d, J = 16.2 Hz) and for *endo*-**2** at δ 2.53 (H, d, J = 16.2 Hz) and 2.83 (H, d, J = 16.2 Hz). The integral peak areas for the above-mentioned methylene hydrogen resonances were compared to give the ratio of *exo*-**2** to *endo*-**2** in each aliquot. The isomerization of *exo*-**2** to an equilibrium mixture of *exo*- and *endo*-**2** was carried out similarly.

Acknowledgment. This work was supported by a grant from the National Science Foundation. We thank Prof. Gilles Klopman for access to his ChemGraph and Chemlab programs.

Registry No. **1nt**, 114976-79-3; **1nc**, 114906-85-3; **1xt**, 114906-84-2; **1xc**, 114976-78-2; *endo*-**2**, 114906-86-4; *exo*-**2**, 114976-80-6; **3**, 114906-87-5; **XT**, 114906-88-6; **XC**, 114976-81-7; **NT**, 114976-82-8; **NC**, 114976-83-9.

On the Photobiology of the Gilvocarcins. Total Synthesis of Defucogilvocarcin V and a Related Photoactive Vinyl Phenol[1]

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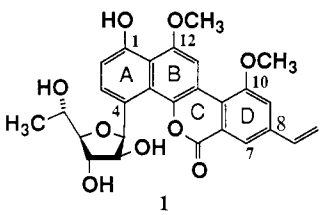
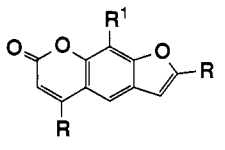
Defucogilvocarcin V (**4a**) and the related vinyl phenol **5a** are important for the study of the photonicking of DNA by gilvocarcin antibiotics such as 1. They have been synthesized from a common precursor, lactone **6a**, which contains the complete carbon framework, prepared in the first step. Key transformations include introduction of functionality at C-10 by a regiospecific selenium dioxide oxidation and at C-12 by Fremy's salt oxidation of the phenol function hidden in ring C. The vinyl group is introduced by sequential radical bromination–dehydrobromination. These vinyl phenols photonick DNA under the same conditions as the natural glucoside 1 and serve as bioorganic tools in the study of the mechanism of the nicking reaction.

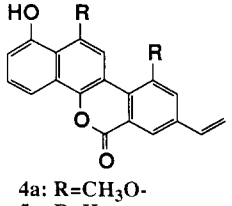
Gilvocarcin V[2,3] (1) represents a new class of aromatic *C*-glycoside antibiotics with significant antitumor activity.



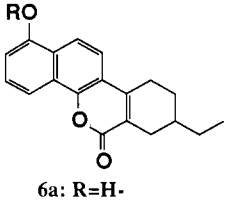
1



2: R=CH_3-, R^1=CH_3O-
3: R=CH_3-, R^1=CH_3-



4a: R=CH_3O-
5a: R=H-



6a: R=H-

The in vitro activity of these molecules is dependent upon activation by low-energy light.[4] In contrast to the photoactive psoralens such as 8-methoxypsoralen (8-MOP) (**2**), and trioxsalen (**3**) which covalently modify or cross-link duplex DNA,[5] the gilvocarcins cause single-strand breaks in double-stranded DNA upon irradiation.[6] Experimen-

(1) Contribution no. 4206. Presented at the 191st National Meeting of the American Chemical Society, New York, NY, April 1986; paper ORGN 195.

(2) Takahashi, K.; Yoshida, M.; Tomita, F.; Shirahata, K. *J. Antibiot.* **1981**, *34*, 271–275.

(3) Toromycin (Horii, S.; Fukase, H.; Mizuta, E.; Hatano, K.; Mizuno, K. *Chem. Pharm. Bull.* **1980**, *28*, 3601–3611) and anandimycin (Balitz, D. M.; Bush, J. A.; O'Herron, F. A.; Nettleton, D. E., Jr. U.S. Patent 4 360 595) are other names for gilvocarcin.

(4) Elespuru, R. K.; Gonda, S. K. *Science (Washington, D.C.)* **1984**, *223*, 69–71.

(5) Straub, K.; Kanne, D.; Hearst, J. E.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 2347–2355. Kanne, D.; Straub, K.; Hearst, J. E.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 6754–6764.

(6) Wei, T. T.; Byrne, K. M.; Warnick-Pickle, D.; Greenstein, M. *J. Antibiot.* **1982**, *35*, 545–548.

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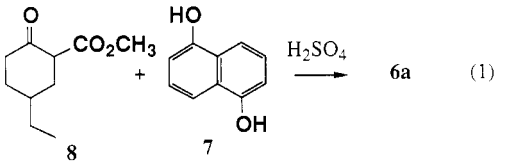
tally, gilvocarcin V is 10^5 times more potent that 8-MOP in a side-by-side assay for photoactive DNA damage.[4] The aglycone[7] itself has recently been isolated as a new natural product, defucogilvocarcin V[8] (**4a**), which has similar antitumor activity to but more selective antibacterial activity than that of the parent aromatic *C*-glycosides.

As part of our study on the mechanism of DNA damage by the gilvocarcins, we developed a total synthesis of the aglycone defucogilvocarcin V (**4a**) and the related vinyl phenol **5a**. The choice of **5a** as a target was derived from molecular modeling[9] of the interaction of gilvocarcin V with DNA and is intended to test the minimum structural requirements for the photobiology observed with the natural products. In the retrosynthetic consideration of these structures we desired a common, flexible approach to these as well as other partial structures necessary to test our modeling. We therefore focused on the formation of the lactone ring C and the carbon–carbon bond between the B and D rings and elected an approach that targets an "underoxidized" intermediate, the versatile lactone **6a**. This key intermediate can be aromatized to provide precursors to the vinyl phenol **5** and also contains sufficient functionality for the regiospecific introduction of the methoxyl groups at C-10 and C-12 and substituents at C-4. Since our initial report,[1] alternate syntheses of **4a**[10] and the related aglycone of gilvocarcin M[11] have been reported.

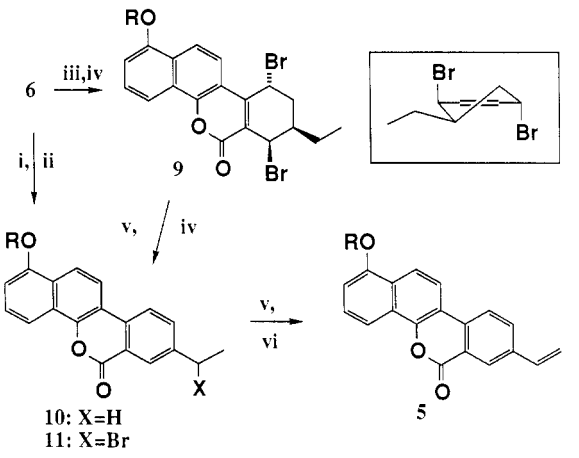
Synthesis of the Vinyl Phenol 5a. Lactone **6a** is the product of a Pechmann condensation[12] (eq 1) between 1,5 dihydroxynaphthalene (**7**) and the β-keto ester **8**,[13] readily obtained from 4-ethylcyclohexanone. Treatment of these in concentrated sulfuric acid provides **6a**, which contains the complete carbon framework of defucogilvocarcin V, in a single step in 56% yield.



(1)

Dehydrogenation to aromatize the D ring of this system has been studied in some detail and is subject to a number of intervening side reactions.[14] In our study (Scheme I), catalytic dehydrogenation of the methyl ester **6b** proceeded in 80% yield to **10b**. Similar treatment of the pivaloate ester **6c** was unsuccessful. A related system, protected as an acetate ester, is reported to give hydrogenolysis of the aryl-ester bond and loss of the C-1 functional group.[14] Therefore ester **6c** was oxidized with NBS/benzoyl peroxide in refluxing carbon tetrachloride. The 7,10-dibromide **9c** obtained was predominantly a single diastereomer, and no significant overbromination at either allylic site was observed, even with excess reagent. The lack of overoxidation and the stereochemistry of the dibromination product **9c** reflect A-strain interactions that preclude the initially brominated product from adopting the requisite conformation for subsequent hydrogen atom abstraction. Aromatization of **9c** is accomplished by bisdehydrobromination[15] to afford **10c** in 91% yield from **6c**. The vinyl group is introduced via the benzylic bromide **11c** with a similar bromination/dehydrobromination sequence; however, in this case, overoxidation to the geminal dibromide is a significant problem but can be minimized by careful monitoring of the bromination step. After chromatography the vinyl pivaloate **5c** was obtained in 65% yield from **10c**. Deprotection provides in 95% yield the vinyl phenol **5a**, desired as the minimum structure expected to nick DNA in a manner similar to gilvocarcin V.

Scheme I[a]



a: R=H- ; b: R=CH_3- ; c: R=tBuCO-

[a] (i) CH_3I, K_2CO_3, DMF; (ii) 10% Pd/C, air, Ph–O–Ph, Δ; (iii) C_4H_9COCl/DMAP; (iv) NBS/$(PhCO_2)_2$/CCl_4, Δ; (v) LiBr/Li_2CO_3/DMF, Δ; (vi) KO-*t*-Bu/CH_3OH; HCl.

Synthesis of Defucogilvocarcin V (4a). The synthesis of the fully substituted aglycone **4a** involves sequential oxidations at C-10 and C-12 directed by the functionality already present in lactone **6**. Initial experiments were conducted with the methyl ether **6b**. We anticipated that selective allylic oxidation at C-10 could be directed by the polarity of the α,β-unsaturated lactone double bond in preference to the competing allylic position at C-7. Oxidation at C-12 would be directed by the latent phenol group present in the lactone ester.

Our initial approach involved enolization of the conjugated lactone carbonyl for functionalization at C-10. However, a variety of strong-base conditions (LDA, LDEA, KH/KO-*t*-Bu, KH/DMSO) gave either recovered starting material or nucleophilic addition of the base to the lactone carbonyl. Additionally, acid-mediated enolization conditions (TMSCl/Et_3N, TMS triflate, etc.) returned only unreacted ether **6b**. Further, quenching these attempts with oxidizing agents afforded no sign of oxidation at C-10 (or at the synthetically equivalent α position).

Alternate allylic oxidation procedures have little precedent for selectivity between the C-7 and C-10 allylic positions. With chromium-based oxidants[16] we observed primarily destruction of the starting material, in accord with literature precedents for the degradation of the natural products.[17] The only isolable product, obtained

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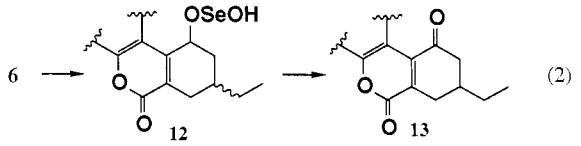
in 5% yield, is a bright yellow ketone, which proved to be the unwanted 7-keto derivative. The regioselectivity of this procedure is perhaps the result of faster destruction of the desired 10-keto derivative, **13b**.

Since radical bromination of **6** was completely unselective between the C-7 and C-10 positions, we also examined selective manipulation of the 7,10-dibromide **9b**. Under solvolytic conditions ($AgNO_3$/THF/H_2O), only one of the two bromine atoms is exchanged, even under forcing conditions. That the bromine atom at C-10 is inert to these conditions mirrors the electronic influence of the lactone carbonyl group. The synthetic manipulations required to utilize the resulting hydroxy bromide, however, precluded this procedure as a route to the fully substituted aglycone **4**.

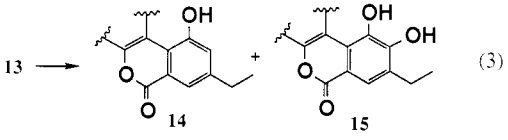
A few examples of selenium-based allylic oxidation of α,β-unsaturated carbonyl derivatives are known,[18,19] but none with the regiochemical ambiguity of this tetrasubstituted olefin. At 160 °C (refluxing diglyme)[20] selenium dioxide oxidation of **6b** forms the epimeric esters **12b**, which, in a slower step, deposit selenium and form the C-10 ketone, **13b** (eq 2). The oxidation is facilitated by the



(2)

addition of a small amount of water (4 mol %), and no oxidation at C-7 is observed. The procedure failed with the phenolic ester derivatives **6c** and **6e** under anhydrous conditions. The addition of water led to hydrolysis of the protecting ester groups but no allylic oxidation. The observed regiochemistry with **6** is consistent with the formation of polar intermediates, which have been suggested to account for the regioselectivity of selenium dioxide allylic oxidation of simple trisubstituted olefins.[21]

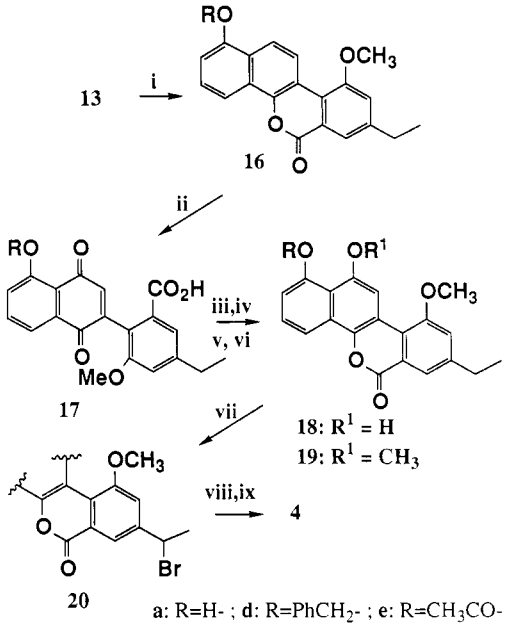
Although the ketone **13b** is formed directly in a slower step by decomposition of the intermediate esters **12b** under the reaction conditions, the reaction could not be driven to completion either to the initial allylic oxidation products or to the derived ketone since extended reaction caused aromatization of **13b** to the C-10 phenol, **14b**, and overoxidation to the C-9,C-10 catechol, **15b**, in equal amounts (eq 3). There were characterized as the corresponding



(3)

methyl ethers after exhaustive methylation of the reaction residues. Optimization of these competing processes requires initial treatment with selenium dioxide at 160 °C for 20 min followed by flash chromatography to recover the relatively nonpolar starting material contaminated by a small amount of coeluting ketone. The more polar selenium-containing esters **12b** (and corresponding alcohols) are then eluted and oxidized directly with PCC[22] in dichloromethane to afford the crystalline yellow ketone

Scheme II[a]



a: R=H- ; d: R=$PhCH_2$- ; e: R=CH_3CO-

[a] (i) $(CH_3O)_3CH/CH_3OH$/DDQ; (ii) H_2O/C_2H_5OH/KO-*t*-Bu; pH 7 buffer/$K_2ON(SO_3)_2$; HCl; (iii) $Na_2S_2O_4/H_2O$; H^+; (iv) CH_3I/KO-*t*-Bu/DMF; (v) H_2, 10% Pd/C; (vi) $(CH_3CO)_2O$/pyridine; (vii) NBS/$(PhCO_2)_2/CCl_4$, Δ; (viii) LiBr/Li_2CO_3/DMF, Δ; (ix) $NaOCH_3/CH_3OH$; HCl.

13b. Despite these drastic conditions, application to the key benzyl ether **6d** proceeds similarly to afford **13d** in 30% yield (50% yield based on consumed **6d**) with no observable oxidation at the benzylic ether position. Subsequent steps (Scheme II), also developed for the methyl ethers, were applicable to the benzyl ethers. The ketone **13d** was converted to the aromatic 10-methoxy derivative **16d** in 88% yield by ketalization with trimethyl orthoformate in methanol followed by aromatization with DDQ.[23]

The latent phenol at C-4b is used to direct the functionalization at C-12 via a Fremy's salt oxidation.[24] Basic hydrolysis of the phenolic lactone of **16d** in wet ethanol provides a material that readily relactonizes on acidification. This is somewhat problematic since Fremy's salt requires the free phenol but decomposes under both acidic and basic conditions and is active over a narrow range of pH conditions.[25] Nevertheless, this oxidation is accomplished by adding the initial hydrolysis mixture to a solution of Fremy's salt buffered at pH 7. After standing overnight and filtration to remove the re-formed lactone **16d**, mild acidification causes the precipitation of the bright orange quinone acid **17d** in 71% yield after recrystallization.

Attempts at catalytic reduction of the quinone under mild conditions lead to extensive hydrogenolysis of the C-1 functionality and even saturation of the A ring. Reduction of **17d** to the corresponding hydroquinone is accomplished with sodium dithionite in dioxane/water.[26] During the reduction and subsequent recrystallization from ethyl acetate the lactone ring closes to the phenol **18d**, which was isolated in 93% yield. Methylation with methyl iodide and potassium *tert*-butoxide in DMF provides the 12-

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(20) At lower temperatures (80 °C, dioxane) no reaction was observed with **6b**. The 8-des-ethyl analogue of **6b** does react at 80 °C (with the same regioselectivity).
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methoxyl derivative **19d** in 77% yield. Catalytic debenzylation of **19d** with Pd/C affords defucogilvocarcin E[27] (**19a**) in 88% yield.

The vinyl double bond is introduced in a sequence analogous to that developed for the minimum structure **5a**. Pivaloylation is incomplete on the now sterically encumbered phenol, which is therefore acetylated in 65% yield to **19e**[28] with acetic anhydride in pyridine. Radical bromination with NBS followed by dehydrobromination affords the acetate **4e**. Mild basic methanol hydrolysis of the acetyl group followed by acidification yields defucogilvocarcin V (**4a**) in 20% yield from **19e**.

Synthetic **4a** is identical with the natural aglycone. In particular, it nicks supercoiled plasmid DNA (pUC8) at the same concentrations as gilvocarcin V as was reported for the natural aglycone.[8] In addition, the minimum vinyl phenol **5a** also nicks plasmid DNA under the same conditions[29] as gilvocarcin V but at concentrations 10^2–10^3-fold higher. This level of activity is placed in perspective by the reported comparisons of gilvocarcin V with the very potent psoralens, **2** and **3**, which require 10^3- and 10^5-fold higher concentrations relative to gilvocarcin V in another assay[4] for DNA damage. Thus these aglycones have utility as bioorganic tools in the study of the mechanism of this nicking reaction. We have reported[30] more extensive comparisons of the aglycone **4a** with the natural glycoside **1** that reveal significant differences in their behavior toward DNA. The aglycone moiety serves to report on the effect of the glycosyl residue, presumably coordinating to the DNA surface. Additional studies on the mechanism of the gilvocarcin V photoactivity will be reported shortly.

Experimental Section

Infrared spectra were recorded on a Nicolet 60SX FTIR spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a GE QE300 NMR spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane or to the residual solvent signals in $CDCl_3$ at 7.25 ppm or in DMSO-d_6 at 2.52 ppm. Ultraviolet spectra were recorded on a Varian Cary 2300 UV/visible spectrophotometer. Mass spectra were taken on a VG ZEB-SE multifocusing high-resolution mass spectrometer. Melting points were measured on an Mel-Temp melting point device and are uncorrected. Elemental analyses were performed by Micro-Analysis, Inc.

Abbreviations: DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAP, 4-(dimethylamino)pyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; LDA, lithium diisopropylamide; LDEA, lithium diethylamide; MPLC, medium-pressure liquid chromatography; NBS, *N*-bromosuccinimide; PCC, pyridinium chlorochromate; THF, tetrahydrofuran.

8-Ethyl-1-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (6a). 1,5-Dihydroxynaphthalene (**7**) (6.87 g, 42.9 mmol) and keto ester **8** (7.94 g, 43.1 mmol) were combined in an oven-dried 50-mL three-necked fluted flask with mechanical stirring. At 0 °C, concentrated sulfuric acid (20 mL) was added so that the temperature did not rise above 5 °C. After 2 h of vigorous stirring, the slurry was poured onto 1 L of ice. This mixture was stirred for an additional 2 h. The solid was collected by filtration and rinsed with cold ethanol and then with cold ether to dry. This gave 7.07 g (56%) of **6a** as a light tan solid (mp 242–244 °C) suitable for subsequent steps. Recrystallization from ethyl acetate gave an analytical sample: mp 248–250 °C; IR (KBr) 3240 broad, 2960 m, 1675 s, 1635 w, 1568 m, 1370 m, 1275 w cm^{-1}; UV (methanol) (λ (nm) (log ϵ)) 218 (4.598), 284 (4.435), 307 (3.859), 362 (3.764); ^1H NMR (DMSO-d_6) δ 10.39 (br s, 1 H), 7.91 (d, 1 H, J = 8.9 Hz), 7.70 (d, 1 H, J = 8.3 Hz), 7.46 (d, 1 H, J = 8.9 Hz), 7.42 (appt. t, 1 H, J = 7.9 Hz), 7.00 (d, 1 H, J = 7.5 Hz), 2.86 (m, 1 H), 2.59 (m, 1 H), 2.55 (m, 1 H), 1.85 (m, 2 H), 1.43 (m, 1 H), 1.33 (quint., 2 H, J = 7.5 Hz), 1.18 (m, 1 H), 0.92 (t, 3 H, J = 7.3 Hz). Anal. Calcd for $C_{19}H_{18}O_3 \cdot {}^1/_2H_2O$: C, 75.23; H, 6.31. Found: C, 75.37; H, 6.14.

8-Ethyl-1-methoxy-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (6b). Phenol **6a** (2.59 g, 8.8 mmol) was suspended in 50 mL of dry DMF with 18 g (130 mmol) of pulverized K_2CO_3. After 2.0 mL (32 mmol) of methyl iodide was added, the suspension was stirred at room temperature for 30 min and then heated to 80 °C for 4 h. After cooling, the reaction was diluted into ether. The insolubles were rinsed with ether. The combined ether layers were washed with water and dried. After concentration, the methyl ether **6b** was obtained as a white solid (2.35 g, 86%): mp 150–152 °C; IR (KBr) 2960 w, 2930 w, 1710 s, 1635 w, 1610 w, 1590 w, 1570 w, 1505 w, 1260 m, 1068 m, 797 w, 761 w cm^{-1}; UV (CH_3OH) (λ (nm) (log ϵ)) 217 (4.66), 273 (4.43), 283 (4.53), 305 (3.95), 355 (3.79); ^1H NMR ($CDCl_3$) δ 8.08 (d, 1 H, J = 8.3 Hz), 8.02 (d, 1 H, J = 9.2 Hz), 7.49 (dd, 1 H), J = 8.3, 7.8 Hz), 7.47 (d, 1 H, J = 9.0 Hz), 6.91 (d, 1 H, J = 7.7 Hz), 4.00 (s, 3 H), 2.98 (dddd, 1 H, J = 18.5, 2.5, 2.2, 2.1 Hz), 2.85 (dd, 1 H, J = 17.9, 4.5 Hz), 2.77–2.65 (m, 2 H), 2.16–2.0 (m, 2 H), 1.61–1.55 (m, 1 H), 1.46 (quint., 2 H, J = 7.3 Hz), 1.38 (ddd, 1 H, J = 11.1, 5.6, 1.9 Hz), 1.02 (t, 3 H, J = 7.4 Hz). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.99; H, 6.45.

1-(2,2-Dimethyl-1-oxopropoxy)-8-ethyl-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (6c). To a suspension of azeotropically dried phenolic lactone **6a** (2.00 g, 6.8 mmol) in 50 mL of toluene at 5 °C was added trimethylacetyl chloride (1.2 mL, 9.7 mmol) followed by DMAP (1.24 g, 10.2 mmol). As the reaction reaches room temperature, most of the solid dissolves. The mixture was heated to reflux for 45 min. After cooling, the thick white precipitate was collected by filtration. The filtrate was concentrated and the residue along with the precipitate was filtered through silica gel with 10% ethyl acetate in dichloromethane. The fractions containing the ester were concentrated. The solid was triturated with ether to leave 2.21 g (86%) of **6c** as a white solid: mp 200–201 °C; IR (KBr) 2960 w, 2930 w, 1748 m, 1716 s, 1118 m, 796 w, 762 w cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ϵ)) 269 (4.53), 280 (4.69), 295 (3.86), 308 (3.89), 321 (3.82), 347 (3.83), 362 (3.79); ^1H NMR ($CDCl_3$) δ 8.43 (d, 1 H, J = 8.4 Hz), 7.68 (d, 1 H, J = 9.0 Hz), 7.60 (d, 1 H, J = 8.2 Hz), 7.59 (appt. t, 1 H, J = 8 Hz), 7.31 (d, 1 H, J = 7.5 Hz), 3.1–2.7 (m, 4 H), 2.2–2.0 (m, 2 H), 1.47 (s, 9 H), 1.7–1.3 (m, 3 H), 1.02 (t, 3 H, J = 7 Hz). Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found: C, 75.88; H, 6.87.

8-Ethyl-1-(phenylmethoxy)-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (6d). Phenol **6a** (1.88 g, 6.4 mmol) was suspended in 25 mL of dry DMF with 12 g (87 mmol) of pulverized K_2CO_3 and 1.2 mL (9.5 mmol) of benzyl bromide at room temperature for 1 h and then heated to 90 °C for a few minutes. After cooling, a second portion (1.2 mL) of benzyl bromide was added. After an additional cycle of heating, the reaction was diluted into ether. The insolubles were rinsed with ether and then washed with dichloromethane. The benzyl ether was concentrated from the dichloromethane washes and recrystallized from ethyl acetate to give 1.48 g (60%) of **6d** as white crystals suitable for analysis. The ether rinses yielded an additional 0.34 g (14%) of the benzyl ether: mp 167–168 °C; IR (KBr) 2965 w, 2925 w, 1711 s, 1260 m, 1068 m, 797 m, 760 m, 695 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ϵ)) 275 (4.50), 285 (4.63), 307 (3.94), 355 (3.85), 371 (3.79); ^1H NMR ($CDCl_3$) δ 8.16 (d, 1 H, J = 9.0 Hz), 8.14 (d, 1 H, J = 8.2 Hz), 7.53 (m, 4 H), 7.42 (m, 2 H), 7.38 (m, 1 H), 7.00 (d, 1 H, J = 7.7 Hz), 5.25 (s, 2 H), 3.04 (m, 1 H), 2.88 (m, 1 H), 2.79 (m, 2 H), 2.13 (m, 2 H), 1.63 (m, 1 H), 1.46 (m, 2 H), 1.02 (t, 3 H, J = 7.3 Hz). Anal. Calcd for $C_{26}H_{24}O_3$: C, 81.22 H, 6.29. Found: C, 81.16; H, 6.01.

8-Ethyl-1-methoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (10b). A solution of methyl ether **6b** (2.14 g, 6.9 mmol) with 0.21 g of 10% Pd/C in 300 mL of diphenyl ether under an air atmosphere was heated at reflux for 16 h and then allowed to stir at ambient temperature for 48 h. Completion was verified by GC.

(27) Gilvocarcin E is also a natural product. Balitz, D. M.; O'Herron, F. A.; Bush, J.; Vyas, D. M.; Nettleton, D. E.; Grulich, R. E.; Bradner, W. T.; Doyle, T. W.; Arnold, E.; Clardy, J. *J. Antibiot.* **1981**, *34*, 1544–1555.

(28) The acetate of defucogilvocarcin E (**19e**) is an intermediate in Prof. Findlay's route (**20** of ref 10a).

(29) In the presence of a radical inhibitor and with the exclusion of air: Tse-Dinh, Y.-C.; McGee, L. R., unpublished results.

(30) Tse-Dinh, Y.-C.; McGee, L. R. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 808–812.

The reaction mixture was filtered through Celite, diluted into hexane (2 L), and filtered through silica with additional hexane to elute the diphenyl ether. The product was then eluted with ethyl acetate. After recrystallization from ethyl acetate, **10b** was obtained as white crystals (1.69 g, 80%): mp 171–173 °C; IR (KBr) 2960 w, 1732 s, 1522 m, 1450 w, 1422 w, 1372 w, 1262 w, 1250 w, 1105 m, 1042 w, 800 w, 777 m cm^{-1}; UV (CH_3OH) (λ (nm) (log ε)) 234 (4.62), 241 (4.62), 264 (4.56), 273 (4.65), 347 (3.87); ^1H NMR ($CDCl_3$) δ 8.23 (d, 1 H, J = 1.5 Hz), 8.08 (d, 2 H, J = 8.8 Hz), 8.03 (d, 1 H, J = 8.3 Hz), 7.92 (d, 1 H, J = 9 Hz), 7.64 (dd, 1 H, J = 8.3, 2.0 Hz), 7.48 (t, 1 H, J = 8.0 Hz), 6.88 (d, 1 H, J = 7.7 Hz), 3.99 (s, 3 H), 2.78 (q, 2 H, J = 7.6 Hz), 1.32 (t, 3 H, J = 7.6 Hz). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.84; H, 5.12.

1-(2,2-Dimethyl-1-oxopropoxy)-8-ethyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (10c). A solution of pivaloate ester **6c** (0.376 g, 0.99 mmol) in carbon tetrachloride with NBS (0.336 g, 1.9 mmol) and benozyl peroxide (35 mg) was heated to reflux for 30 min. After cooling, the mixture was filtered. The filtrate was concentrated under vacuum and filtered through silica gel with dichloromethane to afford 0.52 g of **9c** as a yellow foam, which was dissolved in 7 mL of DMF with LiBr (0.10 g), Li_2CO_3 (0.11 g), and hydroquinone (30 mg) and heated at 110 °C overnight. After cooling, the mixture was diluted with 70 mL of dichloromethane and filtered. The filtrate was concentrated under vacuum and the residue recrystallized from ether to afford 0.34 g (91%) of **10c** as a white solid: mp 183–185 °C; IR (KBr) 2960 w, 1755 s, 1736 s, 1118 s, 777 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ε)) 240 (4.71), 263 (4.63), 272 (4.76), 300 (4.10), 340 (3.89), 352 (3.88); ^1H NMR ($CDCl_3$) δ 8.44 (d, 1 H, J = 8 Hz), 8.26 (br s, 1 H), 8.05 (d, 1 H, J = 8.2 Hz), 8.03 (d, 1 H, J = 9 Hz), 7.73 (d, 1 H, J = 9.0 Hz), 7.68 (dd, 1 H, J = 8.3, 1.4 Hz), 7.59 (t, 1 H, J = 8.0 Hz), 7.30 (d, 1 H, J = 7.6 Hz), 2.80 (q, 2 H, J = 7.7 Hz), 1.51 (s, 9 H), 1.33 (t, 3 H, J = 7.6 Hz). Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.74; H, 6.16.

8-(1-Bromoethyl)-1-(2,2-dimethyl-1-oxopropoxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (11c). A suspension of pivaloyl ester **10c** (1.32 g, 3.5 mmol) with 1.22 g (6.9 mmol) of NBS and 0.08 g of benzoyl peroxide in 50 mL of carbon tetrachloride was heated to reflux and monitored by GC for disappearance of the starting material. The reaction was continued, in this case 2.5 h,[31] until the dibromination product exceeded the residual starting material at about 95% conversion. After cooling in ice and filtration, the filtrate was concentrated under vacuum and the residue recrystallized from ether. The mother liquors were filtered through silica with 50% hexane/dichloromethane to afford additional material. The combined yield was 1.29 g of **11c** contaminated with some nonbrominated and some dibrominated material. An analytical sample was recrystallized from ethyl acetate: mp 176–178 °C; IR (KBr) 2980 w, 1748 s, 1618 w, 1187 w, 1112 s, 808 w, 778 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ε)) 236 (4.68), 244 (4.66), 275 (4.73), 303 (4.21), 348 (4.00); ^1H NMR ($CDCl_3$) δ 8.36 (br s, 1 H), 8.27 (d, 1 H, J = 8.4 Hz), 7.94 (d, 1 H, J = 8.3 Hz), 7.83 (dd, 1 H, J = 8.3, 1.5 Hz), 7.82 (d, 1 H, J = 9.1 Hz), 7.61 (d, 1 H, J = 8.8 Hz), 7.49 (appt. t, 1 H, J = 8 Hz), 7.23 (d, 1 H, J =7.5 Hz), 5.28 (q, 1 H, J = 6.4 Hz), 2.10 (d, 3 H, J = 6.8 Hz), 1.50 (s, 9 H); HRMS 452.0638 (calcd for $C_{24}H_{21}O_4Br$: 452.0624). Anal. Calcd for $C_{24}H_{21}O_4Br$: C, 63.59; H, 4.67. Found: C, 63.04; H, 4.25.

1-(2,2-Dimethyl-1-oxopropoxy)-8-ethenyl-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (5c). The crude bromination product **11c** (1.136 g, 2.5 mmol) was combined with LiBr (0.25 g), Li_2CO_3 (0.301 g), and hydroquinone (0.09 g) in 30 mL of DMF under nitrogen and heated to 110 °C overnight. After cooling, the solvent was removed under vacuum. The residue was dissolved in dichloromethane and chromatographed with 50% hexane/dichloromethane. Clean fractions were combined to give the desired vinyl derivative **5c** (0.7469 g, 65% from **10c**). An analytical sample was obtained by recrystallization from ethyl acetate: mp 179–180 °C; IR (KBr) 2980 w, 1750 s, 1522 w, 1370 w, 1117 s, 778 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ε)) 233 (4.55), 240 (4.54), 274 (4.59), 283 (4.63), 313 (4.27), 354 (4.06); ^1H NMR ($CDCl_3$) δ 8.40 (d, 1 H, J = 8.7 Hz), 8.39 (s, 1 H), 8.04 (d, 1 H, J = 8.1 Hz), 7.99 (d, 1 H, J = 9.0 Hz), 7.84 (br d, 1 H, J = 8.4 Hz), 7.71 (d, 1 H, J = 9.0 Hz), 7.58 (appt. t, 1 H, J = 7.8 Hz), 7.29 (d, 1 H, J = 7.5 Hz), 6.79 (dd, 1 H, J = 11.1, 17.7 Hz), 5.93 (d, 1 H, J = 17.4 Hz), 5.42 (d, 1 H, J = 10.8 Hz), 1.52 (s, 9 H); HRMS 372.1352 (calcd for $C_{24}H_{20}O_4$: 372.1362).

8-Ethenyl-1-hydroxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (5a). A suspension of pivaloate ester **5c** (0.2178 g, 0.58 mmol) in methanol with 0.32 mL of a 20% solution of potassium *tert*-butoxide in THF was stirred until complete solution occurred (overnight). The reaction was neutralized with 2 N HCl. Additional water caused a precipitate, which was collected by filtration. The solid was rinsed with dichloromethane and diethyl ether to dry. The organic rinses were dried over $MgSO_4$, filtered, and concentrated. Combined **5a** totaled 0.1612 g (96%) as a tan solid: mp 249–251 °C; IR (KBr) 3420 br s, 1708 s, 1632 m, 1612 m, 1523 m, 1375 s, 1318 m, 1102 m, 803 m, 778 s cm^{-1}; UV (DMSO) (λ (nm) (log ε)) 282 (4.50), 361 (4.00); ^1H NMR (DMSO-d_6) δ 10.47 (s, 1 H), 8.46 (d, 1 H, J = 8.4 Hz), 8.31 (br s, 1 H), 8.28 (d, 1 H, J = 9.3 Hz), 8.12 (br d, 1 H, J = 8.7 Hz), 8.08 (d, 1 H, J = 9.0 Hz), 7.80 (d, 1 H, J = 8.4 Hz), 7.48 (appt. t, 1 H, J = 8 Hz), 7.03 (d, 1 H, J = 7.5 Hz), 6.94 (dd, 1 H, J =17.7, 11.1 Hz), 6.08 (d, 1 H, J = 17.7 Hz), 5.45 (d, 1 H, J = 11.1 Hz); HRMS 288.0769 (calcd for $C_{19}H_{12}O_3$: 288.0786).

8-Ethyl-1-(phenylmethoxy)-7,8,9,10-tetrahydro-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6,10-dione (13d). Selenium dioxide (5.04 g, 45.4 mmol) was suspended in a solution of benzyl ether **6d** (6.00 g, 15.6 mmol) in 90 mL of diglyme with 0.12 mL of water. This suspension was placed in an oil bath at 200 °C for 25 min (measured from the point of first reflux), cooled to 25 °C, filtered through paper, and diluted with dichloromethane. The reddish solution was filtered through alumina (50 g) with dichloromethane to elute the unreacted starting material (2.36 g, 40%). The selenium-containing intermediates were eluted with 10% methanol in dichloromethane and concentrated to a red oil (3.43 g). This oil was suspended in 130 mL of dichloromethane and treated with PCC (3.43 g) overnight at ambient temperature. After quenching with 2-propanol, the reaction was concentrated under vacuum, taken up in dichloromethane, washed with 2 N HCl, and dried over $MgSO_4$. Flash chromatography on alumina gave 1.87 g (30% from **6d**, 50% based on consumed starting material) of **13d** as bright yellow crystals: mp 163–165 °C; IR (KBr) 2960 w, 1720 s, 1695 m, 1252 m, 1083 m, 1070 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ε)) 287 (4.23), 297 (4.24), 330 (3.79), 393 (3.52); ^1H NMR ($CDCl_3$) δ 8.67 (d, 1 H, J = 9.3 Hz), 8.15 (d, 1 H, J = 9.3 Hz), 8.07 (d, 1 H, J = 8.4 Hz), 7.52 (d, 2 H, J = 7.0 Hz), 7.4 (m, 4 H), 7.02 (d, 1 H, J = 7.6 Hz), 5.24 (s, 2 H), 3.18 (dd, 1 H, J = 18.8, 3.9 Hz), 2.84 (dd, 1 H, J = 15.5, 2.9 Hz), 2.48 (dd, 1 H, J = 15, 2.0 Hz), 2.45 (d, 1 H, J = 19 Hz) 2.18 (m, 1 H), 1.55 (quint., 2 H, J = 7.1 Hz), 1.02 (t, 3 H, J = 7.3 Hz). Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.38; H, 5.57. Found: C, 78.12; H, 5.84.

8-Ethyl-10-methoxy-1-(phenylmethoxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (16d). Benzyl ketone **13d** (4.80 g, 12 mmol) was suspended in 200 mL of methanol with 13 mL of trimethyl orthoformate and 0.1 g of toluenesulfonic acid and heated to reflux for 1 h. DDQ (3.34 g) was added and reflux continued overnight. After cooling, the precipitate was collected by filtration and rinsed with methanol. The filtrate was resubmitted to the same conditions with an additional 10 mL of trimethyl orthoformate and 2.6 g of DDQ. After the resulting precipitate was collected, the procedure was repeated a third time with 1.2 g of DDQ. The combined precipitates were recrystallized from ethyl acetate to give 4.36 g (88%) of **16d** as a white solid: mp 212–213 °C; IR (KBr) 1728 s, 1377 m, 1260 m, 775 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ε)) 244 (4.70), 275 (4.64), 305 (4.09), 318 (4.02), 335 (4.04), 360 (4.06); ^1H NMR ($CDCl_3$) δ 8.91 (d, 1 H, J = 9.4 Hz), 8.17 (d, 1 H, J = 8.3 Hz), 8.15 (d, 1 H, J = 9.1 Hz), 7.95 (br s, 1 H), 7.51 (d, 2 H, J = 7.1 Hz), 7.46 (t, 1 H, J = 8.2 Hz), 7.4 (m, 3 H), 7.13 (br s, 1 H), 6.97 (d, 1 H, J = 7.7 Hz), 5.24 (s, 2 H), 4.03 (s, 3 H), 2.77 (q, 2 H, J = 7.5 Hz), 1.34 (t, 3 H, J = 7.56 Hz). Anal. Calcd for $C_{27}H_{22}O_4$: C, 79.01; H, 5.40. Found: C, 78.76; H, 5.30.

2-(1,4-Dioxo-5-(phenylmethoxy)-2-naphthalenyl)-5-ethyl-3-methoxybenzoic Acid (17d). A suspension of benzyl ether lactone **16d** (1.34 g, 3.27 mmol) in 300 mL of ethanol with 1 mL of water and potassium *tert*-butoxide (1.3 g, 11.6 mmol)

(31) In the related bromination of methyl ether **6b**, there is a variable induction period during which starting material is only slowly consumed. Once the reaction begins, the reaction is complete in 30 min.

was heated to reflux for 3 h. The resulting solution, at room temperature, was added over 10 min to a degassed solution freshly prepared from 145 mL of distilled water, 124 mL of 0.1 N citric acid, 57 mL of 0.2 N Na_2HPO_4, and Fremy's salt ($K_2ON(SO_3)_2$, 1.82 g, 6.78 mmol). The deep purple color of the Fremy's salt solution gradually faded over about 20 min and a small amount of precipitate formed in the solution. This was allowed to stir overnight as an orange color gradually developed. The solution was filtered to remove insolubles. The orange filtrate was concentrated under vacuum to remove the ethanol. The remaining water solution was, after acidification to pH 4 with 2 N HCl, extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 1.23 g of a bright yellow solid, mp 187–192 °C. This solid was triturated with hot ethyl acetate, diluted with diethyl ether, and allowed to cool. The residual solid was collected as the quinone acid **17d** (0.79 g, mp 191–193 °C). A second crop derived from the filtrate gave an additional 0.24 g (71% total): mp 191–193 °C; IR (KBr) 3600–2500 br, 1720 m, 1695 m, 1655 s, 1605 m, 1585 m, 1500 m, 1285 s, 1255 s, 1243 s cm^{-1}; UV (CH_3OH) (λ (nm) (log ϵ)) 242 (4.33), 277 (4.03), 386 (3.63); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1 H, J = 7.5 Hz), 7.58 (d, 2 H, J = 7.4 Hz), 7.52 (dd, 1 H, J = 16.4 Hz), 7.50 (s, 1 H), 7.38 (t, 2 H, J = 7.3 Hz), 7.28 (t, 1 H, J = 7.3 Hz), 7.25 (d, 1 H, J = 8.4 Hz), 6.98 (s, 1 H), 6.73 (s, 1 H), 5.23 (s, 2 H), 3.72 (s, 3 H), 2.67 (q, 2 H, J = 7.6 Hz), 1.25 (t, 3 H, J = 7.6 Hz); HRMS m/e (relative intensity) 442.1380 (12%) (calcd for $C_{27}H_{22}O_6$: 442.1416), 440.1259 (50%) (calcd for $C_{27}H_{20}O_6$: 440.1259), 424.1329 (59%) (calcd for $C_{27}H_{20}O_5$: 424.1311), 335.0898 (100%) (calcd for $C_{20}H_{15}O_5$: 335.0919).

1-(Benzyloxy)-6-oxo-8-ethyl-10-methoxy-12-hydroxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran (18d). Sodium dithionite (0.71 g) in 40 mL of water was added slowly to a solution of quinone acid **17d** (0.685 g, 1.55 mmol) in 80 mL of dioxane. The yellow color was quenched after about 20 mL had been added. After stirring 30 min at room temperature, the solution was diluted with 300 mL of dichloromethane and washed with 50 mL of water. The organic layer was dried over $MgSO_4$ and concentrated to give a yellow solid, which was recrystallized from ethyl acetate/hexane to afford **18d** (0.613 g, 93%) as a tan solid: mp 228–229 °C; IR (KBr) 3430 m, 1720 s, 1610 m, 1588 m, 1390 m, 1150 m, 1020 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ϵ)) 266 (4.51), 276 (4.70), 307 (4.17), 326 (4.07), 340 (3.99), 380 (4.04); ^1H NMR ($CDCl_3$) δ 9.21 (s, 1 H), 8.37 (s, 1 H), 8.22 (d, 1 H, J = 8.4 Hz), 7.98 (br s, 1 H), 7.54–7.40 (m, 6 H), 7.17 (br s, 1 H), 7.01 (d, 1 H, J = 7.8 Hz), 5.31 (s, 2 H), 4.06 (s, 3 H), 2.79 (q, 2 H, J = 7.5 Hz), 1.34 (t, 3 H, J = 7.5 Hz); HRMS 426.1495 (calcd for $C_{27}H_{22}O_5$: 426.1467).

8-Ethyl-10,12-dimethoxy-1-(phenylmethoxy)-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (19d). The hydroxy ether **18d** (0.502 g, 1.18 mmol) was dissolved in 18 mL of DMF with a suspension of freshly crushed K_2CO_3 (0.5 g). Methyl iodide (0.5 mL) was added at room temperature. The slow alkylation was accelerated with slow dropwise addition of a 20% solution of potassium *tert*-butoxide in THF. The bright red-orange color induced by each drop rapidly disappeared. This addition was continued until a faint orange color persisted. The suspension was then allowed to stir until the orange color faded completely. This procedure was repeated until HPLC analysis revealed no further starting phenol. Decanting the solution into water from the inorganic solid gave a bright yellow precipitate. The inorganic solids were dissolved in water and neutralized with acid. The water layers were combined and filtered from the precipitate. The yellow solid was recrystallized with ethyl acetate to afford **19d** (0.3981 g, 77%) as a light yellow solid: mp 196–198 °C; IR (KBr) 1725 s, 1612 m, 1590 s, 1395 m, 1123 m, 1060 m, 1045 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ϵ)) 243 (4.71), 266 (4.53), 276 (4.70), 305 (4.18), 380 (4.05); ^1H NMR ($CDCl_3$) δ 8.41 (s, 1 H), 8.24 (d, 1 H, J = 8.4 Hz), 7.98 (br s, 1 H), 7.62 (d, 2 H, J = 7.5 Hz), 7.49 (appt. t, 1 H, J = 8.4 Hz), 7.43 (m, 2 H), 7.34 (appt. t, 1 H, J = 7.2 Hz), 7.17 (br s, 1 H), 7.05 (d, 1 H, J = 7.5 Hz), 5.23 (s, 2 H), 4.09 (s, 3 H), 4.00 (s, 3 H), 2.79 (q, 2 H, J = 7.6 Hz), 1.34 (t, 3 H, J = 7.6 Hz). Anal. Calcd for $C_{28}H_{24}O_5$: C, 76.35; H, 5.49. Found: C, 76.28; H, 5.55.

Gilvocarcin E Aglycone. 8-Ethyl-1-hydroxy-10,12-dimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (19a). Benzyl dimethyl ether **19d** (0.10 g, 0.23 mmol) was suspended in 14 mL of 1:1 benzene/acetic anhydride with 0.2 g of sodium acetate and 20 mg of 10% Pd/C. After 24 h of stirring under hydrogen gas at atmospheric pressure, the suspension was filtered through Celite, rinsed with dichloromethane, concentrated under vacuum, and filtered through silica gel with dichloromethane to afford, after concentration, **19a** (0.0726 g, 88%) as an off-white solid: mp 242–244 °C; IR (KBr) 3355 w, 1718 s, 1588 m, 1435 m, 1386 s, 1248 m, 1121 m, 1055 m cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ϵ)) 243 (4.70), 273 (4.60), 302 (4.11), 325 (3.97), 340 (3.81), 377 (4.05); ^1H NMR ($CDCl_3$) δ 9.35 (s, 1 H), 8.27 (s, 1 H), 8.05 (d, 1 H, J = 8.5 Hz), 7.94 (br s, 1 H), 7.48 (appt. t, 1 H, J = 8.2 Hz), 7.13 (br s, 1 H), 6.99 (d, 1 H, J = 7.7 Hz), 4.08 (s, 3 H), 4.06 (s, 3 H), 2.79 (q, 2 H, J = 7.3 Hz), 1.34 (t, 3 H, J = 7.3 Hz). Anal. Calcd for $C_{21}H_{18}O_5 \cdot {}^1/_2H_2O$: C, 70.19; H, 5.33. Found: C, 70.03; H, 5.35.

1-(Acetyloxy)-8-ethyl-10,12-dimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (19e). A solution of phenol **19a** (19 mg) in 4 mL of 3:1 pyridine/acetic anhydride was stirred for 12 h. After concentration under vacuum, MPLC on silica gel with dichloromethane as eluant afforded acetate 19e (13.4 mg, 65%): mp 214–216 °C; IR (KBr) 1770 s, 1725 s, 1610 m, 1590 m, 1485 m, 1455 m, 1385 m, 1368 m, 1210 s cm^{-1}; UV (CH_2Cl_2) (λ (nm) (log ϵ)) 243 (4.61), 266 (4.42), 275 (4.58), 300 (4.04), 314 (3.96), 372 (4.00); ^1H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 8.08 (d, 1 H, J = 8.7 Hz), 8.00 (d, 1 H, J = 0.9 Hz), 7.50 (appt. t, 1 H, J = 8 Hz), 7.20 (br s, 1 H), 7.01 (d, 1 H, J = 8.1 Hz), 4.14 (s, 3 H), 4.10 (s, 3 H), 2.82 (q, 2 H, J = 7.5 Hz), 2.31 (s, 3 H), 1.35 (t, 3 H, J = 7.7 Hz); HRMS 392.1280 (calcd for $C_{23}H_{20}O_6$: 392.1260).

1-(Acetyloxy)-8-ethenyl-10,12-dimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (4e). Under a nitrogen atmosphere, a solution of acetate **19e** (38 mg) in carbon tetrachloride with 37 mg of NBS and 3 mg of benzoyl peroxide was heated at reflux for 20 min. After cooling, the solution was filtered and concentrated to afford a yellow solid that was eluted through a small silica gel column with dichloromethane to afford 48 mg of **20e**, which was characterized by NMR and used directly in the next step. The benzylic bromide **20e** (45 mg, 0.1 mmol) was dissolved in DMF, to which was added 9.6 mg of LiBr, 12 mg of Li_2CO_3, and 3 mg of hydroquinone, and heated under an argon atmosphere at 110 °C overnight. After cooling to room temperature, the solvent was removed under vacuum and the residue was purified by MPLC on silica gel, eluting with 50% hexane in dichloromethane to afford 34 mg of **4e** as a yellow solid: mp 240–242 °C; IR (KBr) 1748 m, 1725 s, 1630 w, 1604 m, 1586 m, 1485 w, 1452 w, 1385 m, 1365 m, 1352 m, 1332 m, 1293 m, 1228 s, 1218 s, 1125 m, 1055 w, 782 w, 758 w cm^{-1}; UV (DMSO) (λ (nm) (log ϵ)) 245 (4.47), 251 (4.46), 285 (4.47), 331 (3.96), 347 (3.94), 382 (4.14); ^1H NMR ($CDCl_3$) δ 8.56 (d, 1 H, J = 8.4 Hz), 8.51 (s, 1 H), 8.23 (d, 1 H, J = 1.2 Hz), 7.62 (appt. t, 1 H, J = 7.9 Hz), 7.43 (d, 1 H, J = 1.2 Hz), 7.24 (d, 1 H, J = 7.2 Hz), 6.86 (dd, 1 H, J = 17.7, 10.8 Hz), 6.00 (d, 1 H, J = 17.7 Hz), 5.50 (d, 1 H, J = 10.8 Hz), 4.16 (s, 3 H), 4.05 (s, 3 H), 2.44 (s, 3 H).

Defucogilvocarcin V. 1-Hydroxy-8-ethenyl-10,12-dimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (4a). A suspension of acetate **4e** (21 mg) in 20 mL of methanol was treated with 3 mL of 25% sodium methoxide in methanol until complete solution occurred. Neutralization with 2 N HCl caused a yellow precipitate, which was rinsed with water and dissolved in 5% methanol/dichloromethane. The solution was dried over $MgSO_4$, filtered, and concentrated to give 8.3 mg of **4a** (20% from **19e**): mp 265–270 °C dec; IR (KBr) 3410 s, 1725 s, 1630 m, 1605 m, 1590 m, 1510 w, 1452 w, 1385 s, 1360 w, 1335 w, 1302 m, 1243 m, 1128 m, 1063 w, 782 m, 753 w cm^{-1}; UV (methanol) (λ (nm)) 248, 284, 388; ^1H NMR ($CDCl_3$) δ 9.26 (s, 1 H), 8.18 (s, 1 H), 8.03 (br s, 1 H), 7.98 (d, 1 H, J = 8.4 Hz), 7.42 (appt. t, 1 H, J = 8.1 Hz), 7.22 (br s, 1 H), 6.93 (d, 1 H, J = 7.5 Hz), 6.71 (dd, 1 H, J = 17.7, 11.1 Hz), 5.87 (d, 1 H, J = 17.4 Hz), 5.39 (d, 1 H, J = 10.8 Hz), 4.17 (s, 6 H). Different samples exhibit small NMR shifts that are concentration dependent. HRMS 348.0969 (calcd for $C_{21}H_{16}O_5$: 348.0997).

Additionally, synthetic **4a** was correlated by capillary GC and HPLC with natural material obtained as a gift from Dr. Renuka Misra at the NCI-FCRF, Frederick, MD. A sample provided to Prof. Samuel Danishefsky, Yale University, was correlated with a sample prepared by an alternate procedure in his laboratories.[10b]

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Registry No. **4a**, 80155-95-9; **4e**, 110582-91-7; **5a**, 114862-70-3; **5c**, 114862-69-0; **6a**, 114862-61-2; **6b**, 114862-62-3; **6c**, 114862-63-4; **6d**, 114862-64-5; **7**, 83-56-7; **8**, 114862-60-1; **9c**, 114862-66-7; **10b**, 114862-65-6; **10c**, 114862-67-8; **11c**, 114862-68-9; **13d**, 114862-71-4; **16d**, 114862-72-5; **17d**, 114862-73-6; **18d**, 114862-74-7; **19a**, 114862-76-9; **19d**, 114862-75-8; **19e**, 110582-87-1; **20e**, 110582-90-6.

Stereoselective Generation and Facile Dimerization of (*E*)-2-Methylene-3-alkenoic Acid Esters[1]

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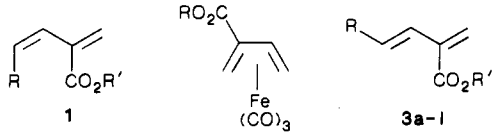
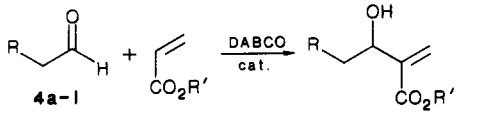
1,4-Diazabicyclo[2.2.2]octane (DABCO)-induced coupling of selected aldehydes and acrylic esters gave some new [2 + 2 + 2] cycloadducts. As a rule, however, aldehydes and acrylic esters coupled to 3-hydroxy-2-methylenealkenoic acid esters **5**. These were dehydrated by a mild and specific procedure (methanesulfonyl chloride, DABCO, catalytic 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, room temperature, 24 h). The novel 2-methylene-3-alkenoic acid esters **3** were generated as *E* isomers and they dimerized spontaneously to give 4-[(*E*)-1-alkenyl]-3-alkyl-1-cyclohexene-1,4-dicarboxylic acid esters **6**. The dimerization was endo-selective (>5:1 to 10:1) with respect to the alkenyl chain and exo with respect to the ester grouping and completely para-selective. Stereoselectivity and separability of the dimers **6** depended on the steric bulk of the alkyl group R. The stereochemical assignments were corroborated by X-ray crystal structures of **6h** (R = $PhCH_2$) (major isomer) and also tricyclic lactone **7a**. Selected (*E*)-2-methylene-3-alkenoic acid esters **3** were intercepted in crossed Diels–Alder reactions with cyclopentadiene and also pyrrolidinoisobutene.

Although a number of (*Z*)-2-methylene-3-alkenoic acid esters[2] **1** and the simple iron tricarbonyl protected **2**[3] have

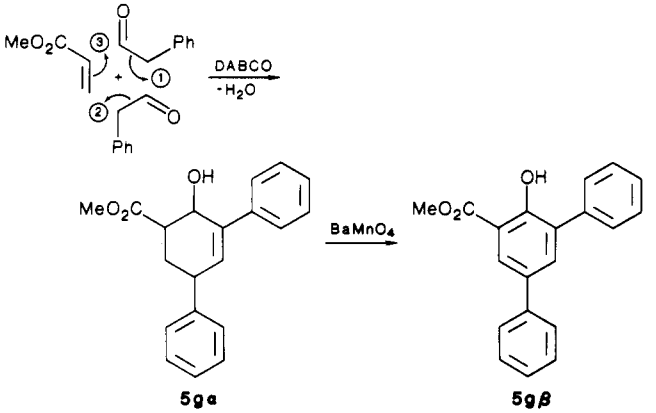


been prepared and isolated, the class of stereoisomeric (*E*)-2-methylene-3-alkenoic acid esters **3** is practically unknown.[4] In principle, synthesis of 3-hydroxy-2-methylenealkanoic acid esters **5** and their dehydration should yield 1,3-diene esters. In practice, a number of experimental hurdles had to be overcome first of all.

We begin by describing the preparation of α-(hydroxyalkyl)acrylic acid esters **5**, which are known to arise by coupling of aldehydes **4** with acrylic acid esters in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane).[1,6–8]



We have now found that suitably functionalized aldehydes enter into interesting tandem processes. For example, 2-phenylethanal (**4g**), which enolizes more readily than a simple aliphatic aldehyde, reacted with methyl acrylate in the presence of DABCO to give not only **5g** (17%) but also **5gα** (40%). The formation of cyclohexenol **5gα** is



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