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Synthesis of Defucogilvocarcin V Isosteres Via MAD-Mediated Conjugate Addition of Carbanions to Naphthoquinone Ketals

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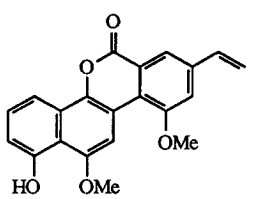
Abstract: *Treatment of a complex between naphthoquinone ketal 7 and methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide (MAD) with aryllithium reagents prepared by metallation of oxazoline 13 and amide 18, gave conjugate adducts which were converted to defucogilvocarcin V analogs 2 and 3 via a short reaction sequence. Some problems encountered in the metallation of oxazoline 19, a structural analog of amide 18, are also described.*

Introduction. Defucogilvocarcin V (**1**) is the aglycone common to a number of C-aryl glycoside antitumor antibiotics including gilvocarcin V, chrysomycin A and ravidomycin.[1-4] A number of syntheses of defucogilvocarcin V have been reported in addition to one report of a synthesis of gilvocarcin V itself.[5] Syntheses of several defucogilvocarcin V analogs have also been described.[6] Benzofurans **2** and **3** can be regarded as defucogilvocarcin V isosteres in which the vinyl group is restricted to two conformational extremes in which it is conjugated to the aryl group. As part of our own program in the area of C-aryl glycoside synthesis, we have prepared these analogs by a MAD-mediated conjugate addition strategy previously used in a synthesis of defucogilvocarcin M.[7] Here we report the details of this study including biological evaluation of **2**, **3** and several related structures.[8]



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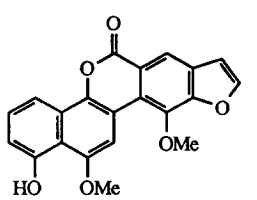

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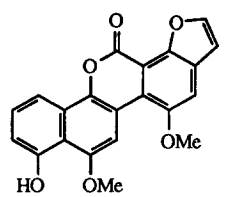
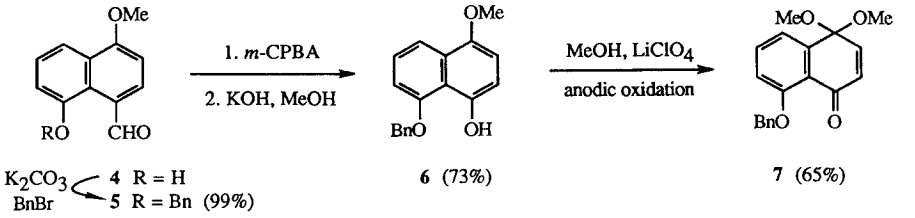


3

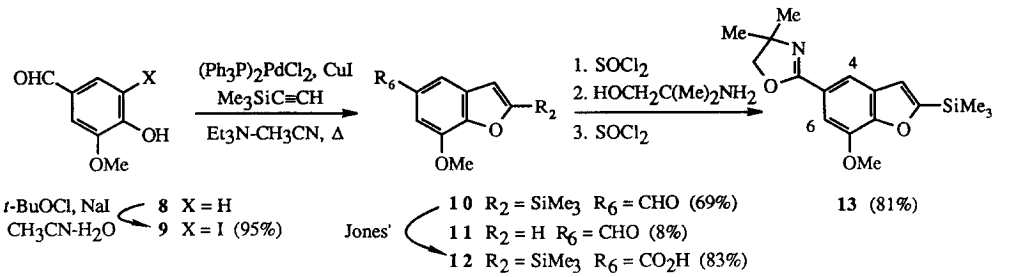
Preparation of Coupling Components: The key step in our projected syntheses of **2** and **3** was to be the coupling of carbanions derived from *o*-metallation of benzofurans **13** and **19** with naphthoquinone ketal **7**, based on the pioneering work of Swenton and Stern on the methylaluminum bis(2,6-di-*tert*-butyl)-4-methylphenoxide (MAD) mediated conjugate addition of carbanions to *p*-benzoquinone ketals and *p*-quinols.[9,10] The synthesis of naphthoquinone ketal **7** is described in Scheme 1. Naphthol **4**, prepared on a healthy scale using the procedure of Rapoport,[11] was subjected to a Williamson ether synthesis to provide **5** in 99% yield. Bayer-Villiger oxidation of the aldehyde followed by hydrolysis of the intermediate formate gave naphthol **6** in 73% yield. Anodic oxidation of **6**, using lithium perchlorate as the electrolyte in methanol, provided naphthoquinone ketal **7** in 65% yield.[9]

Scheme 1



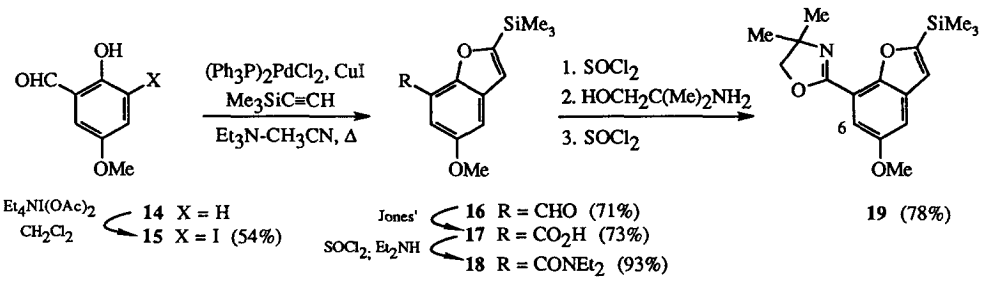
The synthesis of benzofuran **13** is shown in Scheme 2. Iodination of vanillin (**8**) using a published procedure provided **9** in 95% yield.[12] The conversion of **9** to benzofuran **10** was best accomplished using aryl halide-acetylene coupling conditions developed by Sonogashira.[13] Thus, treatment of **9** with trimethylsilylacetylene in the presence of bis(triphenylphosphine)palladium(II) chloride and cuprous iodide in triethylamine-acetonitrile at reflux for 18 h gave **10** in 69% yield along with 8% of the desilylated benzofuran **11**.[14] Jones oxidation of **10** gave carboxylic acid **12** (83%) which was converted to oxazoline **13** using a straightforward procedure in 81% overall yield.[15,16]

Scheme 2



The preparation of benzofuran **19** is described in Scheme 3. Iodination of **14** was initially problematic. For example, treatment of **14** with *tert*-butyl hypochlorite and sodium iodide under conditions used to prepare **9**, gave no reaction.[12] Reaction of **14** with chloramine-t and sodium iodide at room temperature afforded principally a dimeric oxidative coupling product and only 3% of iodide **15**.[17] The yield of **15** was improved to 28% by conducting this reaction in N,N-dimethylformamide at -15 °C. Sequential treatment of **14** with mercuric acetate in acetic acid and hydrochloric acid, followed by iodination of the intermediate arylmercuric chloride in chloroform, gave **15** in 31%.[18] The best results were obtained when **14** was treated with tetraethylammonium diacetoxyiodate in dichloromethane at -15 °C for one day.[19] This reaction gave iodide **15** in 54% yield, along with 14% of the aforementioned dimer. The remainder of the synthesis of **19** was uneventful. Palladium-copper mediated coupling of **15** with trimethylsilylacetylene gave benzofuran **16** (71%), Jones oxidation gave **17** (73%), and conversion of **17** to **19**, via an intermediate acid chloride, proceeded in 78% yield.[13-16]

Scheme 3



Synthesis of Analogs 2 and 3. The preparation of defucogilvocarcin V analog **2** was accomplished as outlined in Scheme 4. A series of metallation-alkylation experiments determined that treatment of **13** with *n*-butyllithium in TMEDA-THF at -45 °C provided a 2:1 mixture of aryllithium reagents derived from metallation at C(6) and C(4), respectively.[20] This result was somewhat surprising as prior studies had suggested that metallation would occur with high selectivity between the methoxy and oxazolinyl groups.[7] In the event, addition of a THF-TMEDA solution of the aforementioned mixture of aryllithium reagents (prepared from three equivalents of **13**) to a solution of **7** precomplexed to methylaluminum bis(2,6-di-tert-butyl)-4-methylphenoxide (MAD) in toluene at -78 °C, gave a mixture of ketones **20** and **21**.[9,10] Separation of the two adducts was accomplished by column chromatography to afford **20** (53%) as an unstable oil and **21** (21%) as a sharp-melting solid. Treatment of **20** with aqueous hydrochloric acid in tetrahydrofuran gave **22** (97%) and similar treatment of **21** provided **23** (98%).

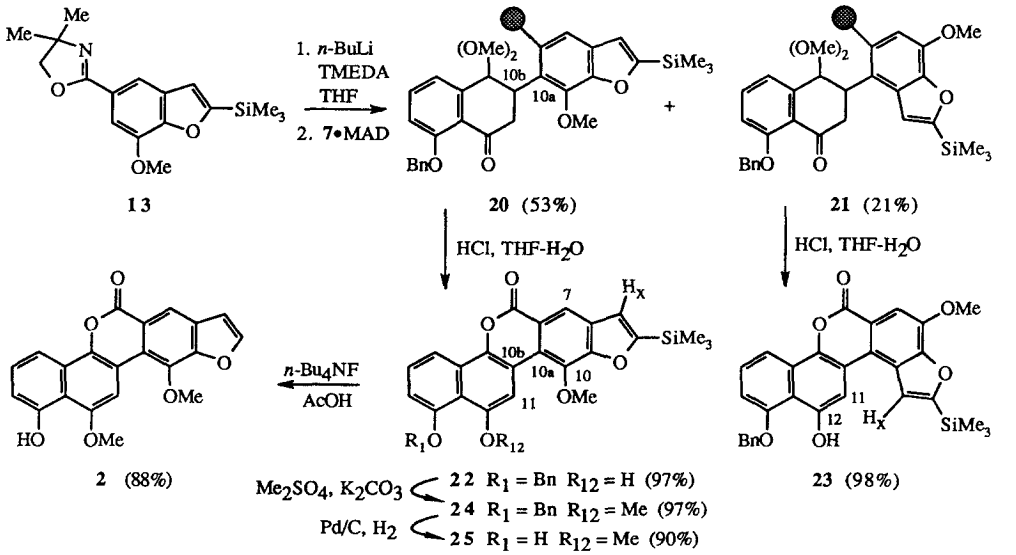
The structures of the isomeric pentacycles (**22** and **23**), and by inference the isomeric conjugate adducts **20** and **21**, were assigned on the basis of nOe experiments. For example, irradiation of the trimethylsilyl group in **22** gave a 6% enhancement of the signal due to H_X and irradiation of H_X gave a 5% nOe at H_7. In addition, irradiation of the C(10) methoxy group gave a 7% enhancement of H_{11} and irradiation of the C(12) phenolic hydrogen gave a 4% enhancement at H_{11}. On the other hand, irradiation of the trimethylsilyl group in **23** gave a 3% enhancement at H_X and irradiation of H_X gave a 30% nOe at H_{11}. Finally, irradiation of the C(12) phenolic hydrogen in **23** also showed a small nOe (2%) at H_{11}.

The synthesis of the target compound (**2**) was completed in a straightforward manner. Methylation of phenol **22** gave **24** in 97% yield. Hydrogenolysis of the benzyl group afforded **25** (90%) and removal of the trimethylsilyl group using tetra-*n*-butylammonium fluoride gave **2** in 88% yield.

Defucogilvocarcin V analog **3** was originally to be prepared from oxazoline **19** and naphthoquinone ketal **7**. This plan, however, was modified when difficulties were encountered with the metallation of **19**. For example, the conditions used to metallate **13** met with failure and treatment of **19** with *sec*-butyllithium in THF-TMEDA, followed by an iodomethane quench, gave an equal mixture of materials derived from methylation of the desired aryllithium and methylation of the carbanion derived from addition of the *sec*-butyllithium to C(6) of **19**.[21] Given this discouraging result, we turned to metallation of diethylamide **18**, easily prepared from **17** in 93% yield (Scheme 3).[22] Treatment of **18**

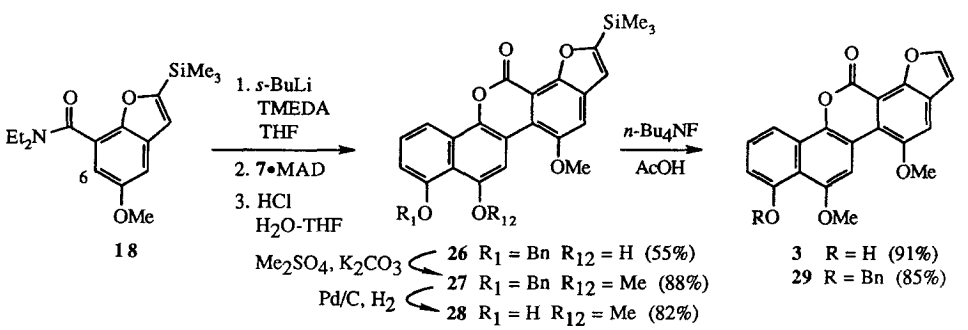
(two equivalents) with *sec*-butyllithium in THF-TMEDA at -78 °C gave the desired carbanion which, upon treatment with the complex of **7** with MAD (one equivalent) gave the desired conjugate addition product. The adduct was not purified, but was treated directly with aqueous hydrochloric acid to provide **26** in 55% overall yield based on **7** as the limiting reagent (Scheme 5).

Scheme 4



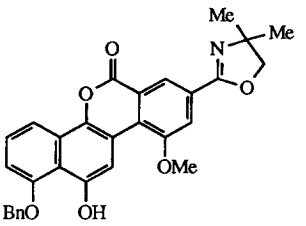
The synthesis of **3** was completed using the same procedure used to prepare **2**. Methylation of **26** gave **27** (88%) which was subjected to hydrogenolysis to give **28** (82%). Removal of the trimethylsilyl group afforded **3** in 91% yield.

Scheme 5

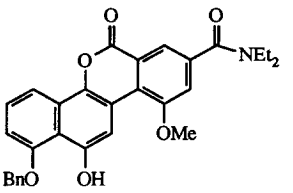


Biological Evaluation. Biological evaluation of compounds **2**, **3**, **25**, **27**, **28**, and **29** (prepared by desilylation of **27** using TBAF) was done through the preclinical antitumor drug discovery

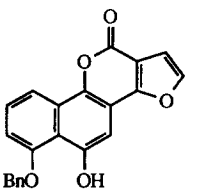
screening program of the National Cancer Institute.[23] This testing protocol screens sixty human tumor cell lines from seven cancer types (lung, colon, melanoma, renal, ovarian, brain and leukemia). Compound **27** showed activity at a high concentration (10^{-4} M) against a variety of cancer cell lines, but activity was insignificant at concentrations of 10^{-5} M or less. In addition, compound **29** showed weak activity against two renal cell lines at a concentration of 10^{-4} M. All of the other compounds were inactive in this screening protocol.[24]



30 (36%)



31 (25%)



32 (58%)

Conclusions. An efficient procedure for the preparation of defucogilvocarcin V analogs has been developed. To underscore this point, we note that compounds **30-32** have also been prepared in 36%, 25%, and 58% yield, respectively, by addition of the appropriate carbanion to **7**•MAD followed by aromatization of the resulting conjugate adducts. Unfortunately, none of the compounds prepared during this study showed significant antitumor activity. Perhaps this is not surprising due to the low solubility of these compounds in almost any solvent. Whether improving solubility will enhance biological activity remains an unanswered question.

Experimental

General Information. All melting points are uncorrected. The ^{1}H NMR spectra are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. ^{13}C NMR data are reported as follows: chemical shift (multiplicity).

Solvents and reagents were dried and purified prior to use where indicated: tetrahydrofuran, diethyl ether, toluene and benzene were distilled from sodium metal. Acetonitrile was dried over 4 Å molecular sieves for 12 hr and then sequentially distilled from calcium hydride and phosphorus pentoxide. Solvents were degassed by bubbling argon or nitrogen through them. Reactions requiring an inert atmosphere were carried out under argon. The electrochemical oxidation was carried out with a solid platinum cathode (1 cm^2) and a cylindrical platinum gauze anode (5.0 x 2.5 cm) using a Kepco Inc. Model JQE 0-36 V, 0-3 A power supply.

8-(Benzyloxy)-1-formyl-4-methoxynaphthalene (5). A heterogeneous mixture of 16.89 g (83.20 mmol) of **4**, 18.69 g (13 mL, 109 mmol) of benzyl bromide, 54 g (391 mmol) of potassium carbonate and 330 mL of acetone was heated at reflux for 48 h. The reaction was filtered, and the potassium carbonate was rinsed with acetone. The filtrate was concentrated in vacuo and the excess

benzyl bromide was removed by Kugelrohr distillation (80 °C, 0.5 mmHg) to afford 24 g (99%) of **5** as a yellow solid: mp 127-128 °C; IR (CH_2Cl_2) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.05 (s, 3H, $ArOCH_3$), 5.28 (s, 2H, CH_2O), 6.89 (d, *J* = 8.2 1H, ArH), 7.10 (d, *J* = 7.7, 1H, ArH), 7.41 (m, 6H, ArH), 7.97 (d, *J* = 7.4, 1H, ArH), 8.08 (d, *J* = 8.3, 1H, ArH), 11.05 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 55.9 (q), 71.1 (t), 103.9 (d), 109.3 (d), 115.7 (d), 124.9 (s), 125.7 (d), 127.2 (s), 127.7 (d), 127.8 (s), 128.2 (d), 128.8 (d), 129.5 (d), 136.1 (s), 155.46 (s), 159.4 (s), 194.3 (d); exact mass calcd. for $C_{19}H_{16}O_3$ *m/z* 292.1099, found *m/z* 292.1095. Anal. calcd. for $C_{19}H_{16}O_3$: C, 78.05; H, 5.52. Found: C, 77.97; H, 5.54.

8-(Benzyloxy)-1-hydroxy-4-methoxynaphthalene (6). To a solution of 10.0 g (34.3 mmol) of **5** in 350 mL of dichloromethane was added in one portion 15.5 g (67.6 mmol, 75% by iodometric titration) of *m*-chloroperoxybenzoic acid. The reaction was stirred for 3 h and 125 mL of 10% aqueous sodium thiosulfate was added. The resulting heterogeneous mixture was stirred for 0.5 h and an additional 350 mL of 10% aqueous sodium thiosulfate was added along with 400 mL of dichloromethane. The mixture was shaken, the layers were separated, and the aqueous layer was extracted with 400 mL of dichloromethane. The combined organic phases were washed with two 700-mL portions of 10% aqueous sodium thiosulfate and 700-mL portion of aqueous saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 9.6 g of a red solid. This material was dissolved in 307 mL of degassed (with argon) THF:MeOH (1:1) and cooled with an ice bath. To the cold solution under argon was added 60 mL of degassed (with argon) ice cold methanolic potassium hydroxide (1.1 M) via a cannula. The resulting dark mixture was stirred for 0.5 h at 0 °C, acidified to a pH of 1 with 10% aqueous hydrochloric acid, diluted with 900 mL of water, and extracted with two 400-mL portions of dichloromethane. The combined organic phases were washed with 300 mL of water, and 300 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford a red solid. This material was dissolved in a minimal amount of dichloromethane and filtered though 80 g of silica gel, eluted with 800 mL of dichloromethane. The filtrate was concentrated in vacuo to afford 7 g (73%) of **6** as a brown solid: mp 112-114 °C (lit[25] 108 °C); ^1H NMR ($CDCl_3$) δ 3.94 (s, 3H, $ArOCH_3$), 5.26 (s, 2H, CH_2O), 6.77 (s, 2H, ArH), 6.93 (d, *J* = 7.7 Hz, 1H, ArH), 7.41 (m, 6H, ArH), 7.9 (d, *J* = 8.57 Hz, 1H, ArH), 8.99 (s, 1H, ArOH).

8-(Benzyloxy)-4,4-dimethoxynaphthalene-1-one (7). A solution of 3.00 g (10.7 mmol) of **6** and 9.67 g (91 mmol) of lithium perchlorate in 1400 mL of methanol was degassed with nitrogen for 1.5 h. The reaction was cooled with ice water and was electrolyzed at 0.1 amps (3 volts) for 6 h while nitrogen was bubbled through the mixture. The reaction was concentrated to about 500 mL and then poured into 700 mL of aqueous saturated sodium bicarbonate. The resulting milky mixture was extracted with two 700-mL portions of dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to afford a dark oily residue. This material was chromatographed over 120 g of alumina (eluted with petroleum ether-ethyl acetate,10:1) to afford 2.15 g (65%) of **7** as a yellow solid: mp 103-105 °C; ^1H NMR ($CDCl_3$) δ 3.18 (s, 6H, $(OCH_3)_2$), 5.24 (s, 2H, OCH_2), 6.54 (d, *J* = 10.4 Hz, 1H, C_2H), 6.74 (d, *J* = 10.4 Hz, 1H, C_3H), 7.06 (d, *J* = 7.6 Hz, 1H, C_7H), 7.35 (m, 5H, ArH), 7.6 (m, 2H, ArH). Anal. calcd. for $C_{19}H_{18}O_4$: C, 73.51; H, 5.71; Found: C, 73.52; H, 5.85.

7-Methoxy-2-trimethylsilylbenzofuran-5-carboxaldehyde (10) and 7-Methoxybenzofuran-5-carboxaldehyde (11). A solution of 2.0 g (7.19 mmol) of 3-iodovanillin (**9**),[12] 88 mg (0.12 mmol) of bis(triphenylphosphine)palladium (II) chloride, 48 mg (0.24 mmol) of copper (I) iodide, 42 mL of triethylamine and 164 mL of acetonitrile was stirred under argon for 2 min followed by addition of 1.39 g (2 mL, 14.2 mmol) of trimethylsilylacetylene. The solution was heated at reflux for 18 h and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with petroleum ether-ethyl acetate, 10:1) to give 1.23 g (69%) of aldehyde **10** as a light brown solid: mp 65-65.5 °C (after recrystallization from methanol-water); IR ($CDCl_3$) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.38 (s, 9H, $Si(CH_3)_3$), 4.07 (s, 3H, $ArOCH_3$), 7.05 (s, 1H, C_3H), 7.34 (d, J = 1.1 Hz, 1H, C_6H), 7.67 (d, J =1.1 Hz, 1H, C_4H), 9.99 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ -1.8 (q), 56.1 (q), 104.2 (d), 116.9(d), 119.8 (d), 129.8 (s), 132.1 (s), 146.2 (s), 151.3 (s), 166.2 (s), 191.8 (d); exact mass calcd. for $C_{13}H_{16}O_3Si$ *m/z* 248.3562, found *m/z* 248.0868. Anal. calcd. for $C_{13}H_{16}O_3Si$; C, 62.86; H, 6.51. Found: C, 62.75; H, 6.51. Continued elution afforded 0.1 g (8%) of aldehyde **11** as a white solid: mp 78-80 °C; IR (CH_2Cl_2) 1613 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.04 (s, 3H, $ArOCH_3$), 6.87 (d, J = 2.2 Hz, 1H, C_3H), 7.35 (d, J = 1.2 Hz, 1H, C_6H), 7.71 (m, 2H, C_2H and C_4H), 9.98 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 56.1 (q), 104.3 (d), 107.6 (d), 119.7 (d), 129.0(s), 133.55 (s), 146.3 (s), 146.5 (d), 147.9 (s), 191.6 (d); exact mass calcd. for $C_{10}H_8O_3$ *m/z* 176.0573, found *m/z* 176.0502. Anal. calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.17; H, 4.55.

7-Methoxy-2-trimethylsilylbenzofuran-5-carboxylic acid (12). To a solution of 1.19 g (4.8 mmol) of aldehyde **10** in 17 mL of acetone cooled in an ice bath was added 6 mL of Jones reagent (16 mmol of 2.65 M stock solution) over 2 min. The cooling bath was removed, the reaction was stirred for 3.5 h, and the mixture was filtered through a plug of celite which was rinsed with acetone. The acetone was removed in vacuo and the resulting heterogeneous mixture was partitioned between 100 mL of water and 100 mL of dichloromethane. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give 1.04 g (83%) of carboxylic acid **12** as a cream colored solid: mp 231-232 °C; IR ($CDCl_3$) 3100-2800, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.38 (s, 9H, $Si(CH_3)_3$), 4.08 (s, 3H, $ArOCH_3$), 7.02 (s, 1H, C_3H), 7.53 (d, J = 1.3 Hz, 1H, C_6H), 8.06 (d, J = 1.3 Hz, 1H, C_4H), 12.00 (br s, 1H, CO_2H); ^{13}C NMR ($CDCl_3$) δ -1.81 (q), 56.1 (q), 107.4 (d), 116.9 (d), 117.3 (d), 124.5 (s), 129.6 (s), 145.2 (s), 150.8 (s), 165.8 (s), 172.6 (s); exact mass calcd. for $C_{13}H_{16}O_4Si$ *m/z* 264.082, found *m/z* 264.082. Anal. calcd. for $C_{13}H_{16}O_4Si$: C, 59.06; H, 6.11. Found: C, 58.40; H, 5.91.

2-Trimethylsilyl-5-(4',4'-dimethyloxazolin-2'-yl)-7-methoxy-benzofuran (13). A heterogeneous mixture of 1.21 g (4.58 mmol) of carboxylic acid **12**, 1.63 g (1 mL, 13.92 mmol) of thionyl chloride and 18 mL of benzene was heated at reflux for 2 h. The resulting solution was concentrated in vacuo and the crude acid chloride was dissolved in 12 mL of dichloromethane. This mixture was slowly added to a solution of 1.0 g (12 mmol) of 2-amino-2-methyl-1-propanol in 10 mL of dichloromethane and stirred at room temperature for 2 h. The heterogeneous mixture was diluted with 50 mL of dichloromethane and washed with 40 mL of 10% aqueous citric acid. The acidic wash was extracted with two 30-mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was stirred in 7 mL of thionyl chloride at room

temperature for 1 h followed by addition of 60 mL of petroleum ether-ethyl ether (2:1). This mixture was stirred for 1 h and the resulting solid was collected and washed with three 20-mL portions of ice-cold ethyl ether. The solid was dissolved in 60 mL of dichloromethane, washed for 5 min with 100 mL of 10% aqueous sodium hydroxide, and the basic phase was extracted with two 30-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give 1.17 g (81%) of oxazoline **13** as a tan solid: mp 92-93 °C; IR ($CDCl_3$) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.34 (s, 9H, $Si(CH_3)_3$), 1.38 (s, 6H, $C(CH_3)_2$), 4.03 (s, 3H, $ArOCH_3$), 4.09 (s, 2H, CH_2O), 6.93 (s, 1H, C_3H), 7.40 (d, J = 1.4 Hz, 1H, C_6H), 7.77 (d, J = 1.4 Hz, 1H, C_4H); ^{13}C NMR ($CDCl_3$) δ -1.8 (q), 28.4 (q), 56.1 (q), 67.5 (s), 79.1 (t), 106.2 (d), 114.3 (d), 116.7 (d), 123.3 (s), 129.4 (s), 145.1 (s), 149.3 (s), 162.4 (s), 165.0 (s); exact mass calcd. for $C_{17}H_{23}NO_3Si$ *m/z* 317.144, found *m/z* 317.148. Anal. calcd. for $C_{17}H_{23}NO_3Si$: C, 64.32; H, 7.31. Found: C, 64.38; H, 7.36.

2-Hydroxy-3-iodo-5-methoxybenzaldehyde (15) and 2,2'-Dihydroxy-5,5'-dimethoxybiphenyl-3,3'-dicarboxaldehde. To a solution of 0.2 g (1.32 mmol) of 2-hydroxy-5-methoxybenzaldehyde (**14**) in 5 mL of dichloromethane at -15 °C was added 0.6 g (1.58 mmol) of tetraethylammonium diacetoxyiodate.[19] After stirring for 12 h, an additional 0.3 g (0.78 mmol) of tetraethylammonium diacetoxyiodate was added. The reaction was stirred for an additional 10 h and concentrated in vacuo. To the residue was added 30 mL of an acidic hydrosulfite solution (3 g sodium hydrosulfite and 2.5 mL of concentrated hydrochloric acid in 30 mL of water). This mixture was extracted with two 200-mL portions ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was loaded onto 2 g of silica gel and chromatographed over 20 g of silica gel (petroleum ether:ethyl acetate,10:1) to afford 0.2 g (54%) of iodide **15** as a yellow solid: mp 102-104 °C; IR (CH_2Cl_2) 1667, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H, $ArOCH_3$), 7.05 (d, J = 3 Hz, 1H, ArH), 7.61 (d, J = 3 Hz, 1H, ArH), 9.72 (s, 1H, CHO), 11.32 (s, 1H, ArOH); ^{13}C NMR ($CDCl_3$) δ 56.2 (q), 85.6 (s), 116.9 (d), 119.5 (s), 133.4 (d), 153.2 (s), 154.9 (s), 195.5 (d); exact mass calcd. for $C_8H_7IO_3$ *m/z* 277.941, found *m/z* 277.943. Anal. calcd. for $C_8H_7IO_3$: C, 34.54; H, 2.54. Found: C, 34.68; H, 2.44. Continued elution afforded 55 mg (14%) of dihydroxy-5,5'-dimethoxybiphenyl-3,3'-dicarboxaldehyde as a light orange solid: mp 217-218 °C; IR (CH_2Cl_2) 1658, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 6H, $ArOCH_3$), 7.08 (d, J = 3 Hz, 2H, ArH), 7.26 (d, J = 3 Hz, 2H, ArH), 9.91 (s, 2H, CHO), 10.99 (s, 2H, ArOH); ^{13}C NMR ($CDCl_3$) δ 56.0 (q), 115.9 (d), 120.5 (s), 126.0 (s), 126.6 (d), 152.3 (s), 153.5 (s), 196.1 (d); exact mass calcd. for $C_{16}H_{14}O_6$ *m/z* 302.079, found *m/z* 302.078. Anal. calcd. for $C_{16}H_{14}O_6$: C, 63.56; H, 4.67. Found: C, 63.59; H, 4.66.

7-Formyl-5-methoxy-2-(trimethylsilyl)benzofuran (16). A solution of 5 g (17.98 mmol) of **15**, 200 mg (0.253 mmol) of bis(triphenylphosphine)palladium (II) chloride, 108 mg (0.57 mmol) of copper (I) iodide, 95 mL of triethylamine and 365 mL of acetonitrile was stirred under argon for 2 min followed by addition of 3.47 g (5 mL; 39 mmol) of trimethylsilylacetylene. The solution was heated to reflux for 18 h and concentrated in vacuo. The residue was chromatographed over 120 g of silica gel (eluted with petroleum ether-ethyl acetate, 20:1) to afford 3.16 g (71%) of the benzofuran **16** as a brown oil which solidified on standing. A sample of this solid was recrystallized from methanol-water (charcoal) to afford a white solid: mp 46-47 °C; IR ($CDCl_3$) 1689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.37

(s, 9H, $Si(CH_3)_3$), 3.88 (s, 3H, $ArOCH_3$), 6.95 (s, 1H, C3H), 7.32 (d, J = 2.6 Hz, 1H, C4H), 7.37 (d, J = 2.6 Hz, 1H, C6H), 10.58 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ -1.9 (q), 56.2 (q), 109.6 (d), 111.9 (d), 115.5 (d), 120.5 (s), 130.8 (s), 153.7 (s), 155.7 (s), 166.5 (s), 188.0 (d); exact mass calcd. for $C_{13}H_{16}O_3Si$ *m/z* 248.0869, found 248.0893. Anal. calcd. for $C_{13}H_{16}O_4Si$: C, 62.86; H, 6.51. Found: C, 62.79; H, 6.53.

5-Methoxy-2-trimethylsilylbenzofuran-7-carboxylic acid (17). To a solution of 3.16 g (12.74 mmol) of **16** in 40 mL of acetone at 0 °C was added 16 mL of Jones reagent (42 mmol, 2.65 M stock solution) dropwise. The ice bath was removed, and the reaction was stirred for 5 h. The reaction was filtered through a plug of celite, which was rinsed with acetone. The filtrate was concentrated in vacuo and the residue was partitioned between 100 mL of water and 100 mL of dichloromethane. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give 2.46 g (73%) of carboxylic acid **17** as a white solid: mp 169-170 °C; IR (CH_2Cl_2) 3000, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.40 (s, 9H, $Si(CH_3)_3$), 3.89 (s, 3H, $ArOCH_3$), 6.95 (s, 1H, C3H), 7.31 (d, J = 2.6 Hz, 1H, C4H), 7.63 (d, J = 2.6 Hz, 1H, C6H), 11.30 (s, 1H, CO_2H); ^{13}C NMR ($CDCl_3$) δ -1.8 (q), 56.2 (q), 111.0 (d), 113.9 (s), 114.3 (d), 115.7 (d), 130.8 (s), 152.1 (s),155.2 (s), 166.3 (s), 169.7 (s); exact mass calcd. for $C_{13}H_{16}O_4Si$ *m/z* 264.082, found *m/z* 264.080. Anal. calcd. for $C_{13}H_{16}O_4$ Si: C, 59.06; H, 6.11. Found: C, 58.87; H, 6.05.

2-Trimethylsilyl-7-(4',4'-dimethyloxazolin-2'-yl)-5-methoxy-benzofuran (19). A heterogeneous mixture of 1.00 g (3.79 mmol) of carboxylic acid **17**, 2.66 g (1.67 mL, 23 mmol) of thionyl chloride and 30 mL of benzene was heated to reflux for 2 h. The reaction was concentrated in vacuo and the crude acid chloride was dissolved in 15 mL of dichloromethane. This mixture was slowly added to a solution of 1.0 g (12 mmol) of 2-amino-2-methyl-1-propanol in 10 mL of dichloromethane. The reaction was stirred at room temperature for 2.5 h. The resulting heterogeneous mixture was diluted with 100 mL of dichloromethane and washed with 75 mL of 10% aqueous citric acid. The acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was stirred in 15 mL of thionyl chloride at room temperature for 1 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in 100 mL of dichloromethane. This was washed for 5 min with 100 mL of 10% aqueous sodium hydroxide. The basic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 50 g of silica gel (eluted with petroleum ether-ethyl acetate, 7:1) to afford 0.94 g (78%) of oxazoline **19** as tan solid: mp 69-70 °C; IR ($CDCl_3$) 1650, 1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.36 (s, 9H, $Si(CH_3)_3$), 1.42 (s, 6H, $C(CH_3)_2$), 3.85 (s, 3H, $ArOCH_3$), 4.18 (s, 2H, CH_2O), 6.89 (s, 1H, C3H), 7.14 (d, J = 2.6 Hz, 1H, C4H), 7.45 (d, J = 2.6 Hz, 1H, C6H); ^{13}C NMR ($CDCl_3$) δ -1.8 (q), 28.3 (q), 56.1 (q), 67.3 (s), 79.1 (t), 107.7 (d), 112.7 (d), 112.7 (s), 115.7 (d), 130.3 (s), 150.8 (s), 155.1 (s), 160.2 (s), 165.4 (s); exact mass calcd. for $C_{17}H_{23}NO_3Si$ *m/z* 317.144, found *m/z* 317.145. Anal. calcd. for $C_{17}H_{23}NO_3Si$: C, 64.32; H, 7.31. Found: C, 64.54; H, 7.39.

N,N-Diethyl-5-methoxy-2-trimethylsilylbenzofuran-7-carboxamide (18). A heterogeneous mixture of 3.93 g (14.89 mmol) of carboxylic acid **17**, 14.67 g (9 mL, 124 mmol) of

thionyl chloride and 130 mL of benzene was heated to reflux for 2 h. The reaction was concentrated in vacuo and the crude acid chloride was dissolved in 60 mL of dichloromethane. The mixture was added to a solution of 4.13 g (5.9 mL, 56 mmol) of diethylamine in 40 mL of dichloromethane. The mixture was stirred for 2 h, diluted with 200 mL of dichloromethane, and washed with 100 mL of 10% aqueous hydrochloric acid. The acidic wash was extracted with 50 mL of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford a dark orange oil. The residue was chromatographed over 50 g of silica gel (eluted with petroleum ether-ethyl acetate, 4:1) to yield 4.4 g (93%) of **18** as an orange oil: IR ($CDCl_3$) 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.31 (s, 9H, $Si(CH_3)_3$), 1.06 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.30 (t, J = 7.1, 3H, CH_2CH_3), 3.21 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.65 (q, J = 7.1, 2H, CH_2CH_3), 3.83 (s, 3H, $ArOCH_3$), 6.88 (s, 1H, C_3H), 6.90 (d, J = 2.5 Hz, 1H, C_4H), 7.03 (d, J = 2.5 Hz, 1H, C_6H); ^{13}C NMR ($CDCl_3$) δ -1.9 (q), 12.8 (q), 14.1 (q), 39.0 (t), 42.9 (t), 56.1 (q), 104.8 (d), 111.3 (d), 116.0 (d), 121.6 (s), 129.2 (s), 148.5 (s), 155.7 (s), 165.2 (s), 167.0 (s); exact mass calcd. for $C_{17}H_{25}NO_3Si$ *m/z* 319.161, found *m/z* 319.161.

1-(Benzyloxy)-13-hydroxy-11-methoxy-9-(trimethylsilyl)-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (22) and 8-(Benzyloxy)-3,4-dihydro-4,4-dimethoxy-3-[7-methoxy-2-(trimethylsilyl)-4-benzofuranyl]-1(2H)naphthalenone (21). To a solution of 4.5 g (14.2 mmol) of oxazoline **13** and 2.7 mL (18 mmol) of tetramethylethylenediamine in 135 mL of dry tetrahydrofuran at -45 °C (dry ice-acetonitrile) was slowly added 11.36 mL (17.04 mmol, 1.5 M in hexanes) of *n*-butyllithium via a syringe and the solution was stirred for 1.5 h. In a separate flask, a solution of MAD was prepared by dissolving 4.26 g (19.35 mmol) 2,6-di-butyl-4-methylphenol in 150 mL of toluene and slowly adding 4.8 mL (9.69 mmol, 2 M in hexane) of trimethylaluminum at room temperature followed by stirring for 30 min. The resulting solution was cooled to -78 °C (dry ice-acetone) and 1.50 g (4.83 mmol) of naphthoquinone monoketal **7** was added in a solution of 50 mL of toluene. The resulting dark solution was stirred for 15 min followed by addition of the aryl lithium via a cannula. The color of the solution slowly turned light orange during the addition. Upon completion of this addition the reaction was stirred for 15 min followed by addition of 30 mL of water. The cooling bath was removed and the reaction was allowed to warm to room temperature. The resulting heterogeneous mixture was filtered through a plug of celite which was rinsed with dichloromethane. The filtrate was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 300 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1, 4:1 and 2:1) to afford 1.48 g of **20** as an off-white foam. Attempts to purify **20** for full characterization caused its decomposition. Therefore, this conjugate adduct was fully characterized after the next step. Continued elution afforded 0.62 g (21%) of **21** as a light green foam. A sample of this material was recrystallized from petroleum ether to afford a tan solid: mp 163-165 °C; IR (CH_2Cl_2) 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.27 (s, 9H, $Si(CH_3)_3$), 1.28 (s, 3H, CCH_3), 1.33 (s, 3H, CCH_3), 2.77 (s, 3H, OCH_3), 2.99 (s, 3H, OCH_3), 3.02 (dd, J = 18, 8 Hz, 1H, CH_2), 3.29 (dd, J = 18, 8 Hz, 1H, CH_2), 4.01 (s, 3H, $ArOCH_3$), 4.04 (m, 2H, CH_2OPh), 4.88 (t, J = 8.5 Hz, 1H, CH), 5.25 (s, 2H, OCH_2Ph), 6.79 (s, 1H, C_3H-furan), 7.01 (s, 1H, ArH), 7.09 (d, J = 8 Hz, 1H, C_7H), 7.5 (m, 7H, ArH); ^{13}C NMR (acetone-d_6) δ -1.74 (q), 28.3 (q), 28.4 (q). 43.9 (d), 44.7 (t), 49.7 (q), 50.3 (q), 56.3 (q), 69.0 (s), 71.1 (t), 79.1 (t), 100.8 (s), 108.8 (d), 115.4 (d), 119.2 (d), 119.7 (d), 124.3 (s), 126.0 (s), 127.3 (s), 127.8 (d), 128.4 (d), 129.2 (d), 130.0 (s),

133.5 (d), 138.2 (s), 145.1 (s), 145.6 (s), 149.6 (s), 158.08 (s), 163.1 (s), 163.5 (s), 195.4 (s); exact mass calcd. for $C_{36}H_{41}NO_7Si$ *m/z* 627.2652, found *m/z* 627.2641. Anal. calcd. $C_{36}H_{41}NO_7Si$: C, 68.87; H, 6.58. Found: C, 68.90; H, 6.77.

A solution of 1.55 g (2.47 mmol) of conjugate adduct **20** in 45 mL of tetrahydrofuran and 6 mL 5 N aqueous HCl was heated to reflux for 3 h. The reaction was diluted with 200 mL of dichloromethane and washed with 200 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford 1.26 g (51%) of **22** as an orange solid: mp 222-226 °C (dec.); IR (CH_2Cl_2) 3410, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.42 (s, 9H, $Si(CH_3)_3$), 4.34 (s, 3H, $ArOCH_3$), 5.30 (s, 2H, CH_2O), 7.00 (d, *J* = 7.8 Hz, 1H, C_2H), 7.08 (s, 1H, C_8H), 7.5 (m, 6H, ArH), 8.22 (d, *J* = 8.5 Hz, 1H, C_4H), 8.43 (s, 1H, $C_{12}H$), 8.51 (s, 1H, C_7H), 9.20 (s, 1H, ArOH); ^{13}C NMR($CDCl_3$) δ -1.9 (q), 60.8 (q), 71.9 (t), 107.1 (d), 107.2 (d), 115.1 (s), 115.7 (s), 116.5 (d), 116.6 (d), 118.6 (s), 119.1 (d), 122.0 (s), 126.1 (s), 126.6 (d), 128.0 (d), 128.96 (d), 129.1 (d), 131.0 (s), 135.1 (s), 139.0 (s), 142.5 (s), 150.1 (s), 153.6 (s), 154.8 (s), 161.9 (s), 167.4 (s); exact mass calcd. for $C_{30}H_{26}O_6Si$ *m/z* 510.150, found *m/z* 510.152.

1-(Benzyloxy)-13-hydroxy-8-methoxy-10-(trimethylsilyl)-6H-furo[2,3-f]naphtho[1,2-c][2]benzopyran-6-one (23). A solution of 0.62 g (0.99 mmol) of **21**, 45 mL of tetrahydrofuran, and 6 mL 5 N aqueous HCl was heated to reflux for 3 h. The reaction was diluted with 200 mL of dichloromethane and washed with 200 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford 0.51 g (98%) of **23** as an orange solid: 240-244 °C (dec.); IR (CH_2Cl_2) 3300, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.45 (s, 9H, $Si(CH_3)_3$) , 4.11 (s, 3H, $ArOCH_3$), 5.24 (s, 2H, CH_2O), 6.94 (d, *J* = 7.8 Hz, 1H, C_2H), 7.46 (m, 6H, ArH), 7.6 (s, 1H, $C_{12}H$), 7.68 (s, 1H, $C_{11}H$), 7.78 (s, 1H, C_7H), 8.13 (d, *J* = 8.6 Hz, 1H, C_4H), 9.25 (s, 1H, ArOH); ^{13}C NMR ($CDCl_3$) δ -1.7 (q), 56.3 (q), 72.0 (t), 104.3 (d), 106.3 (d), 107.4 (d), 114.9 (s), 115.9 (s), 116.3 (d), 116.7 (d), 118.3 (s), 123.9 (s), 125.0 (s), 126.4 (s), 127.0 (d), 128.0 (d), 129.1 (d), 129.1 (d), 134.9 (s), 139.6 (s), 146.5 (s), 150.7 (s), 152.1 (s), 155.0 (s), 161.8 (s), 166.5 (s); exact mass calcd. for $C_{30}H_{26}O_6Si$ *m/z* 510.149, found *m/z* 510.150.

1-(Benzyloxy)-11,13-dimethoxy-9-(trimethylsilyl)-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (24). To a solution of 100 mg (0.196 mmol) of **22** in 25 mL of dichloromethane was added 235 mg (1.7 mmol) of potassium carbonate and 0.284 mg (0.214 mL, 2.25 mmol) of dimethyl sulfate. The mixture was heated to reflux under argon for six days. The reaction was diluted with 100 mL of dichloromethane, filtered, and the residual potassium carbonate was rinsed with 50 mL of dichloromethane. The filtrate was washed with 50 mL of 10% aqueous citric acid, and the acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford 100 mg (97%) of **24** as a yellow solid: mp 187-188.5 °C; IR (CH_2Cl_2) 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.43 (s, 9H, $Si(CH_3)_3$), 4.04 (s, 3H, $ArOCH_3$), 4.34 (s, 3H, $ArOCH_3$), 5.20 (s, 2H, OCH_2), 7.01 (d, 1H, ArH), 7.08 (s, 1H, ArH), 7.40 (m, 4H, ArH), 7.61 (m, 2H, ArH), 8.20 (d, *J* = 8.5 Hz, 1H, C_7H), 8.48 (m, 2H, C_4H and $C_{12}H$); ^{13}C NMR ($CDCl_3$) δ -1.9 (q), 56.4 (q), 60.9 (q), 71.4 (t), 103.2 (d), 110.2 (d), 114.1 (s), 115.4 (d), 116.6

(d), 118.0 (s), 118.5 (s), 119.4 (d), 122.3 (s), 126.9 (s), 126.9 (d), 127.1 (d), 127.6 (d), 128.4 (d), 130.8 (s), 137.4 (s), 140.1 (s), 142.0 (s), 153.1 (s), 153.7 (s), 155.6 (s), 161.8 (s), 167.3 (s); exact mass calcd. for $C_{31}H_{28}O_6Si$ *m/z* 524.165, found *m/z* 524.165. Anal. calcd. for $C_{31}H_{28}O_6Si$: C,70.97; H, 5.38. Found: C, 70.81; H, 5.42.

1-Hydroxy-11,13-dimethoxy-9-(trimethylsilyl)-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (25). To a solution of 200 mg (0.381 mmol) of **24** in 120 mL of ethanol-dichloromethane (6:1) was added 50 mg of 5% palladium on carbon. The solution was hydrogenated at 50 psi for 26 h using a Parr hydrogenation apparatus. The mixture was dissolved by adding dichloromethane and filtered through a plug of celite which was rinsed with dichloromethane. The filtrate was concentrated in vacuo, and the residue was dissolved in chloroform and precipitated with petroleum ether to afford 149 mg (90%) of **25** as a white solid: mp 228-230 °C; IR (CH_2Cl_2) 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.44 (s, 9H, $Si(CH_3)_3$), 4.16 (s, 3H, $ArOCH_3$), 4.34 (s, 3H, $ArOCH_3$), 6.98 (dd, *J* = 7.7, 0.8 Hz, 1H, C_2H), 7.08 (s, 1H, C_8H), 7.44 (t, *J* = 8 Hz, 1H, C_3H), 8.06 (dd, *J* = 8.4, 0.8 Hz, 1H, C_4H), 8.46 (s, 1H, $C_{12}H$), 8.51 (s, 1H, C_7H), 9.34 (s, 1H, ArOH); ^{13}C NMR ($CDCl_3$) δ -1.9 (q), 56.1 (q), 60.9 (q), 100.9 (d), 112.5 (d), 113.4 (s), 113.5 (d), 114.7 (s), 116.6 (d), 118.3 (s), 119.3 (d), 122.0 (s), 126.3 (s), 128.4 (d), 130.9 (s), 141.0 (s), 141.8 (s), 152.0 (s), 153.5 (s), 154.1 (s), 161.6 (s), 167.4 (s); exact mass calcd. for $C_{24}H_{22}O_6Si$ *m/z* 434.118, found *m/z* 434.119.

1-Hydroxy-11,13-dimethoxy-6H-furo[2,3-g]naphtho[1,2-c][2]benzopyran-6-one (2). To a solution of 307 mg (0.71 mmol) of **25**, and 0.041 mL (0.71 mmol) acetic acid in 80 mL of dichloromethane-tetrahydrofuran (3:1) was added 0.71 mL (1.42 mmol) 1M tetra-*n*-butylammonium fluoride in tetrahydrofuran. The mixture was stirred for 2 h and diluted with 150 mL of dichloromethane. The mixture was washed with two 100-mL portions of water and the aqueous wash was extracted with two 100-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford an off-white solid. This material was recrystallized from nitromethane to afford 226 mg (88%) of **2** as a rosy white solid: mp 249-252 °C (dec.); IR (CH_2Cl_2) 3685, 1716 cm^{-1}; UV_{Max} CH_2Cl_2 (log e) 258 (4.75), 282 (4.15), 316 (4.10), 366 (4.15), 384 (4.12); ^1H NMR ($CDCl_3$) δ 4.18 (s, 3H, $ArOCH_3$),4.34 (s, 3H, $ArOCH_3$), 6.96 (d, *J* = 2.2 Hz, 1H, C_8H), 7.01 (dd, *J* = 7.7, 1.0 Hz, 1H, C_2H), 7.49 (t, *J* = 7.9 Hz, 1H, C_3H), 7.81 (d, *J* = 2.2 Hz, 1H, C_9H), 8.08 (dd, *J* = 8.4, 1.0 Hz, 1H, C_4H), 8.44 (s, 1H, $C_{12}H$), 8.57 (s, 1H, C_7H), 9.35 (s, 1H, ArOH); ^{13}C NMR (DMSO-d_6 at 335 K) δ 56.1 (q), 60.9 (q), 100.7 (d), 107.4 (d), 112.1 (d), 112.2 (d), 112.9 (s), 114.4 (s), 118.0 (s), 118.8 (d), 121.2 (s), 125.6 (s), 128.4 (d), 130.2 (s), 139.6 (s), 141.7 (s), 148.8 (d), 149.9 (s), 151.8 (s), 153.8 (s), 160.0 (s); exact mass calcd. for $C_{21}H_{14}O_6$ *m/z* 362.079, found *m/z* 362.083.

8-(Benzyloxy)-7-hydroxy-5-methoxy-2-(trimethylsilyl)-13-H-furo[3.2-h]naptho-[1,2c][2]benzopyran-13-one (26). To a solution of 3.08 g (9.66 mmol) of amide **18**, 1.8 mL (12 mmol) of tetramethyl-ethylenediamine in 130 mL of dry tetrahydrofuran at -45 °C (dry ice-acetonitrile) was slowly added 10.54 mL (11.59 mmol, 1.1 M in hexanes) of *s*-butyllithium via a syringe, and the solution was stirred for 2 h. In a separate flask, a solution of MAD was prepared by dissolving 2.84 g (12.90 mmol) 2,6-di-*t*-butyl-4-methylphenol in 100 mL of dry toluene and slowly adding 3.22 mL (6.45 mmol, 2 M in hexane) of trimethylaluminum at room temperature under argon followed by stirring for 30

min. The resulting solution was cooled to -78 °C (dry ice-acetone) and 1.0 g (3.22 mmol) of naphthoquinone monoketal **7** in 32 mL of dry toluene was added. The resulting dark solution was stirred for 15 min followed by addition of the aryl lithium via a cannula. The color of the solution slowly turned light orange during the addition. Upon completion of the addition, the reaction was stirred for 15 min followed by addition of 30 mL of water. The cooling bath was removed, and the reaction was allowed to warm to room temperature. The resulting heterogeneous mixture was filtered through a plug of Celite which was rinsed with dichloromethane. The filtrate was dried (Na_2SO_4), concentrated in vacuo and the residue was chromatographed over 150 g of silica gel (eluted with petroleum ether-ethyl acetate, 5:1, 4:1 and 2:1) to afford 1.3 g (64%) of conjugate adduct as an brown foam. Attempts to purify the conjugate adduct resulted in its decomposition. Therefore, characterization was performed after the next reaction.

A solution of 1.3 g (2.06 mmol) of the conjugate adduct in 45 mL of tetrahydrofuran and 9 mL of aqueous 5 N HCl was heated at reflux for 24 h under argon. The reaction was diluted with 150 mL of dichloromethane and washed with 100 mL of saturated aqueous sodium bicarbonate. The basic wash was extracted with two 100-mL portions of dichloromethane, the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford 1.16 g of an orange solid. This material was recrystallized from chloroform-hexanes to afford 0.9 g (86%) of pentacycle **26** as a yellow solid: mp 206-209 °C; IR ($CDCl_3$) 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.44 (s, 9H, $Si(CH_3)_3$), 4.08 (s, 3H, $ArOCH_3$), 5.32 (s, 2H, CH_2O), 7.00 (m, 2H, C9H and C3H), 7.46 (m, 7H, ArH), 8.22 (d, J = 11.7, 1H, $C_{11}H$), 8.52 (s, 1H, C_6H), 9.17 (s, 1H, ArOH); ^{13}C NMR ($CDCl_3$) δ - 1.7 (q), 56.5 (q), 71.9 (t), 107.3 (d), 107.9 (d), 108.2 (s), 109.4 (d), 115.1 (s), 115.4 (s), 115.5 (d), 116.7 (d), 122.1 (s), 125.9 (s), 126.5 (d), 128.0 (d), 128.9 (d), 129.1 (d), 129.5 (s), 135.1 (s), 139.9 (s) 149.7 (s), 152.0 (s), 153.5 (s), 154.7 (s), 157.9 (s), 167.7 (s); exact mass calcd. for $C_{30}H_{26}O_6Si$ *m/z* 510.150, found *m/z* 510.150.

8-(Benzyloxy)-5,7-dimethoxy-2-(trimethylsilyl)-13-H-furo[3.2-h]naptho[1,2c]-[2]benzopyran-13-one (27). A mixture of 0.5 g (0.98 mmol) of **26**, 1.17 g (0.88 mL, 9.3 mmol) of dimethyl sulfate, 1.28 g (9.3 mmol) of potassium carbonate, and 16 mL of dichloromethane was heated at reflux for five days. The reaction mixture was filtered and the potassium carbonate was rinsed with dichloromethane. The filtrate was diluted with 100 mL of dichloromethane, washed with 50 mL of 10% aqueous citric acid and the acidic wash was extracted with two 50-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford a yellow solid. This material was recrystallized from chloroform-petroleum ether to afford 0.41 g (88%) of **27** as a yellow solid: mp 227-228 °C; IR ($CDCl_3$) 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.45 (s, 9H, $Si(CH_3)_3$), 3.99 (s, 3H, $ArOCH_3$), 4.08 (s, 3H, $ArOCH_3$), 5.20 (s, 2H, CH_2O), 6.98 (s, 1H, C3H), 7.02 (d, J = 7.4 Hz, 1H, C9H), 7.50 (m, 7H, ArH), 8.57 (d, J = 8.5 Hz, 1H, $C_{11}H$), 8.51 (s, 1H, C_6H); ^{13}C NMR ($CDCl_3$) δ - 1.7 (q), 56.4 (q), 56.8 (q), 71.5 (t), 104.2 (d), 108.1 (s), 109.7 (d), 110.4 (d), 113.8 (s), 115.4 (d), 115.6 (d), 118.1 (s), 122.3 (s), 126.7 (s), 126.9 (d), 127.0 (d), 127.5 (d), 128.3 (d), 129.2 (s), 137.5 (s), 141.1 (s), 152.0 (s), 152.6 (s), 153.2 (s), 155.5 (s), 157.9 (s), 167.5 (s); exact mass calcd. for $C_{31}H_{28}O_6Si$ *m/z* 524.1655, found *m/z* 524.1660. Anal. calcd. for $C_{31}H_{28}O_6Si$: C, 70.97; H, 5.32. Found: C, 70.73 ; H, 5.42.

8-Hydroxy-5,7-dimethoxy-2-(trimethylsilyl)-13-H-furo[3.2-h]naptho[1,2c][2]-benzopyran-13-one (28). To a solution of 60 mg (0.13 mmol) of **27** in 60 mL ethyl alcohol-

dichloromethane (1:1) was added 25 mg of 10% palladium on carbon. This mixture was hydrogenated with a Parr hydrogenator at 50 psi of hydrogen for 14 h. The reaction mixture was dissolved in 100 mL of dichloromethane, filtered through a plug of celite and the filtrate was concentrated in vacuo to afford a yellow solid which was recrystallized from dichloromethane-hexanes to afford 40 mg (82%) of **28** as a yellow solid: mp 227-228 °C; IR (CH_2Cl_2) 1728 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 0.47 (s, 9H, $Si(CH_3)3$), 4.14 (s, 3H, $ArOCH_3$), 4.18 (s, 3H, $ArOCH_3$), 7.00 (d, *J* = 7.7 Hz, 1H, C9H), 7.11 (s, 1H, C3H), 7.54 (dd, *J* = 7.9, 8.2 Hz, 1H, $C_{10}H$), 7.61 (s, 1H, C4H), 8.07 (d, *J* = 8.4 Hz, 1H, $C_{11}H$), 8.61 (s, 1 H, C6H), 9.39 (s, 1H, ArOH); ^{13}C NMR (CD_2Cl_2) δ -1.73, 56.50, 57.20, 102.42, 110.23, 112.79, 113.72, 116.12, 126.57, 128.84, 129.95, 152.21, 153.69, 154.75, 168.16.(because of low solubility in variety of deuterated solvents, multiplicities could not be obtained and some signals were not detected); exact mass calcd. for $C_{24}H_{22}O_6Si$ *m/z* 434.1186, found *m/z* 434.1176.

8-Hydroxy-5,7-dimethoxy-13-H-furo[3.2-h]naptho-[1,2c][2]benzopyran-13-one (3). To a heterogeneous mixture of 0.04 g (0.092 mmol) of **28** and 7 mL dichloromethane-tetrahydrofuran (2.5:1) was added 0.092 mL (0.184 mmol) of 2 M tetra-*n*-butylammonium fluoride in tetrahydrofuran. The resulting red mixture was stirred for 3 h and diluted with 100 mL of dichloromethane. This mixture was washed with 50 mL of water, and the aqueous phase was extracted with five 50-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford a yellow solid. This material was triturated with toluene to afford 30 mg (91%) of **3** as a yellow solid: mp > 350 °C; IR (CD_2Cl_2) 1722 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 4.15 (s, 3H, $ArOCH_3$), 4.18 (s, 3H, $ArOCH_3$), 6.95 (d, *J* = 2.1 Hz, 1H, C_3H), 7.00 (dd, *J* = 8, 0.8 Hz, 1H, $C_{11}H$), 7.35 (s, 1H, C_4H), 7.52 (t, *J* = 8 Hz, 1H, $C_{10}H$), 7.95 (d, *J* = 2.1 Hz, 1H, C_2H), 8.07 (dd, *J* = 8, 0.9 Hz, 1H, $C_{11}H$), 8.62 (s, 1H, C_6H), 9.40 (s, 1H, ArOH); ^{13}C NMR (DMSO-d_6, at 333 K) δ 56.1, 56.9, 101.7, 106.6, 111.3, 112.2, 112.9, 114.3, 128.8, 140.9, 148.5, 151.5, 153.1, 153.7; exact mass calcd. for $C_{21}H_{14}O_6$ *m/z* 362.0790, found *m/z* 362.0781. Because of low solubility in variety of deuterated solvents, ^{13}C multiplicities could not be obtained and some signals were not detected.

8-(Benzyloxy)-5,7-dimethoxy-13-H-furo[3.2-h]naptho-[1,2c][2]benzopyran-13-one (29). To a solution of 0.22 g (0.42 mmol) of **27**, 0.024 mL (0.025 g, 0.042 mmol) of acetic acid in 40 mL dichloromethane-tetrahydrofuran (1:1) was added 0.42 mL (0.84 mmol) of 2 M tetra-*n*-butylammonium fluoride in tetrahydrofuran. The reaction was stirred for 5 h, washed with 50-mL of water and the aqueous phase was extracted with three 50-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was triturated with ethyl acetate to yield 160 mg (85%) of **29** as a yellow solid: mp 252-255 °C (dec.) ; IR ($CDCl_3$) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) d 4.04 (s, 3H, $ArOCH_3$), 4.15 (s, 3H, $ArOCH_3$), 5.26 (s, 2H, CH_2O), 6.89 (s, 1H, C_4H), 7.10 (d, *J* = 2.1 Hz, 1H, C_3H), 7.50 (m, 7H, ArH), 7.94 (d, *J* = 2.1 Hz, 1H, C_2H), 8.33 (d, *J* = 7.6 Hz, 1H, $C_{11}H$), 8.61 (s, 1H, C_6H); ^{13}C NMR ($CDCl_3$) d 59.2 (q), 59.7 (q), 74.3 (t), 106.9 (d), 109.2 (d), 111.2 (s), 112.8 (d), 113.3 (d), 116.6 (s), 118.4 (d), 121.0 (s), 125.5 (s), 129.5 (s), 129.8 (d), 130.0 (d), 130.5 (d) 131.3 (d), 140.3 (s), 143.9 (s), 150.7 (d), 151.4 (s), 155.8 (s), 156.4 (s), 158.5 (s), 161.0 (s), 171.9 (s); exact mass calcd. for $C_{28}H_{20}O_6$ *m/z* 452.1260, found *m/z* 452.1261.

1-Benzyloxy-12-hydroxy-8-(4,4-dimethyl-2-oxazolin-2-yl)-10-methoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one (30). Prepared from **7** and 4-Bromo-1,3-bis(4',4'-dimethyloxazonlin-2'-yl)-5-methoxybenzene[26] as per the preparation of **26**: mp 224-226 °C (orange solid); IR (CH_2Cl_2) 3407, 1726, 1608 cm $^{-1}$; ^{1}H NMR δ 1.28 (s, 6H, $C(CH_3)_2$), 4.15 (s, 3H, $ArOCH_3$),4.24 (s, 2H, CH_2O), 5.34 (s, 2H, OCH_2Ph), 7.09 (d, J = 7.9 Hz, 1H, C_2H), 7.50 (s, 6H, ArH), 7.99 (d, J = 1.6 Hz, 1H, C_9H), 8.27 (d, J = 8.4, 1H, C_4H), 8.42 (s, 1H, $C_{11}H$), 8.76 (d, J = 1.6 Hz, 1H, C_7H), 9.28 (br s, 1H, ArOH); ^{13}C NMR (DMSO-d_6 at 333K) δ 23.3 (q), 26.1 (q), 49.0 (s), 56.4 (q), 67.3 (t), 71.0 (t), 73.2 (s), 106.7 (d), 109.2 (d), 113.2 (s), 114.7 (s), 116.4 (s), 116.8 (d), 120.5 (d), 122.4 (d), 124.0 (s), 127.3 (d), 127.6 (d), 128.0 (d), 128.0 (d), 128.4 (d), 130.4 (s), 135.8 (s), 149.6 (s), 154.5 (s), 157.5 (s), 159.3 (s); exact mass calcd. for $C_{30}H_{25}NO_6$ *m/z* 495.1682, found *m/z* 495.1691.

12-Hydroxy-10-methoxy-8-(N,N-diethylamide)-6H-benzo[d]naphtho[1,2-b]pyran-6-one (31). Prepared from **7** and bis-(N,N-diethyl-5-methoxybenzene-1,3-dicarboxamide[27] as per the preparation of **26**: mp 209-210 °C (yellow solid); IR ($CDCl_3$) 3412, 1720 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 1.26 (broad s, 6H, $(CH_3)_2$), 3.37 (broad s, 2H, CH_2), 3.59 (broad s, 2H, CH_2), 4.10 (s, 3H, $ArOCH_3$), 5.33 (s, 2H, CH_2O), 7.04 (d, J = 7.5 Hz, 1H, C_2H), 7.49 (m, 7H, ArH), 8.12 (d, J = 1.6 Hz, 1H, C_7H), 8.23 (dd, J = 8.6, 0.6 Hz, 1H, C_4H), 8.39 (s, 1H, $C_{11}H$), 9.23 (s, 1H, ArOH); ^{13}C NMR ($CDCl_3$) δ 10.7, 12.9, 39.6 (t), 43.6 (t), 56.2 (q), 71.9 (t), 107.6 (d), 107.7 (d), 114.5 (s), 115.2 (d), 115.5 (s), 116.4 (s), 119.8 (d), 123.2 (s), 125.1(s), 125.8 (s), 126.7 (d), 128.0 (d),129.0 (d), 129.1 (d), 135.0 (s), 137.9 (s), 140.0 (s), 150.7 (s), 154.7 (s), 158.0 (s), 160.7 (s), 169.3 (s); exact mass calcd. for $C_{30}H_{27}NO_6$ *m/z* 497.1838, found *m/z* 497.1859. The multiplicity of the signals at 10.7, and 12.9 in the ^{13}C spectrum, was not attainable because of broadening.

5-Hydroxy-6-(phenylmethoxy)-11H-furo[2,3-d]naphtho[1,2-b]pyran-11-one (32). Prepared from **7** and 2-(3-furyl)-4,4-dimethyl-2-oxazoline[28] as per the preparation of **26**: mp 265-267 °C; IR (CH_2Cl_2) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.35 (s, 2H, OCH_2Ph), 7.05 (d, J = 1 Hz, 1H, C_2H), 7.1 (d, J = 8 Hz, 1H, C_7H), 7.2 (s, 1H, C_4H), 7.4-7.6 (m, 6H, ArH), 7.67 (d, J = 1 Hz, 1H, C_1H), 8.22 (d, J = 8 Hz, 1H, C_9H), 9.45 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 72.2, 99.5, 108.4, 108.7, 109.7, 111.2, 116.2, 116.7, 126.3, 127.6, 128.1, 129.1, 129.2, 134.7, 142.5, 144.9, 151.5, 155.4, 158.2, 158.4; exact mass calcd. for $C_{22}H_{14}O_5$ *m/z* 358.0842, found *m/z* 358.0861.

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