Programs for partial financial assistance in the purchase of a high field nuclear magnetic resonance spectrometer and a high-resolution mass spectrometer.

Registry No. **1a**, 98122-97-5; **1b**, 112597-27-0; **1c**, 112597-28-1; **1d**, 112597-29-2; **1e**, 112597-30-5; **1f**, 112597-31-6; **1g**, 112597-32-7; **1h**, 112597-33-8; **1i**, 112597-34-9; **1j**, 112597-35-0; **1k**, 112597-36-1; **1l**, 112597-37-2; **1m**, 112597-38-3; **1n**, 112597-39-4; **1o**, 112597-40-7; **1p**, 112597-41-8; **1q**, 112597-42-9; **1r**, 112597-43-0; **2a**, 6956-96-3; **2b**, 102632-08-6; **2c**, 62345-17-9; **2d**, 102632-07-5; **2e**, 62345-18-0; **2f**, 51783-58-5; **3g**, 102683-49-8; **3h**, 102683-53-4; **3i**, 102683-51-2; **3j**, 102683-50-1; **3k**, 112597-44-1; **4**, 102683-52-3; **8**, 112597-45-2; **12**, 112597-46-3; **13**, 112597-47-4; **21**, 112597-48-5; **22**, 112597-49-6; **23**, 5222-73-1; **25**, 102632-27-9; **26**, 91037-30-8; **27**, 91431-42-4; *p*-BrC_6H_4Me, 106-38-7; *p*-BrC_6H_4OMe, 104-92-7; *o*-BrC_6H_4Me, 95-46-5; *o*-BrC_6H_4OMe, 578-57-4; 2-Br-1,4-$(OMe)_2C_6H_3$, 25245-34-5; *m*-BrC_6H_4Me, 591-17-3; *m*-BrC_6H_4OMe, 2398-37-0; *p*-BrC_6H_4Cl, 106-39-8; *m*-$(OMe)_2C_6H_4$, 151-10-0; 2-bromothiophene, 1003-09-4; 3-bromofuran, 22037-28-1; 2-bromonaphthalene, 580-13-2; 1-bromonaphthalene, 90-11-9; furan, 110-00-9; 1-methylpyrrole, 96-54-8; 1,4-dimethoxynaphthalene, 10075-62-4; 3-methyl-4-phenylcyclobutenedione, 711-78-4.

A Concise Total Synthesis of Defucogilvocarcin V by Application of the Meyers Biaryl Strategy: Ortho- and Para-Selective Functionalizations of the A Ring

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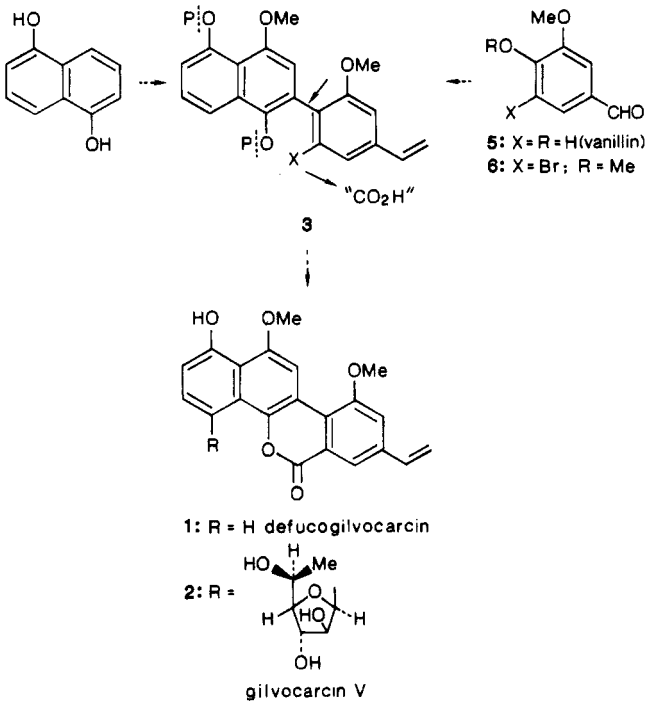
Coupling of the Grignard reagent derived from 1,5-bis(methoxymethoxy)-4-methoxy-2-bromonaphthalene with the oxazoline derived from 2,3-dimethoxy-5-ethenylbenzoic acid is the key step in a very concise synthesis of defucogilvocarcin V. Functionalization of the A ring in a fashion required for a synthesis of gilvocarcin has been achieved.

A variety of structures containing aromatic and carbohydrate segments are of considerable current and potential importance in cancer chemotherapy. The best known of these compounds are of the anthracycline type such as adriamycin and daunomycin. In these systems, the carbohydrate sector is attched through an *O*-glycosidic bond.[1] Apparently, neither the anthracycline nor the carbohydrate exhibit useful biological properties. There is a newer class of antibiotic–antitumor agents wherein the aromatic and carbohydrate domaines are joined through a carbon–carbon bond.[2] While none of these *C*-(aryl)glycosyl compounds has reached the stage of serious clinical application, the broad range of such compounds with promising activity has already begun to engender interest in their mode of action, as well as in their synthesis.[3] Since in such *C*-glycosyl compounds the cleavage of the aromatic system from the carbohydrate is not simply executed, there is a dearth of information on the activity of the individual "aglycon" and carbohydrate moieties.

A striking situation is found in the gilvocarcin family.[4] A variety of such compounds, of which gilvocarcin V (**2**) is typical, has been isolated from various *Streptomyces* species.[5] Compound **2** possesses antitumor properties as well as the capacity to induce bacteriophage λ in *Escherichia coli* upon activation by low doses of light.[6] On the basis of some structure activity work, the two properties appear to be related. Analogy with the psoralens has already been drawn.[6]

Interestingly, the compound defucogilvocarcin V (**1**), formally the "aglycon" of **2** has itself been isolated from *Streptomyces arenae* 2064.[7] Compound **1** is also active in promoting light-dependent prophage activity identical

Scheme I



(1) Cf. inter alia: (a) *The Chemistry of Antitumor Antibiotics*; Remers, W. A., Ed.; Wiley: New York, 1978. (b) *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic: New York, 1980. (c) *Antineoplastic Agents*; Remers, W. A., Ed.; Wiley: New York, 1984.

(2) Cf. inter. alia: (a) Nogalamycin: Hauser, F. M.; Adams, T. C. *J. Org. Chem.* **1984**, *49*, 2296 and references therein. (b) Pluramycin A: Kondo, S.; Muyamoto, M.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 1143. (c) Granaticin: Chang, C. J.; Floss, H. G.; Soong, P.; Chan, C. T. *Ibid.* **1975**, *28*, 156. (d) Griseusin: Kometani, T.; Takeuchi, Y.; Yoshi, E. *J. Org. Chem.* **1983**, *48*, 2311. (e) Aquayamycin: Sezaku, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron* **1970**, *26*, 5171.

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

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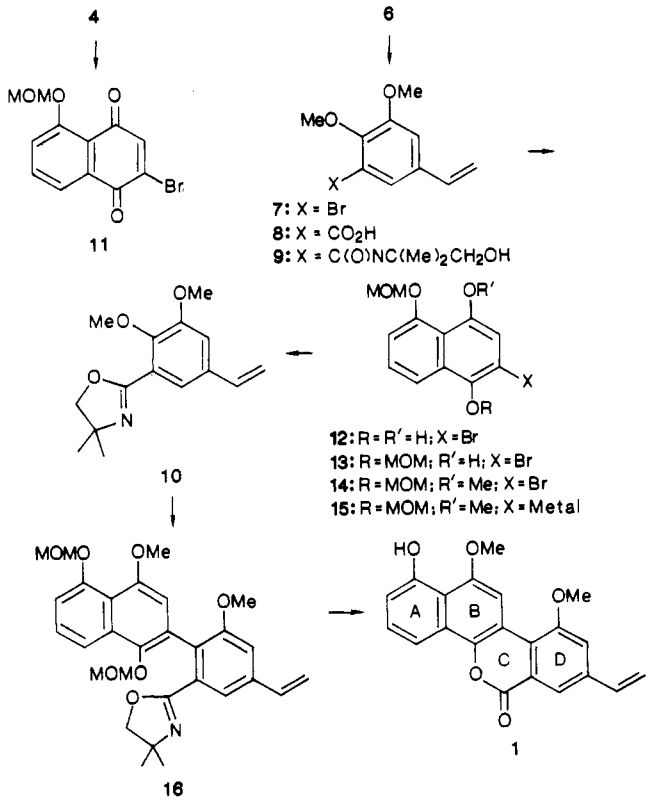
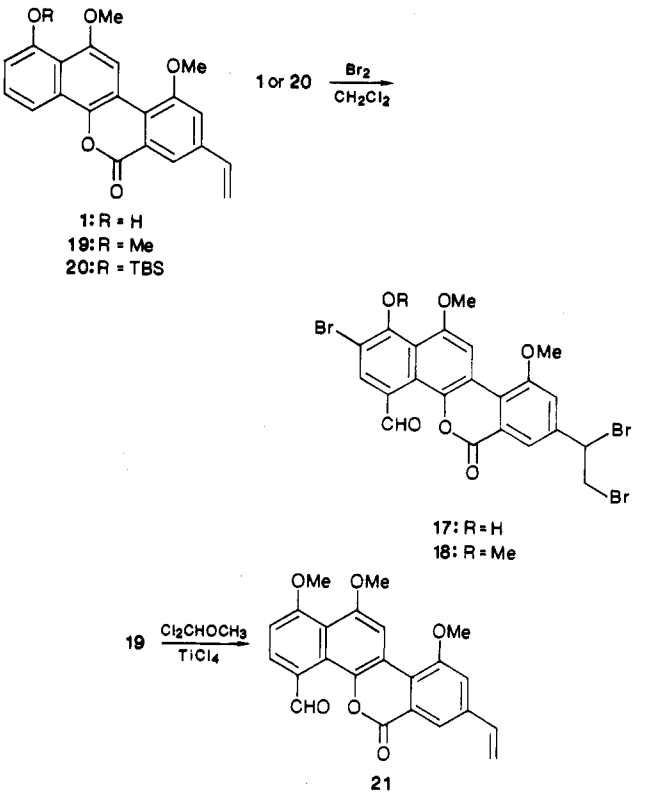
0022-3263/88/1953-1003$01.50/0

Scheme II



Scheme III



with that of gilvocarcin V. The defuco compound shows antimicrobial activity against typical Gram-positive but not Gram-negative species. In contrast, gilvocarcin V itself is active against both Gram-positive and Gram-negative organisms. The identification of **1** as a natural product is interesting from a biogenetic standpoint, since the basic chromophore is found in several other antibiotics such as ravidomycin[8] and the chrysomycins.[9] It would seem that sugar moieties are attached biogenetically after elaboration of the aromatic substructure, **1**. As part of a broader interest in the field of *C*-(aryl)glycosyl compounds,[10] we have undertaken a total synthesis of both **1** and **2**. Below we describe a concise and efficient synthesis of **1**.[11]

The basic strategy is adumbrated in Scheme I. The key intermediate was to be a biaryl of the type **3**, with the proviso that the protecting groups P could be removed as the X function becomes a carboxyl function or its equivalent. The provocative bond is of course, the one linking the two aromatic domains (see bold arrow). *It was recognized that an oxazolin-2-yl group might facilitate the coupling to produce the biaryl and might serve as the carboxyl surrogate.* With that presumption, the readily available compounds **4** and **6** emerged as starting materials. Compound **6** is obtained in high yield from vanillin (**5**).[12] The realization of this scheme in practice is described below.

Wittig reaction on **6** with triphenylmethylenephosphorane (THF; −60 °C → room temperature) afforded a 90% yield of **7**, which upon lithiation followed by carboxylation gave rise (89%) to **8**. The latter was converted to its acid chloride and thence into the (hydroxy-*tert*-butyl)amide **9**. Treatment of the latter with thionyl chloride afforded the oxazoline **10** in 46% yield from **8**.

The readily available 2-bromojuglone, prepared from **4** by the method of Grunwell,[13] was converted (55%) to its MOM ether **11**, mp 142–144 °C, via the action of Hunig's base and MOM chloride in CH_2Cl_2. Catalytic reduction of **11** (H_2/Pd (10%)/C) gave the corresponding bromonaphthohydroquinone **12** (Scheme II). A major simplification in the synthesis was achieved by the selective protection of the 1-hydroxyl group of **12** as its MOM derivative **13** via treatment of **12** with Hunig's base and MOM chloride.[14] At this point, methylation of the 4-hydroxyl group was carried out ($NaOH/Me_2SO_4$), and the bromo compound **14** (37% from **11**), mp 87–88 °C, was in hand. Lithiation of **14** with *n*-butyllithium (hexane–THF) was followed by treatment with anhydrous magnesium bromide (ether). The presumed Grignard version of **15** reacted with **10** via a Meyers coupling reaction[13] to afford **16** in 50–60% yield. *Treatment of **16** with 4.8 N HCl brought about its conversion, in 86% yield, to defucogilvocarcin V (**1**), mp 267–272 °C.* The ^1H NMR and mass spectra of fully synthetic **1** were identical with those of an authentic specimen sample provided by Dr. L. McGee of Du Pont.

(8) Sehgal, S. N.; Czerkawski, H.; Kudelski, A.; Pandev, K.; Saucier, R.; Vezina, C. *J. Antibiot.* **1983**, *36*, 355. It should be noted that compound **1** was first obtained by KOH degradation of ravidomycin; see: Findlay, J. A.; Liu, J.-S.; Radics, L.; Rakhit, S. *Can. J. Chem.* **1981**, *59*, 3018.

(9) Weiss, U.; Yoshihira, K.; Highet, R. J.; White, R. J.; Wei, T. T. *J. Antibiot.* **1982**, *35*, 1194.

(10) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285.

(11) A total synthesis of defucogilvocarcin was achieved by Findlay and co-workers. The Findlay synthesis also uses the Meyers coupling reaction though on a ring D ethyl rather than a ring D vinyl compound. The double bond is introduced at a late stage. The synthesis described herein has advantages in providing regiochemical control and in distinguishing the ring A phenolic function. See: Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427. See also: Abstracts of the 68th Conference of the Chemical Institution of Canada; Kingston, Ontario, 1985. Daljeet, A. Ph.D. Thesis, University of New Brunswick, 1985.

(12) Shriner, R. H.; McCutchan, P. *J. Am. Chem. Soc.* **1929**, *51*, 2193.

(13) (a) Grunwell, J. R.; Heinzman, S. W. *Tetrahedron Lett.* **1980**, *21*, 4305. (b) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1983**, *48*, 5359.

(14) (a) Meyers, A. I.; Gabel, R.; Mikelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372. (b) Meyers, A. E.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881.

We emphasize that this highly convergent synthesis is amenable to large-scale application. Accordingly, the defuco compound **1** is a reasonable possibility for a synthesis of gilvocarcin itself. We have begun to investigate this possibility. The bromination of **1** and its derivatives was explored first. Reaction of **1** with bromine in dichloromethane gave a 50% yield of a tribromo compound, **17** (Scheme III). The regiochemistry of nuclear bromination that occurred in the A ring was revealed by NOE experiments on the derived methyl ether **18** in conjunction with those of the parent compound, **19**. It was thus shown that in **18** there is no proton ortho to the ring A methoxyl group. Similar ortho bromination occurred on the OTBS silyl ether **20**. Under the conditions of the experiment, desilylation occurred and the same compound, **17**, was obtained. However, reaction of **19** with dichloromethyl methyl ether gave an 11:1 mixture of monoformyl derivatives. NOE measurements on the major product clearly revealed it to be the desired **21**.

Investigations into the nature of the reactions of the rather potent defuco drug with DNA strands are planned. At the synthetic level, investigations into the use of aldehyde **21** as a precursor to **2**, as well as to ravidomycin[8] and the chrysomycins, will go forward.

Experimental Section[15]

3-Bromo-4,5-dimethoxystyrene (7). Methyltriphenylphosphonium bromide (8.52 g, 23.8 mmol) was added to a solution of potassium *tert*-butoxide (2.48 g, 22.1 mmol) in 80 mL of THF at room temperature. The yellow slurry was stirred at room temperature for 40 min and cooled to −60 °C. A solution of 3-bromo-4,5-dimethoxybenzaldehyde[12] (**6**) (4.17 g, 17.0 mmol) in 20 mL of THF was added slowly, and the mixture was allowed to warm slowly to room temperature over 6 h. The yellow slurry was diluted with ether (100 mL) and filtered through Celite. The filtrate was washed with saturated aqueous sodium chloride solution (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to a yellow oily solid. The crude material was flash chromatographed on a 5 × 14 cm column with use of 25% ethyl acetate in hexane as eluant to give 3.75 g (90%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 3.90 (s, 3 H), 5.26 (d, 1 H, J = 10.8 Hz), 6.67 (d, 1 H, J = 17.5 Hz), 6.59 (dd, 1 H, J = 17.5, 10.8 Hz), 6.90 (d, 1 H, J = 1.9 Hz), 7.19 (d, 1 H, J = 1.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.9, 60.4, 109.3, 114.2, 117.6, 122.7, 134.7, 135.2, 146.2, 153.6; IR ($CDCl_3$) 1631, 1593, 1553 cm^{-1}; MS, m/e (%) 244 (100.0), 242 (M^+, 91.9), 229 (47.2), 227 (46.3).

2,3-Dimethoxy-5-ethenylbenzoic Acid (8). A 1.66 M solution of *n*-butyllithium in hexane (12.1 mL, 20.0 mmol) was added slowly to a solution of 3-bromo-4,5-dimethoxystyrene (**7**) (3.75 g, 15.4 mmol) in 150 mL of THF at −78 °C. The resulting purple solution was stirred at −78 °C for 15 min, and carbon dioxide (from evaporation of dry ice) was bubbled through the solution for 10 min. The purple color was gradually dispelled, leaving a clear golden solution. The reaction mixture was warmed slowly to room temperature, with evolution of carbon dioxide. The warm solution was diluted with ether (200 mL) and extracted with 5% aqueous sodium hydroxide solution (3 × 50 mL). The base extracts were acidified with solid sodium hydrogen sulfate and extracted with ether (3 × 50 mL). The ether extracts were dried ($MgSO_4$) and concentrated under reducted pressure to 2.86 g (89%) of a yellow oil, contaminated with a small amount of pentanoic acid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 4.00 (s, 3 H), 5.25 (d, 1 H, J = 10.9 Hz), 5.70 (d, 1 H, J = 17.5 Hz), 6.61 (dd, 1 H, J = 17.5, 10.9 Hz), 7.13 (d, 1 H, J = 2.0 Hz), 7.62 (d, 1 H, J = 2.0 Hz), 9.6 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.0, 61.9, 114.4, 114.8, 121.5, 122.3, 134.3, 135.2, 148.0, 152.4, 166.5; IR ($CDCl_3$) 1740, 1435, 915 cm^{-1}; MS, m/e (%) 208 (M^+, 100.0), 175 (31.2).

3-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-4,5-dimethoxystyrene (10). A small amount of dimethylformamide was added to a mixture of 2,3-dimethoxy-5-ethenylbenzoic acid (**8**) (2.86 g, 13.7 mmol) and oxallyl chloride (2.4 mL, 27.4 mmol) in 70 mL of benzene at room temperature. The effervescent solution was stirred at room temperature for 1 h, and the volatile materials were removed by rotary evaporation. The residue was dissolved in dichloromethane (50 mL) and cooled to 0 °C, and 2-amino-2-methyl-1-propanol (2.6 mL, 27.4 mmol) was added. The cloudy solution was stirred at 0 °C, warming gradually to room temperature, for 5 h. The mixture was filtered and recooled to 0 °C, and thionyl chloride (4.8 mL, 54.8 mmol) was added. After being stirred at 0 °C for 2 h, the reaction mixture was added to ether (200 mL) and water (100 mL) and mixed. The aqueous layer was made basic by addition of solid sodium hydroxide, the layers were separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to a cloudy yellow oil. Flash chromatography on a 5 × 15 cm column using 30% ethyl acetate in hexane as eluant gave 1.65 g (46%) of a colorless oil. The compound was stored in the freezer as a 0.5 M solution in benzene to avoid polymerization: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.39 (s, 6 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 4.12 (s, 2 H), 5.22 (d, 1 H, J = 10.8 Hz), 5.68 (d, 1 H, J = 17.5 Hz), 6.64 (dd, 1 H, J = 17.5, 10.8 Hz), 7.06 (d, 1 H, J = 2.0 Hz), 7.34 (d, 1 H, J = 2.0 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.9, 55.7, 60.9, 66.9, 78.7, 111.8, 113.3, 120.4, 122.8, 133.1, 135.4, 148.1, 153.0, 160.8; IR ($CDCl_3$) 1650, 1575, 1490 cm^{-1}; MS, m/e (%) 261 (M^+, 100.0), 189 (86.9), 161 (72.9).

2-Bromo-5-(methoxymethoxy)-1,4-naphthoquinone (11). Diisopropylethylamine (3.4 mL) was added to a mixture of 2-bromojuglone[13] (14.89 g, 58.8 mmol) and chloromethyl methyl ether (6.7 mL, 88.3 mmol) in 80 mL of dichloromethane at 0 °C. The initially orange solution turned brown immediately. Four additional aliquots of amine (3.0 mL, 88.3 mmol total) were added, each followed by stirring at 0 °C for 1 h. After the additions were complete, the dark reaction mixture was stirred for 4 h at room temperature (TLC, ethyl acetate–hexane, 1:3; R_f 0.40, 2-bromojuglone; R_f 0.18, **11**). The reaction was diluted with dichloromethane (250 mL) and washed with 0.4 M hydrochloric acid (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to a black solid. The crude material was flash chromatographed on a 9 × 20 cm column with use of dichloromethane as eluant to give 9.65 g (55%) of a yellow solid: mp 142–144 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.54 (s, 3 H), 5.36 (s, 2 H), 7.41 (s, 1 H), 7.57 (dd, 1 H, J = 8.4, 1.1 Hz), 7.67 (dd, 1 H, J = 8.4, 7.6 Hz), 7.89 (dd, 1 H, J = 7.6, 1.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.62, 95.05, 120.22, 121.81, 122.68, 132.92, 134.72, 137.01, 142.15, 157.43, 178.01, 181.17; IR ($CHCl_3$) 1680, 1660, 1600, 1585, 1000 cm^{-1}; MS, m/e (%) 298 (57.2), 297 (M^+, 59.4), 238 (95.0), 236 (100.0). Anal. Calcd for $C_{12}H_9BrO_4$: C, 48.51; H, 3.05. Found: C, 48.53; H, 3.23.

2-Bromo-1,5-bis(methoxymethoxy)-4-naphthol (13). A mixture of 2-bromo-5-(methoxymethoxy)-1,4-naphthoquinone (**11**) (11.75 g, 39.5 mmol) and 10% palladium on carbon (0.75 g) in 200 mL of dichloromethane was degassed (by successive evacuation and venting to hydrogen) and stirred under hydrogen (1 atm) for 20 h. The mixture was cooled to 0 °C and chloromethyl methyl ether (4.5 mL, 59.2 mmol) was added, followed by diisopropylethylamine (13.8 mL, 79.0 mmol). The reaction mixture was stirred under nitrogen for 8 h (TLC, ethyl acetate–hexane, 1:1; R_f 0.77, **12**; R_f 0.71, **13**, R_f 0.61, **11**) and filtered through Celite. The filtrate was washed with 0.4 M hydrochloric acid (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave a brown oil, which was filtered through a 5 × 8 cm pad of silica gel with dichloromethane as eluant to give 12.22 g (90%) of an orange oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.50 (s, 3 H), 3.66 (s, 3 H), 5.12

(15) Commercial reagents were used as obtained without further purification. Solvents were generally purified and dried by standard methods before use. Flash chromatography was performed on the column size indicated using E. Merck silica gel 60 (230–400 mesh). Melting points were determined using a Thomas-Hoover apparatus (<225 °C) or a laboratory devices Mel-Temp apparatus (>225 °C) and are uncorrected. ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WH250 spectrometer with chemical shifts reported in parts per million relative to internal tetramethylsilane. ^{13}C NMR spectra were recorded at 62.9 MHz on a Brucker WH250 spectrometer with chemical shifts reported in parts per million relative to deuteriochloroform. IR spectra were recorded in solution on a Perkin-Elmer 1420 spectrophotometer with use of NaCl cells. Mass spectra were recorded on a Hewlett-Packard 5985 GC/MS system. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

(s, 2 H), 5.34 (s, 2 H), 6.99 (s, 1 H), 7.01 (d, 1 H, J = 7.7 Hz), 7.31 (dd, 1 H, J = 8.4, 7.7 Hz), 7.76 (d, 1 H, J = 8.4 Hz), 9.19 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.60, 57.59, 95.70, 99.94, 108.50, 113.54, 113.98, 114.99, 116.98, 126.73, 131.53, 142.72, 151.14, 153.62; IR ($CHCl_3$) 1620, 1610, 1455, 1430, 1375 cm^{-1}; MS, m/e (%) 344 (100.0), 342 (M^+, 89.7).

2-Bromo-1,5-bis(methoxymethoxy)-4-methoxynaphthalene (14). A mixture of 2-bromo-1,5-bis(methoxymethoxy)-4-naphthol (**13**) (12.22 g, 35.6 mmol) and dimethyl sulfate (33.7 mL, 356 mmol) in 240 mL of dioxane was treated with 40% aqueous sodium hydroxide solution (150 mL, 2.14 mol). The resulting heterogeneous mixture quickly darkened, but gradually became lighter during the course of the reaction. After being stirred at room temperature for 9 h, the reaction mixture was diluted with water (500 mL) and extracted with dichloromethane (500 mL, 2 × 250 mL). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a brown solid. The crude material was flash chromatographed on a 5 × 19 cm column, eluting with dichloromethane to give 12.1 g of a greenish solid. Recrystallization five times from petroleum ether gave 1.64 g of fine, off-white needles. The mother liquors were concentrated and flash chromatographed to give an additional 3.19 g of white needles after recrystallization six times from petroleum ether (total yield 37%): mp 87–88 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.57 (s, 3 H), 3.70 (s, 3 H), 3.91 (s, 3 H), 5.17 (s, 2 H), 5.23 (s, 2 H), 6.91 (s, 1 H), 7.11 (dd, 1 H, J = 7.7, 1.1 Hz), 7.42 (dd, 1 H, J = 8.4, 7.7 Hz), 7.84 (dd, 1 H, J = 8.4, 1.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.27, 56.80, 58.07, 96.87, 100.11, 110.50, 112.66, 114.07, 116.94, 118.95, 127.41, 132.65, 144.46, 154.00, 154.53; IR ($CHCl_3$) 1610, 1580, 1370 cm^{-1}; MS, m/e (%) 358 (27.3), 356 (M^+, 32.1), 277 (100.0). Anal. Calcd for $C_{15}H_{17}BrO_5$: C, 50.44; H, 4.80. Found: C, 50.73; H, 5.27.

2-[4-Ethenyl-2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-6-methoxyphenyl]-1,5-bis(methoxymethoxy)-4-methoxynaphthalene (16). A 2.40 M solution of n-butyllithium in hexane (3.4 mL, 8.16 mmol) was added dropwise to a solution of 2-bromo-1,5-bis(methoxymethoxy)-4-methoxynaphthalene (**15**) (2.65 g, 7.42 mmol) in 50 mL of THF at −78 °C. After the mixture was stirred at −78 °C for 5 min, the cooling bath was removed, and an approximately 1 M solution of magnesium bromide in a 3:1 mixture of ether and benzene (7.4 mL, 7.42 mmol) was added. Following the addition of the magnesium bromide, a solution of 3-(4,5-dihydro-4,4-dimethyl-2-oxazoyl)-4,5-dimethoxystyrene (**10**) (1.27 g, 4.85 mmol), prepared by concentration of 9.7 mL of a 0.5 M stock solution in benzene immediately before use, in 8 mL of THF was added. The resulting mixture was allowed to warm to room temperature for 1.5 h (TLC, ethyl acetate–hexane, 1:1; R_f 0.54, np-H; R_f 0.41, **12**; R_f 0.32, **16**). The reaction mixture was added to water (50 mL) and extracted with ether (3 × 50 mL). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a yellow oil. Flash chromatography on a 5 × 18 cm column eluting with 40% ethyl acetate in hexane gave 1.19 g of the quenched anion, followed by 1.25 g (50%) of the coupling product as a slightly yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.21 (s, 3 H), 3.18 (s, 3 H), 3.60–3.69 (m, 5 H), 3.81 (s, 3 H), 3.90 (s, 3 H), 3.75 (AB quartet, 2 H, $\Delta\nu$ = 13.2 Hz, J = 5.5 Hz), 4.27 (AB quartet, 2 H, $\Delta\nu$ = 5.0 Hz, J = 6.3 Hz), 5.34 (d, 1 H, J = 11.0 Hz), 5.86 (d, 1 H, J = 17.2 Hz), 6.71 (S, 1 H), 6.76 (dd, 1 H, J = 17.5, 11.0 Hz), 7.11 (dd, 1 H, J = 7.7, 1.1 Hz), 7.13 (d, 1 H, J = 1.5 Hz), 7.39 (dd, 1 H, J = 8.4, 7.7 Hz), 7.49 (br s, 1 H), 7.93 (dd, 1 H, J = 8.4, 1.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.87 (2 C), 56.15, 56.27, 56.74, 56.98, 67.19, 79.47, 97.26, 99.38, 110.21, 110.80, 114.28, 114.93, 117.72, 119.40, 120.49, 125.67, 126.12, 127.47, 131.03, 132.18, 136.24, 138.51, 144.90, 152.23, 154.15, 157.80, 163.11; IR ($CHCl_3$) 1730, 1600, 1375, 1260 cm^{-1}; MS, m/e (%) 507 (M^+, 100.0), 492 (47.4), 462 (55.2).

Defucogilvocarcin V (1). A 4.8 M aqueous solution of hydrochloric acid (8 mL, 24.0 mmol) was added to a solution of 2-[4-ethenyl-2-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-6-methoxyphenyl]-1,5-bis(methoxymethoxy)-4-methoxynaphthalene (**16**) (1.25 g, 2.46 mmol) in 25 mL of THF. The resulting yellow solution was heated to reflux for 2 h (TLC, ethyl acetate–hexane, 1:1, plus 2% triethylamine; R_f 0.41, **1**; R_f 0.34, **16**). The reaction mixture gradually developed a yellow precipitate. The slurry was cooled and diluted with water (50 mL). The solid was collected by suction filtration and washed with water (2 × 20 mL) and ether (2 × 20 mL). The solid was dried under vacuum to give 0.7411 g (86%) of a yellow powder: mp 267–272 °C (lit.[7] mp 253–257 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.10 (s, 6 H), 5.45 (d, 1 H, J = 11.0 Hz), 5.94 (d, 1 H, J = 17.5 Hz), 7.79 (dd, 1 H, J = 17.5, 11.0 Hz), 7.10 (d, 1 H, J = 7.7 Hz), 7.32 (br s, 1 H), 7.49 (dd, 1 H, J = 8.4, 7.7 Hz), 8.06 (d, 1 H, J = 8.4 Hz), 8.13 (br s, 1 H), 8.29 (s, 1 H), 9.34 (s, 1 H); ^{1}H NMR (250 MHz, DMSO-d_6) δ 4.08 (s, 3 H), 4.14 (s, 3 H), 5.49 (d, 1 H, J = 11.0 Hz), 6.14 (d, 1 H, J = 17.5 Hz), 6.92 (dd obscured, 1 H, J = 17.5, 11.0 Hz), 6.96 (d, 1 H, J = 7.7 Hz)8 7.52 (dd, 1 H, J = 8.4, 7.7 Hz), 7.70 (br s, 1 H), 7.82 (d, 1 H, J = 8.4 Hz), 7.98 (br s, 1 H), 8.34 (s, 1 H), 9.52 (s, 1 H); IR ($CHCl_3$) 1720, 1605, 1585, 1385 cm^{-1}; MS, m/e (%) 348 (M^+, 56.5), 210 (63.7), 166 (57.2).

2-Bromo-13,14-dibromo-13,14-dihydrodefucogilvocarcin V (17). Bromine (8 μL, 0.155 mmol) was added to a suspension of defucogilvocarcin V (**1**) (27.1 mg, 77.8 μmol) in 1 mL of dichloromethane at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, and 10% aqueous sodium sulfite solution (2 mL) was added. The mixture was extracted with dichloromethane (5 × 5 mL), and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a yellow solid. Flash chromatography on a 2 × 13 cm column eluting with dichloromethane gave 22.9 mg (50%) of a yellow powder: mp 249–252 °C (HBr); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.09–4.16 (m, 2 H), 4.17 (s, 6 H), 5.25 (dd, 1 H, J = 10.2, 5.1 Hz), 7.37 (d, 1 H, J = 1.4 Hz), 7.72 (d, 1 H, J = 8.9 Hz), 7.98 (d, 1 H, J = 8.9 Hz), 8.20 (d, 1 H, J = 1.4 Hz), 8.45 (s, 1 H), 10.07 (s, 1 H); IR (CH_2Cl_2) 3680, 1610, 900 cm^{-1}; MS, m/e (%) 508 (17.9), 506 (35.8), 504 (M^+ − HBr, 19.4), 469 (67.2), 84 (100.0), 82 (85.1), 80 (85.1).

2-Bromo-1-dehydroxy-13,14-dibromo-13,14-dihydro-1-methoxydefucogilvocarcin V (18). A mixture of 2-bromo-13,14-dibromo-13,14-dihydrodefucogilvocarcin V (**17**) (34.7 mg, 60.0 μmol), dimethyl sulfate (50 μL, 0.53 mmol), and a small amount of tetra-n-butylammonium bromide in 2 mL of dichloromethane at room temperature was treated with 40% aqueous sodium hydroxide solution (0.1 mL, 1.43 mmol). The mixture was stirred at room temperature for 1 h (TLC, ethyl acetate–hexane, 1:1; R_f 0.43, **18**; R_f 0.39, **18**-HBr; R_f 0.23, **17**), and water (2 mL) was added. The reaction was extracted with dichloromethane (3 × 5 mL), and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a yellow solid. Flash chromatography on a 1 × 12 cm column eluting with dichloromethane gave 21.0 mg (59%) of **18** as a yellow solid (followed by 9.7 mg of the α-bromovinyl compound formed by loss of HBr from **18**): mp 104–106 °C (HBr); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 4.03 (s, 3 H), 4.08–4.17 (m, 2 H), 4.15 (s, 3 H), 5.25 (dd, 1 H, J = 9.8, 6.2 Hz), 7.34 (d, 1 H, J = 1.8 Hz), 7.67 (d, 1 H, J = 9.1 Hz), 8.16 (d, 1 H, J = 9.1 Hz), 8.17 (d, 1 H, J = 1.8 Hz), 8.37 (s, 1 H); NOE difference spectrum, irradiation of the δ 3.93 methyl signal showed little (<1%) enhancement of any aromatic signal; IR ($CHCl_3$) 1725, 1610, 1580, 1380 cm^{-1}; MS, m/e (%) 604 (4.4), 602 (11.0), 600 (17.2), 598 (M^+, 7.9), 522 (44.5), 520 (93.4), 518 (44.5), 442 (100.0), 440 (99.6).

1-Dehydroxy-1-methoxydefucogilvocarcin V (19). A mixture of defucogilvocarcin V (**1**) (31.3 mg, 89.8 μmol), dimethyl sulfate (43 μL, 0.45 mmol), and a small amount of tetra-n-butylammonium bromide in 2 mL of dichloromethane was treated with 40% aqueous sodium hydroxide solution (0.31 mL, 4.5 mmol). The mixture was stirred at room temperature for 2 h, and water (3 mL) was added. The reaction was extracted with dichloromethane (3 × 5 mL), and the extracts were dried ($MgSO_4$), and concentrated under reduced pressure to a yellow solid. Flash chromatography on a 2 × 12 cm column using 5% ethyl acetate in dichloromethane as eluant gave 23.5 mg (72%) of a yellow solid: mp 244–247 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.02 (s, 3 H), 4.05 (s, 3 H), 4.13 (s, 3 H), 5.44 (d, 1 H, J = 11.0 Hz), 5.95 (d, 1 H, J = 17.5 Hz), 6.81 (dd, 1 H, J =17.5, 11.0 Hz), 7.00 (d, 1 H, J = 7.7 Hz), 7.37 (d, 1 H, J = 1.4 Hz), 7.52 (dd, 1 H, J = 8.4, 7.7 Hz), 8.17 (d, 1 H, J = 1.4 Hz), 8.22 (dd, 1 H, J = 8.4, 1.1 Hz), 8.43 (s, 1 H); NOE difference spectrum, irradiation of the δ 4.02 methyl signal showed a 6.4% enhancement in the doublet at δ 7.00; IR ($CHCl_3$) 1720, 1590, 1395, 1130 cm^{-1}; MS, m/e (%) 362 (M^+, 100.0), 130 (24.5).

1-Dehydroxy-4-formyl-1-methoxydefucogilvocarcin V (21). Titanium tetrachloride (16 μL, 0.143 mmol) was added to a mixture of 1-dehydroxy-1-methoxydefucogilvocarcin V (**19**) (10.4

mg, 28.7 mmol) and dichloromethyl methyl ether (5 μL, 57.4 μmol) in 1 mL of dichloromethane at 0 °C. The instantly black mixture was stirred at 0 °C for 15 min (TLC, ethyl acetate–hexane, 1:1; R_f 0.32, ortho isomer; R_f 0.17, **20**), and 1 M aqueous hydrochloric acid (1 mL) was added. After being stirred for 15 min, the mixture was extracted with dichloromethane (4 × 5 mL), and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a yellow solid. Flash chromatography on a 1 × 12 cm column using 5% ethyl acetate in dichloromethane gave 0.5 mg (4%) of the ortho isomer, followed by 5.8 mg (51%) of the desired para isomer **21**.

Ortho isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.05 (s, 3 H), 4.15 (s, 3 H), 4.17 (s, 3 H), 5.50 (d, 1 H, J = 10.6 Hz), 6.00 (d, 1 H, J = 17.5 Hz), 6.83 (dd, 1 H, J = 17.5, 10.6 Hz), 7.42 (br s, 1 H), 8.00 (d, 1 H, J = 9.0 Hz), 8.21 (d, 1 H, J = 1.1 Hz), 8.45 (d, 1 H, J = 9.0 Hz), 8.57 (s, 1 H), 10.63 (s, 1 H).

21: mp 195–200 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 4.04 (s, 3 H), 4.13 (s, 3 H), 5.47 (d, 1 H, J = 11.0 Hz), 5.96 (d, 1 H, J = 17.7 Hz), 6.79 (dd, 1 H, J = 17.7, 11.0 Hz), 6.98 (d, 1 H, J = 8.6 Hz), 7.35 (d, 1 H, J = 1.6 Hz), 8.10 (d, 1 H, J = 8.6 Hz), 8.11 (d, 1 H, J = 1.6 Hz), 8.50 (s, 1 H), 11.15 (s, 1 H); NOE difference spectrum, irradiation of the δ 4.03 methyl signal showed a 5.9% enhancement of the doublet at δ 6.98; IR ($CHCl_3$) 1730, 1675, 1605, 1585, 1140 cm^{-1}; MS, m/e (%) 390 (M^+, 100.0), 362 (15.3), 203 (24.5).

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Registry No. 1, 80155-95-9; 7, 5293-42-5; 8, 110582-82-6; 8 (acid chloride), 112374-25-1; 10, 112374-26-2; 11, 112374-27-3; 13, 112374-28-4; 14, 112374-29-5; 16, 112374-30-8; 17, 112374-31-9; 18, 112374-32-0; 19, 112374-33-1; 21 (*ortho*-formyl), 112374-34-2; 21 (*para*-formyl), 112374-35-3; $Ph_3MeP^+ \cdot Br^-$, 1779-49-3; $H_2NC(CH_3)_2CH_2OH$, 124-68-5; 3-bromo-4,5-dimethoxybenzaldehyde, 6948-30-7; 2-bromojuglone, 69008-03-3.

Oxidation of Polynuclear Aromatic Hydrocarbons with Ceric Ammonium Sulfate: Preparation of Quinones and Lactones[1,2]

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The oxidation of polynuclear aromatic hydrocarbons with ceric ammonium sulfate (CAS) in sulfuric acid was investigated. Oxidation of benzo[*k*]fluoranthene (**1**) gave a mixture of the 7,12- and 2,3-diones **3** and **4**. The 2,3-dione (**4**) was used as the starting material for a facile synthesis of 2,3-dihydro-2,3-dihydroxybenzo[*k*]fluoranthene (**5**) and the corresponding diol epoxide **6**, which are potentially important metabolites of benzo[*k*]fluoranthene. In a similar manner, 2,3-dihydro-2,3-dihydroxyfluoranthene (**7**) and its diol epoxide **8** were prepared from fluoranthene. Oxidation of benzo[*b*]fluoranthene (**2**) with CAS did not yield quinones, but instead gave benzo[*d*]fluoreno[2,1-*b*]pyran-5,13-dione (**9**), which was identified by its spectral properties and by reduction with $LiAlH_4$. The lactone **9** formed via initial *K*-region oxidation of **2**. It was not formed from 1-hydroxybenzo[*b*]fluoranthene (**12**), which gave benzo[*b*]fluoranthene-1,2-dione (**13**) upon CAS oxidation. CAS oxidation of benzo[*a*]pyrene (**14**) gave a mixture of the 1,6- and 3,6-quinones **17** and **18**. Treatment of benz[*a*]anthracene (**15**) with CAS yielded 7-oxo-12-hydroxy-7,12-dihydrobenz[*a*]anthracene (**19**) and the 7,12-quinone **20**. Oxidation of chrysene (**16**) with CAS gave 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**21**) and the 5,6-quinone **22**. The results of this study demonstrate that CAS oxidation is useful for the synthesis of certain PAH quinones or lactones, from polynuclear aromatic hydrocarbons, depending on the ring system.

Polynuclear aromatic hydrocarbons (PAH) are an important class of environmental carcinogens. Their carcinogenic properties are due in part to an initial interaction of specific metabolites with DNA. Although diol epoxides are believed to be key metabolites involved in DNA binding, other pathways of metabolic activation may also play a role, and consequently it is essential that PAH metabolites be thoroughly characterized.[3,4] Extensive synthetic methods have been developed for the preparation of PAH metabolites.[5] In some cases, multistep syntheses are required. We are interested in new methods that might yield key metabolites of PAH efficiently and inexpensively. Therefore, we have investigated the reaction of ceric ammonium sulfate (CAS) with several PAH. In previous studies, CAS has been shown to oxidize naphthalene, phenanthrene, anthracene, fluoranthene, and some substituted naphthalenes to quinones in good yield but the application of the method to higher PAH has not been reported.[6-9] Ceric ammonium nitrate has also been used to oxidize substituted aromatic systems.[10-13]

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