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An Inverse Electron Demand Diels–Alder-Based Total Synthesis of Defucogilvocarcin V and Some C-8 Analogues

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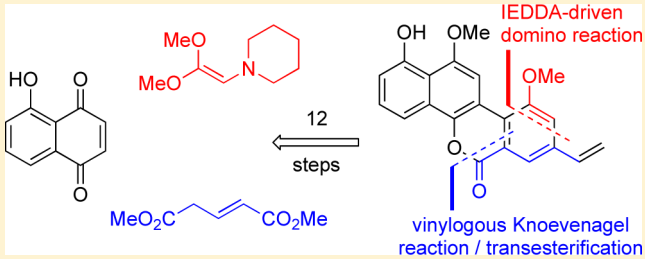
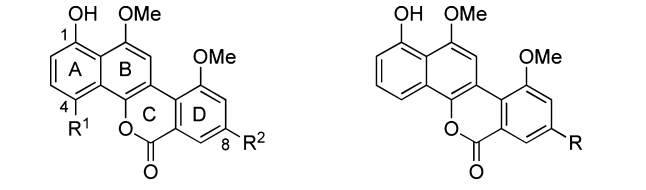
Supporting Information

ABSTRACT: A concise total synthesis of defucogilvocarcin V is reported. The key features of the approach are the formation of the C-ring using a vinylogous Knoevenagel/transesterification reaction and construction of the D-ring by way of an inverse electron demand Diels–Alder-driven domino reaction. The resulting C-8 ester functionality provides a handle for the synthesis of defucogilvocarcin V as well as some C-8 analogues from a common late-stage intermediate.



INTRODUCTION

A class of aryl *C*-glycoside-containing natural products, composed of the gilvocarcins,[1−4] ravidomycin (**2**),[5,6] the chrysomycins (**3**),[7,8] and polycarcin (**4**),[9] has been isolated from different species of *Streptomyces*. These compounds exhibit impressive biological properties, including antibacterial[2,10] and strong antitumor activity.[11−14] Structurally, they share a common tetracyclic aromatic core (6*H*-benzo[*d*]-naphtho[1,2-*b*]pyran-6-one) to which a sugar is attached at C-4. Individual gilvocarcins (Figure 1) are distinguished by variation of the R group at C-8 by which they were named as gilvocarcin M (R = methyl), gilvocarcin E (R = ethyl), and gilvocarcin V (R = vinyl). Furthermore, the aglycon of one of them, defucogilvocarcin V (**5c**), was isolated from the fermentation broth of *Streptomyces arenae* 2064 by Mishra and co-workers.[15] Studies suggested that the antitumor activity of defucogilvocarcin V (**5c**), on activation by light, is similar to that of the parent gilvocarcin V (**1c**).[15,16] This implies that the role of sugar moiety in the anticancer activity may be of minor importance.



1a gilvocarcin M (R^1=**I**, R^2=methyl)
1b gilvocarcin E (R^1=**I**, R^2=ethyl)
1c gilvocarcin V (R^1=**I**, R^2=vinyl)
2 ravidomycin (R^1=**II**, R^2=vinyl)
3a chrysomycin A (R^1=**III**, R^2=vinyl)
3b chrysomycin B (R^1=**III**, R^2=methyl)
4 polycarcin (R^1=**IV**, R^2=vinyl)

5a defucogilvocarcin M (R=methyl)
5b defucogilvocarcin E (R=ethyl)
5c defucogilvocarcin V (R=vinyl)

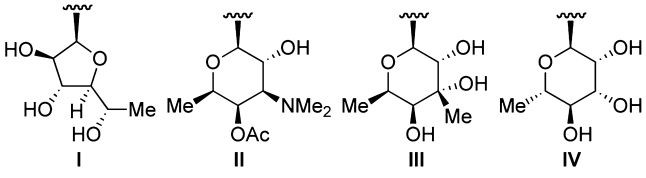


Figure 1. Gilvocarcin family of natural products.

The gilvocarcins (**1**) and their aglycons (defucogilvocarcins, **5**) have been targets of the synthetic community because of their impressive biological profiles. Whereas only a handful of total syntheses of gilvocarcins have been accomplished,[17−20] a relatively large number of defucogilvocarcin syntheses has been reported. The strategies used to approach the defucogilvocarcins can be sorted into three categories according to the ring(s) generated during the key step(s): (1) formation of the C ring using (a) Suzuki coupling followed by lactonization,[21−23] (b) esterification/intramolecular biaryl bond formation,[24] (c) nucleophilic aromatic substitution/lactonization,[25,26] (d) Pechmann condensation,[27] and (e) conjugate addition/lactonization;[28] (2) formation of the A and C rings using (f) Diels–Alder reaction (A ring)/Meerwein coupling/lactonization (C ring);[29−31] and (3) formation of the B and C rings using (g) a Dötz chromium carbene benzannulation/lactonization,[32] (h) a [2 + 2] cycloaddition/pericyclic ring-opening–ring closing/lactonization,[33] and (i) a condensation reaction between a styryl sulfone and a phthalide.[34] More recently, a one-pot enzymatic synthesis of defucogilvacarcin M starting from acetyl-CoA and malonyl-CoA using 15 enzymes has been reported.[35] Notably, none of the nonenzymatic synthetic approaches to the defucogilvocarcins involves the formation of the D-ring, which is where variations at C-8 of natural products are present.

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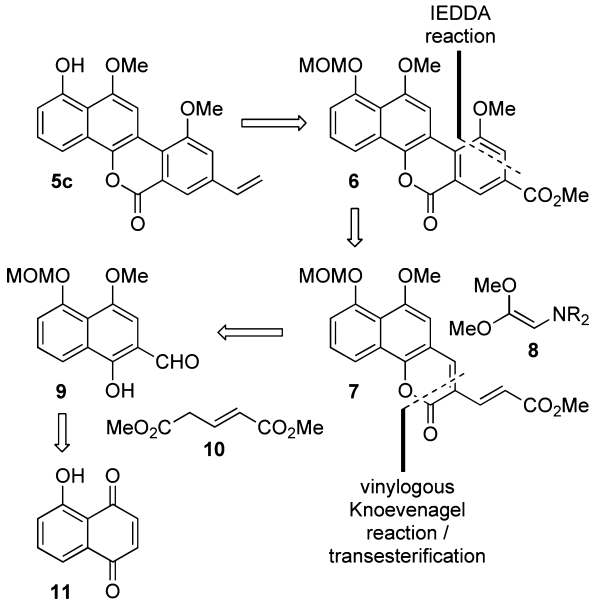
RESULTS AND DISCUSSION

In connection with ongoing work aimed at the development and application of the inverse electron demand Diels–Alder (IEDDA) reaction,[36] our group has reported the synthesis of a variety of electron deficient dienes.[37−44] The common structural feature of these systems is the presence of two electron withdrawing groups on the diene unit with a 1,3-relationship. This motif allows the two electron-withdrawing groups to electronically bias the diene in a co-operative fashion, which results in completely regioselective cycloaddition upon reaction with electron rich dienophiles. This chemistry has provided access to several different classes of compounds, including 2-hydroxybenzophenones,[38] isophthalates,[39] xanthones,[40] pyrido[2,3-*c*]coumarins,[41] and 6*H*-dibenzo[*b*,*d*]-pyran-6-ones (DBPs).[42−44] Additionally, the methodology developed for the synthesis of DBPs has been exploited in total syntheses of cannabinol[44] and urolithin M7,[45] as well as in the synthesis of an elaborate chiral cyclophane.[46] To further demonstrate the value of this methodology, defucogilvocarcins were identified as attractive synthetic targets. Reported herein are details of the total synthesis of defucogilvocarcin V (**5c**) and some of its C-8 analogues.

The retrosynthetic analysis of **5c** based on our DBP-forming methodology commences with functional group interconversion to provide 6*H*-benzo[*d*]naphtho[1,2-*b*]benzopyran-6-one (**6**) (Scheme 1). The D-ring and C-ring are then opened

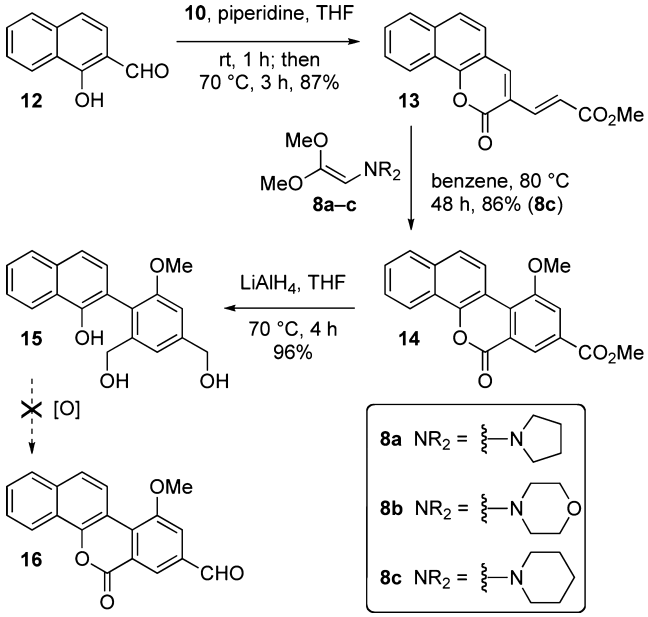
Scheme 1. Retrosynthetic Analysis of Defucogilvocarcin V (5c)



successively using an IEDDA-driven domino transform,[42,43,45] (giving naphthalene-derived diene **7** and electron rich dienophile **8**) and a vinylogous Knoevenagel condensation/transesterification transform to afford 1-hydroxy-2-naphthaldehyde **9** and dimethyl glutaconate (**10**). The differentially *O*-protected 1-hydroxy-2-naphthaldehyde **9** leads back to commercially available juglone (**11**).

Before initiating work on the synthesis of **9**, a model study starting from more abundantly and inexpensively available 1-hydroxy-2-naphthaldehyde (**12**) was conducted to test the viability of the key steps (Scheme 2). The reaction of **12** with

Scheme 2. Model Study



dimethyl glutaconate (**10**) afforded diene **13** in high yield (87%). Diene **13** was then subjected to the key IEDDA reaction with a series of enamines derived from dimethoxyacetaldehyde, i.e., **8a–c**, whereby it was found that the nature of the secondary amine used to generate the enamine played a critical role in the reaction. While the use of the pyrrolidine-derived enamine **8a** resulted in the consumption of the starting diene, no identifiable product was obtained from the reaction. However, the morpholine-derived enamine **8b** did not undergo reaction with **13** under the same conditions. After some experimentation, it was found that diene **13** reacted smoothly with the piperidine-derived enamine **8c** to afford **14** (86%). In this case, more concentrated solutions were required to drive the reaction to completion. The reasons for differences in reactivity between the various enamines **8a–c** are not immediately obvious. In any event, the IEDDA reaction involving **8c** proceeded with complete regioselectivity, in line with previous observations.[37−45] Consequently, the newly generated D-ring was endowed with correctly placed methoxy and methoxycarbonyl groups, the latter of which was poised for conversion to the required vinyl functionality. Both the ester and lactone functionalities present in **14** were reduced with $LiAlH_4$ to give triol **15** (96%). It was envisaged that oxidation of **15** would afford lactone-aldehyde **16** (via a hemiacetal), but all attempts to accomplish this transformation using various oxidizing agents (PCC, MnO_2, IBX, and Fétizon's reagent) failed. In all cases, the starting material was consumed to give a deeply colored reaction mixture, from which no identifiable product was isolated. Quinone formation may compete with the desired transformation.

Although the viability of the two key steps had been established, an alternative approach to functional group management was required. Accordingly, methods for achieving the chemoselective reduction of the ester over the lactone were investigated. To this end, hydrolysis of **14** afforded carboxylic acid **17** (93%) (Scheme 3). In this reaction, both the ester and lactone were presumably hydrolyzed, and the lactone reformed during the acidic workup. Weinreb amide **18** was then prepared in moderate yield (55%) in preparation for a chemoselective

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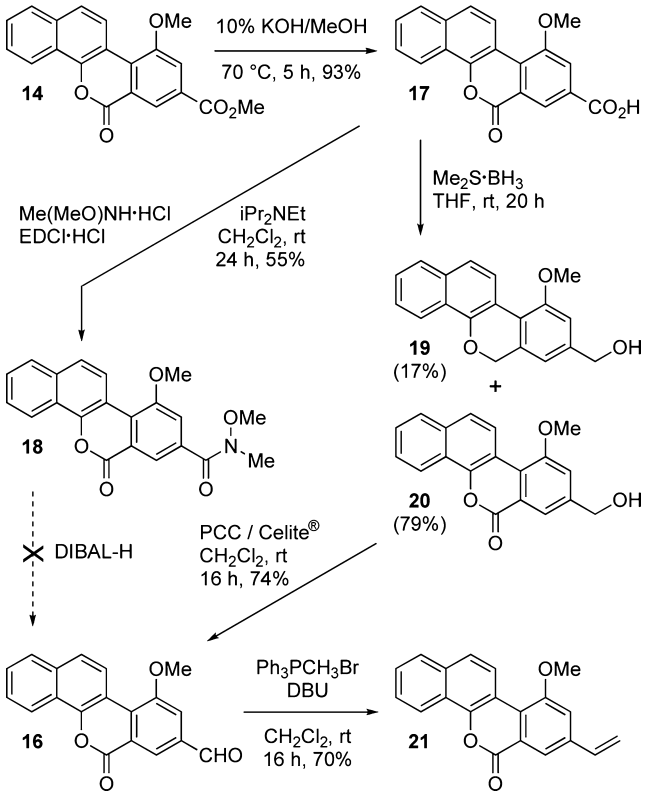
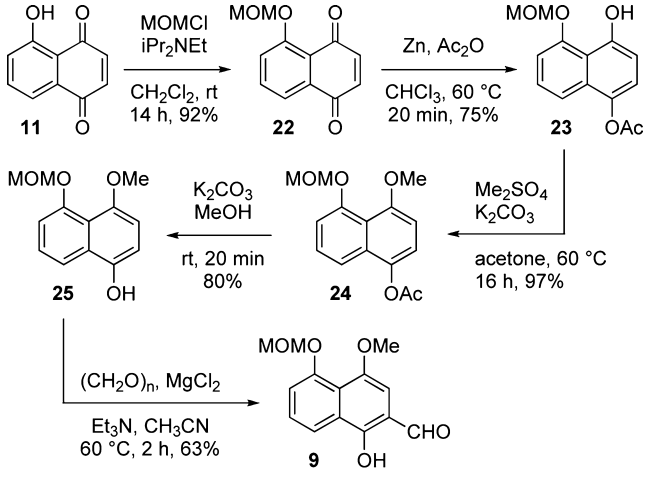
Scheme 3. Completion of the Model Study



reduction with DIBAL-H, which was intended to result in the formation of aldehyde **16**. Unfortunately, this reaction showed no evidence of progress at −78 °C, the temperature typically used for this transformation.[47] Upon warming the reaction mixture to room temperature and stirring at this temperature for 12 h, the starting material was consumed, but a complex mixture of products was produced (tlc and ^{1}H NMR analysis). However, a chemoselective reduction of acid **17** was achieved using $Me_2S{\cdot}BH_3$. This afforded benzylic alcohol **20** (79%) along with a minor, but still significant, amount of the overreduced benzylic alcohol **19** (17%). Oxidation of **20** was achieved using PCC/celite to give aldehyde **16** (74%). Finally, a Wittig reaction under mild conditions[48] using DBU as the base was employed to obtain the olefin **21** (70%), thereby completing the model study. Model compound **21** was synthesized in six steps from commercially available 1-hydroxy-2-naphthaldehyde (**12**) in 28% overall yield.

Upon successful completion of the model study, attention was turned to applying the approach to the synthesis of defucogilvocarin V (**5c**). The synthesis began from juglone (**11**), which is commercially available or readily accessible from 1,5-dihydroxynaphthalene.[49] The hydroxy group of juglone (**11**) was MOM-protected,[50] and the resulting 1,4-naphthoquinone **22** (92%) was subjected to a reductive acylation/methylation protocol, which was based upon procedures described for the *O*-methyl analogue of **22** (Scheme 4).[51] This involved reduction of the naphthoquinone **22** with Zn and selective *O*-acetylation at the less sterically hindered site. The monoacylated product **23** (75%) was then *O*-methylated upon treatment with dimethyl sulfate to give **24** (97%). The acetyl group was removed using K_2CO_3 in MeOH to afford naphthol **25** (80%), which was regioselectively formylated using the

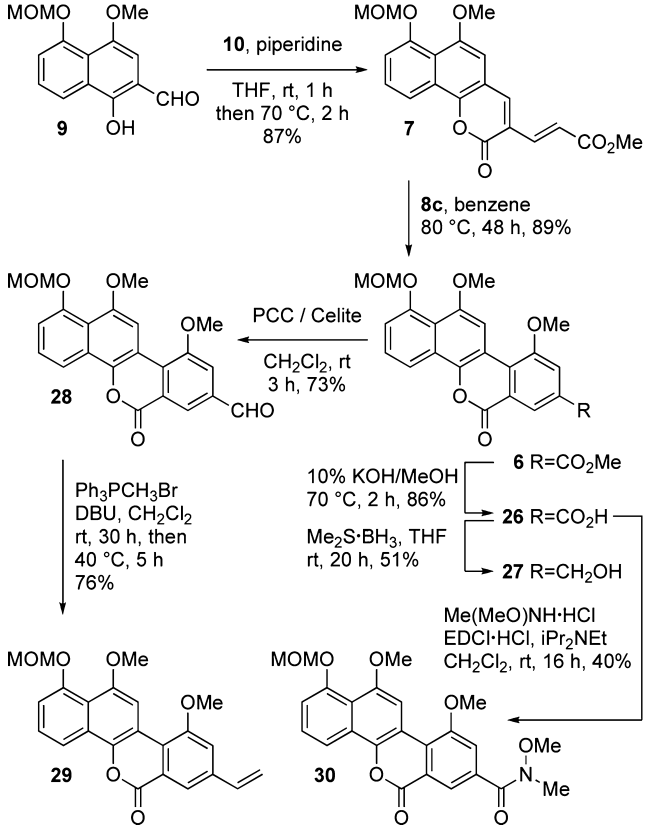
Scheme 4. Synthesis of Hydroxynaphthaldehyde 9



Skattebøl *ortho*-formylation[52] to provide the required hydroxynaphthaldehyde **9** (63%).

With **9** in hand, a vinylogous Knoevenagel reaction was carried out with dimethyl glutaconate (**10**) to generate the corresponding electron deficient diene **7** (87%) (Scheme 5).

Scheme 5. Synthesis of MOM-Protected Defucogilvocarcin V (29)



Reaction of **7** with enamine **8c** resulted in the formation of ester **6** (89%), which differs from the natural product only in the nature of the C-8 substituent and the presence of the protected OH group at C-1. Hydrolysis of the ester provided carboxylic acid **26** (86%), which was then reduced to afford benzylic alcohol **27** (51%). Oxidation of **27** gave aldehyde **28**

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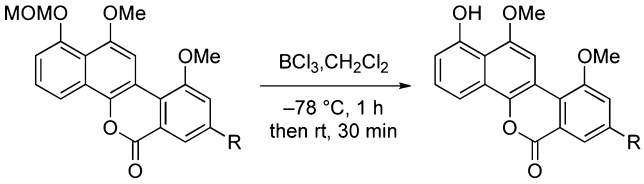
(73%), which was subjected to a Wittig reaction to furnish olefin **29** (76%). To mirror the model study, carboxylic acid **26** was converted into the corresponding Weinreb amide **30** (40%).

Finally, compounds **6**, **28**, **29**, and **30** were deprotected using BCl_3 (Scheme 6). This reaction smoothly afforded defucogilvocarcin V (**5c**) (83%) along with three C-8 analogues, **31** (87%), **32** (82%), and **33** (63%). The total synthesis of defucogilvocarcin V (**5c**) was accomplished in 12 steps from juglone in 5.3% overall yield.

Scheme 6. Synthesis of Defucogilvocarcin V (5c) and C-8 Analogues 31−33



6 R=CO_2Me
28 R=CHO
29 R=$CHCH_2$
30 R=C(O)NMe(OMe)

31 R=CO_2Me (87%)
32 R=CHO (82%)
5c R=$CHCH_2$ (83%)
33 R=C(O)NMe(OMe) (63%)

CONCLUSIONS

The approach to defucogilvocarcin V (**5c**) described here differs from all previously reported approaches in that it involves construction of the D-ring. Not only is the D-ring formed with the required C-10 methoxy group, but it also bears an ester at C-8, which is where differences in the natural defucogilvocarcins and gilvocarcins occur. Synthetic manipulation of the ester group led to the natural product defucogilvocarcin V (**5c**) as well as three C-8 analogues, which all offer opportunities for further elaboration.

EXPERIMENTAL SECTION

General. Reactions were performed using anhydrous solvents under a balloon containing N_2 unless otherwise indicated. All reactions were performed with oven-dried (120 °C) glassware. THF was distilled immediately prior to use from sodium/benzophenone, and acetone was distilled from K_2CO_3. Acetonitrile and triethylamine were distilled over CaH_2. Solvents were removed from reaction mixtures under reduced pressure using a rotary evaporator. Chromatographic separations were achieved using silica gel with a particle size of 40−63 mm. Thin-layer chromatography (TLC) was performed using precoated plastic-backed silica gel plates with a layer thickness of 200 mm. Compounds on TLC plates were visualized using a UV lamp (254 and 365 nm). Melting points are uncorrected. Infrared (IR) spectra were recorded using solid samples. ^{1}H and ^{13}C spectra were obtained from $CDCl_3$ or DMSO-d_6 solutions. Chemical shifts are relative to internal standards: TMS (δ_H = 0.00 ppm) and $CDCl_3$ (δ_C = 77.23 ppm), respectively. For high-resolution mass spectroscopic measurements, a TOF mass analyzer was employed.

*Methyl (E)-3-(6H-Naphtho[1,2-b]pyran-6-on-5-yl)acrylate (**13**).* To a solution of 1-hydroxy-2-naphthaldehyde (**12**) (2.00 g, 11.6 mmol) and dimethyl glutaconate (**10**) (2.76 g, 17.5 mmol) in THF (40 mL) was added piperidine (0.99 g, 12 mmol), and the resulting mixture was stirred at room temperature for 1 h and then at 70 °C for 3 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (600 mL), and the resulting solution was washed with aqueous 1.0 M HCl solution (1×). The layers were separated, and the organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and diethyl ether (15 mL) was added to the residue. The resulting mixture was stirred for 10 min and vacuum filtered. On repetition of this process (ether addition to the solids, stirring, and filtration), **13** (2.83 g, 87%) was obtained as a yellow solid. R_f = 0.30 (30% ethyl acetate/hexanes); mp 191−193 °C; IR (neat) ν = 1708 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.57−8.55 (m, 1H), 7.98 (s, 1H), 7.89−7.87 (m, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.69−7.66 (m, 2H), 7.63 (d, J = 15.9 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 15.8 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.7, 159.3, 151.4, 144.7, 138.5, 135.6, 129.6, 128.2, 127.7, 125.1, 123.9, 123.1, 122.94, 122.86, 121.7, 114.7, 52.1; ESI-(+)-MS m/z (%) 303 (100, [M + Na]$^+$); HRMS [EI-(+)] calcd for $C_{17}H_{12}O_4$ 280.0736, found 280.0732.

*10-Methoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one-8-carboxylic Acid Methyl Ester (**14**).* A mixture of dimethoxyacetaldehyde (1.86 g, 10.7 mmol, 60% solution in water) and piperidine (0.73 g, 8.6 mmol) in benzene (35 mL) was heated at reflux for 1 h using a Dean−Stark apparatus. Solvent (∼30 mL) was removed from the reaction flask through the Dean−Stark condenser. The reaction mixture was cooled to room temperature, and **13** (0.30 g, 1.1 mmol) was added in one portion. The resulting mixture was then heated at reflux for 48 h (note: the low dilution is critical for the complete consumption of the starting material). The reaction was monitored by ^{1}H NMR analysis (an aliquot was taken from the reaction using a pipet, ether (0.5 mL) was added, the supernatant was decanted, and the residue was dried under vacuum; ^{1}H NMR was performed after every 12 h, starting from 24 h). The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (70 mL) and washed with aqueous 1.0 M HCl solution (2×). The layers were separated, and the organic layer dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected column chromatography ($CHCl_3$). The product obtained from chromatography was triturated with ether (2 × 7 mL) to give **14** (0.30 g, 86%) as a pale yellow solid. R_f = 0.30 (30% ethyl acetate/hexanes); mp 247−250 °C; IR (neat) ν = 1715 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.96 (d, J = 9.2 Hz, 1H), 8.75 (d, J = 1.7 Hz, 1H), 8.61−8.57 (m, 1H), 7.93 (d, J = 1.7 Hz, 1H), 7.85−7.82 (m, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.63−7.59 (m, 2H), 4.14 (s, 3H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.9, 160.7, 157.6, 147.7, 134.3, 130.6, 128.7, 128.5, 127.4, 127.0, 124.7, 124.3, 124.0, 123.5, 123.1, 122.8, 116.8, 112.8, 56.6, 52.8; APCI-(+)-MS m/z (%) 335 ([M + H]$^+$, 100); HRMS [CI-(+)] calcd for $C_{20}H_{15}O_5$ 335.0919, found 335.0930.

*2-(2,4-Bis(hydroxymethyl)-6-methoxy)-1-naphthol (**15**).* To a 0 °C slurry of $LiAlH_4$ (0.18 g, 4.7 mmol) in THF (20 mL) was added **14** (0.40 g, 1.2 mmol) in several portions, and the reaction mixture was heated at reflux for 4 h. After cooling to 0 °C, the reaction was quenched by the careful addition of aqueous 1.0 M HCl solution (20 mL). The resulting mixture was vacuum filtered, and the filtrate was washed thoroughly with $CHCl_3$ (4×). The layers were separated, and the aqueous

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layer was washed with $CHCl_3$ (1×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was triturated with ether (2 × 3 mL) to afford **15** (0.39 g, 96%) as a colorless solid. R_f = 0.20 (50% ethyl acetate/hexanes); mp 197−200 °C; IR (neat) ν = 3389 (w) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.18−8.17 (m, 1H), 7.82−7.80 (m, 1H), 7.48−7.42 (m, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 1.6 Hz, 1H), 5.20 (t, J = 5.8 Hz, 1H), 4.56 (d, J = 4.7 Hz, 2H), 4.18 (d, J = 13.9 Hz, 1H), 4.10 (d, J = 13.8 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.8, 149.4, 142.8, 141.9, 133.7, 129.6, 127.4, 125.7, 125.3, 124.7, 122.8, 122.2, 118.7, 117.7, 116.7, 107.6, 63.3, 60.9, 55.3; APCI-(−)-MS m/z (%) 309 (100, $[M-1]^-$); HRMS [EI-(+)] calcd for $C_{19}H_{18}O_4$ 310.1205, found 310.1208.

*10-Methoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one-8-carboxylic Acid (**17**).* A suspension of **14** (0.60 g, 1.8 mmol) in 10% KOH/methanol (30 mL) was heated at reflux for 5 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. To the residue was added water (10 mL), and the pH was adjusted to ∼2.0 using aqueous 5.0 M HCl solution. The resulting mixture was suction filtered. The solids were vacuum-dried for 1 h, and then air-dried in an oven at 90−100 °C for 12 h to afford **17** (0.53 g, 93%) as a pale yellow solid. R_f = 0.60 (ethyl acetate); mp 266−269 °C; IR (neat) ν = 3200−2700 (br, w), 1734 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.99 (d, J = 9.1 Hz, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.42−8.38 (m, 1H), 8.03−7.99 (m, 1H), 7.95 (d, J = 1.7 Hz, 1H), 7.85 (d, J = 9.1 Hz, 1H), 7.72−7.68 (m, 2H), 4.15 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.8, 159.5, 157.1, 146.5, 133.4, 131.3, 128.2, 127.3, 127.0, 126.8, 124.2, 123.6, 122.5, 122.4, 122.3, 121.5, 116.7, 112.2, 56.4; APCI-(−)-MS m/z (%) 319 (100, $[M-1]^-$); HRMS [EI-(+)] calcd for $C_{19}H_{12}O_5$ 320.0685, found 320.0687.

*N-10-Dimethoxy-N-methyl-6H-benzo[d]naphtho[1,2-b]-pyran-6-one-8-carboxamide (**18**).* To a mixture of **17** (0.18 mg, 0.55 mmol) and EDCI·HCl (0.20 g, 1.0 mmol) in CH_2Cl_2 (3.0 mL) was added iPr_2NEt (0.28 g, 2.2 mmol), and the resulting mixture was stirred at room temperature for 1 h. To the resulting mixture was added *N,O*-dimethylhydroxylamine hydrochloride (0.13 g, 1.3 mmol) in one portion, and the mixture was stirred at room temperature for a further 24 h. Water (20 mL) was then added followed by the aqueous 1.0 M HCl solution (15 mL). The layers were separated, and the aqueous layer was washed with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (3% methanol/$CHCl_3$); the product was triturated with ether (2 × 1 mL) to afford **18** (0.11 g, 55%) as a colorless solid. R_f = 0.50 (50% ethyl acetate/hexanes); mp 164−167 °C; IR (neat) ν = 1718 (s), 1633 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.03 (d, J = 9.1 Hz, 1H), 8.64−8.62 (m, 1H), 8.53 (d, J = 1.6 Hz, 1H), 7.89−7.87 (m, 1H), 7.75−7.73 (m, 2H), 7.65−7.61 (m, 2H), 4.15 (s, 3H), 3.67 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 161.0, 157.5, 147.5, 134.5, 134.2, 128.3, 127.5, 127.0, 124.8, 124.0, 123.7, 122.81, 122.79, 122.7, 117.1, 113.0, 61.7, 56.6, 34.0; APCI-(+)-MS m/z (%) 364 (100, $[M+H]^+$); HRMS [EI-(+)] calcd for $C_{21}H_{17}NO_5$ 363.1107, found 363.1111.

*8-(Hydroxymethyl)-10-methoxy-6H-benzo[d]naphtho[1,2-b]pyran (**19**) and 8-(Hydroxymethyl)-10-methoxy-6H-benzo-[d]naphtho[1,2-b]pyran-6-one (**20**).* To a 0 °C suspension of **17** (0.20 g, 0.63 mmol) in THF (20 mL) was added $H_3B{\cdot}SMe_2$ (1.8 mL, 3.7 mmol) dropwise over a period of 5 min, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was cooled to 0 °C, and methanol (3.0 mL) was added dropwise. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (200 mL). The resulting solution was washed with aqueous 1.0 M HCl solution (1×) and then with saturated aqueous $NaHCO_3$ solution (1×). The layers were separated, and the organic layer was dried over Na_2SO_4 and gravity filtered, and the solvent was removed under reduced pressure. The residue was triturated with ether (3 × 3 mL) to afford **20** (153 mg, 79%) as a colorless solid. The ether layer was concentrated under reduced pressure, and the residue was subjected to column chromatography (40% ethyl acetate/hexanes) to afford **19** (30 mg, 17%) as a colorless solid. **20**: R_f = 0.70 (ethyl acetate); mp 231−234 °C; IR (neat) ν = 3433 (m), 1692 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 9.02 (d, J = 9.1 Hz, 1H), 8.43−8.41 (m, 1H), 8.02−8.00 (m, 1H), 7.99 (d, J = 1.5 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.72−7.66 (m, 2H), 7.60 (d, J = 1.6 Hz, 1H), 5.54 (t, J = 5.6 Hz, 1H), 4.70 (d, J = 3.5 Hz, H), 4.11 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 160.2, 157.1, 145.5, 145.1, 132.9, 127.7, 127.5, 127.0, 124.4, 123.5, 122.7, 122.1, 121.8, 121.4, 118.9, 115.8, 113.0, 62.2, 56.4; ESI-(+)-MS m/z (%) 307 (100, $[M+H]^+$); HRMS [EI-(+)] calcd for $C_{19}H_{14}O_4$ 306.0892, found 306.0901. **19**: R_f = 0.80 (ethyl acetate); mp 122−125 °C; IR (neat) ν = 3400−3100 (br, w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.49 (d, J = 8.8 Hz, 1H), 8.28−8.26 (m, 1H), 7.81−7.78 (m, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.48−7.44 (m, 2H), 7.00 (d, J = 1.5 Hz, 1H), 6.86 (d, J = 1.4 Hz, 1H), 5.16 (s, 2H), 4.73 (s, 2H), 3.97 (s, 3H), 1.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 150.8, 141.4, 134.2, 133.8, 127.3, 126.4, 125.9, 125.3, 125.0, 122.2, 120.4, 118.8, 117.0, 115.6, 110.1, 69.3, 65.1, 55.7; APCI-(+)-MS m/z (%) $[M+H]^+$ not observed, 291 (11), 275 (100); HRMS [EI-(+)] calcd for $C_{19}H_{16}O_3$ 292.1099, found 292.1116.

*10-Methoxy-6H-benzo[d]naphtho[1,2-b]pyran-6-one-8-carbaldehyde (**16**).* To a mixture of **20** (0.19 g, 0.62 mmol) and celite (0.20 g) in CH_2Cl_2 (10 mL) was added PCC (0.33 g, 1.5 mmol) in several portions, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was gravity filtered, and the filter cake was washed repeatedly with $CHCl_3$ (3×). The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (4% methanol/$CHCl_3$). The product was triturated with ether (3 × 1 mL) to afford **16** (0.14 g, 74%) as a pale yellow solid. R_f = 0.30 (30% ethyl acetate/hexanes); mp 238−241 °C; IR (neat) ν = 1722 (m), 1688 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.11 (s, 1H), 9.03 (d, J = 9.1 Hz, 1H), 8.64−8.62 (m, 1H), 8.59 (s, 1H), 7.89−7.88 (m, 1H), 7.83 (s, 1H), 7.74 (d, J = 9.1 Hz, 1H), 7.66−7.64 (m, 2H), 4.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.4, 160.3, 158.1, 148.0, 136.2, 134.4, 130.3, 128.6, 127.3, 127.1, 126.9, 124.5, 124.0, 123.33, 123.31, 122.7, 112.8, 112.6, 56.5; ESI-(+)-MS m/z (%) 305 (7, $[M+H]^+$), 102 (100); HRMS [EI-(+)] calcd for $C_{19}H_{12}O_4$ 304.0736, found 304.0725.

*10-Methoxy-8-vinyl-6H-benzo[d]naphtho[1,2-b]pyran-6-one (**21**).* A mixture of PPh_3MeBr (0.59 g, 1.7 mmol) and DBU (0.30 g, 2.0 mmol) in CH_2Cl_2 (8.0 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, and **16** (0.10 g, 0.32 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 16 h. The reaction

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mixture was diluted with $CHCl_3$ (50 mL) and washed with aqueous 1.0 M HCl solution (1×). The organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (CH_2Cl_2) to afford **21** (70 mg, 70%) as a colorless solid. R_f = 0.50 (30% ethyl acetate/hexanes); mp 202−205 °C; IR (neat) ν = 1718 (s), 1599 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.96 (d, J = 9.1 Hz, 1H), 8.60 (dd, J = 7.1, 2.2 Hz, 1H), 8.16 (d, J = 1.7 Hz, 1H), 7.85 (dd, J = 6.8, 2.3 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.62−7.57 (m, 2H), 7.36 (d, J = 1.7 Hz, 1H), 6.81 (dd, J = 17.5, 10.8 Hz, 1H), 5.95 (d, J = 17.5 Hz, 1H), 5.44 (d, J = 10.8 Hz, 1H), 4.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.5, 157.8, 146.7, 138.7, 135.6, 133.8, 127.8, 127.4, 126.8, 124.7, 124.4, 123.8, 123.7, 123.4, 122.6, 120.7, 116.5, 114.2, 113.5, 56.3; APCI-(+)-MS m/z (%) 303 (100, $[M + H]^+$); HRMS [EI-(+)] calcd for $C_{20}H_{14}O_3$ 302.0943, found 302.0934.

*5-Hydroxy-1,4-naphthoquinone (Juglone) (**11**).* This compound was both purchased and synthesized using the following procedure, which is a modified version of a literature procedure.[49] To a mechanically stirred suspension of 1,5-dihydroxynaphthalene (17.5 g, 109 mmol) in acetonitrile (260 mL) was added freshly prepared CuCl[53] (6.50 g, 65.7 mmol) and a strong current of O_2 gas was bubbled through the reaction mixture for 2 h. The reaction mixture was vacuum filtered through a plug of celite, and the filter cake was washed thoroughly with $CHCl_3$ (500 mL). The filtrate was concentrated under reduced pressure, and the residue was subjected to column chromatography ($CHCl_3$) to afford **11** (8.51 g, 45%) as an orange solid. R_f = 0.60 (30% ethyl acetate/hexanes); mp 147−152 °C (lit. mp[49] 154−161 °C); ^1H NMR ($CDCl_3$, 500 MHz) δ 11.90 (s, 1H), 7.66−7.61 (m, 2H), 7.29 (dd, J = 7.8, 1.9 Hz, 1H), 6.96 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 184.3, 161.5, 139.6, 138.7, 136.6, 131.8, 124.5, 119.2, 115.0; HRMS [EI-(+)] calcd for $C_{10}H_6O_3$ 174.0317, found 174.0320.

*5-(Methoxymethoxy)-1,4-naphthoquinone (**22**).* To a 0 °C solution of **11** (5.00 g, 28.7 mmol) and MOMCl (5.78 g, 71.8 mmol) in CH_2Cl_2 (80 mL) was added iPr_2NEt (7.43 g, 57.5 mmol) dropwise over 15 min, and the reaction mixture was stirred at room temperature for 14 h. To this mixture was added saturated aqueous NH_4Cl solution (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (1×), and the combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (25% ethyl acetate/hexanes). The product was triturated with hexanes (2 × 15 mL) to afford **22** (5.80 g, 92%). R_f = 0.30 (30% ethyl acetate/hexanes); mp 98−101 °C (lit. mp[50] 102.5−103 °C); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 7.67 (dd, J = 8.5, 7.5 Hz, 1H), 7.54 (d, J = 8.4, 1.2 Hz, 1H), 6.89 (d, J = 10.3 Hz, 1H), 6.86 (d, J = 10.3 Hz, 1H), 5.36 (s, 2H), 3.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.0, 184.2, 157.1, 140.8, 136.4, 134.7, 134.0, 122.3, 120.7, 120.5, 95.1, 56.6; HRMS [EI-(+)] calcd for $C_{12}H_{10}O_4$ 218.0579, found 218.0582.

*4-Acetoxy-8-(methoxymethoxy)-1-naphthol (**23**).* To a mixture of **22** (1.00 g, 4.59 mmol) and zinc (3.00 g, 45.9 mmol) in $CHCl_3$ (30 mL) was added acetic anhydride (0.93 g, 9.1 mmol) and pyridine (0.89 g, 11 mmol). The resulting mixture was heated at gentle reflux for 20 min. The reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (60 mL), and washed with cold aqueous 1.0 M HCl solution (1×). The layers were separated, and the organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (20% ethyl acetate/hexanes) to afford **23** (0.90 g, 75%) as an off-white solid. R_f = 0.40 (30% ethyl acetate/hexanes); mp 92−93 °C; IR (neat) ν = 1753 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.26 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.45 (s, 2H), 3.58 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 153.8, 152.3, 138.7, 129.3, 126.6, 120.0, 115.9, 115.7, 109.5, 108.4, 95.8, 56.9, 20.9; APCI-(−)-MS m/z (%) 261 (100, $[M - 1]^-$); HRMS [EI-(+)] calcd for $C_{14}H_{14}O_5$ 262.0841, found 262.0844.

*1-Acetoxy-4-methoxy-5-(methoxymethoxy)naphthalene (**24**).* To a solution of **23** (1.00 g, 3.82 mmol) in acetone (20 mL) was added K_2CO_3 (2.63 g, 19.0 mmol) and Me_2SO_4 (3.85 g, 30.5 mmol), and the mixture was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (10% ethyl acetate/hexanes to remove excess dimethyl sulfate, then 25% ethyl acetate/hexanes to elute the product), and the product was triturated with hexanes (2 × 5 mL) to afford **24** (1.02 g, 97%) as a colorless solid. R_f = 0.35 (30% ethyl acetate/hexanes); mp 55−57 °C; IR (neat) ν = 1748 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 5.26 (s, 2H), 3.96 (s, 3H), 3.60 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 154.8, 154.2, 140.0, 130.1, 127.1, 119.4, 118.4, 115.6, 114.1, 105.3, 96.8, 56.6, 56.4, 21.0; ESI-(+)-MS m/z (%) 299 (100, $[M + Na]^+$); HRMS [EI-(+)] calcd for $C_{15}H_{16}O_5$ 276.1008, found 276.0995.

*4-Methoxy-5-(methoxymethoxy)-1-naphthol (**25**).* A 0 °C solution of **24** (2.20 g, 7.97 mmol) in methanol (25 mL) was purged with nitrogen for 15 min, and then, K_2CO_3 (1.21 g, 8.75 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 20 min, and the solvent was removed under reduced pressure. Cold deionized water (50 mL) was added slowly to the residue, and the resulting mixture was extracted with ethyl acetate (3×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (25% ethyl acetate/hexanes) to afford **25** (1.50 g, 80%) as an off-white solid. R_f = 0.30 (30% ethyl acetate/hexanes); mp 108−111 °C; IR (neat) ν = 3413 (br, s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, J = 8.4 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.26 (s, 2H), 4.94 (s, 1H), 3.91 (s, 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7, 150.8, 145.4, 127.8, 125.9, 119.6, 116.5, 114.5, 108.6, 107.2, 97.0, 57.4, 56.4; APCI-(−)-MS m/z (%) 233 (100, $[M - 1]^-$); HRMS [EI-(+)] calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.0887.

*1-Hydroxy-4-methoxy-5-(methoxymethoxy)-2-naphthaldehyde (**9**).* Acetonitrile (21 mL) was purged with nitrogen for a period of 15 min, and then, **25** (0.70 g, 3.0 mmol) was added, followed by *para*-formaldehyde (0.62 g, 21 mmol) and triethylamine (1.50 g, 14.9 mmol). The resulting mixture was heated at 60 °C for 2 h with vigorous stirring. The reaction mixture was cooled to 0 °C and diluted with cold ethyl acetate (30 mL). To the resulting mixture was added slowly cold

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saturated aqueous NH_4Cl solution (20 mL), followed by cold aqueous 1.0 M HCl solution (10 mL). The layers were separated, and the aqueous layer was washed with ethyl acetate (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (30% ethyl acetate/hexanes). The product was triturated with hexanes (2 × 3 mL) to afford **9** (0.49 g, 63%) as a yellow solid. R_f = 0.40 (30% ethyl acetate/hexanes); mp 91−94 °C, IR (neat) ν = 1646 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 12.24 (s, 1H), 9.93 (s, 1H), 8.19 (dd, J = 8.4, 1.2 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.35 (dd, J = 7.7, 1.2 Hz, 1H), 6.83 (s, 1H), 5.26 (s, 2H), 3.96 (s, 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.9, 156.2, 153.8, 149.8, 128.1, 127.0, 123.1, 119.09, 119.05, 113.2, 105.1, 97.1, 57.1, 56.5; APCI-(−)-MS m/z (%) 261 (100, $[M - 1]^-$); HRMS [EI-(+)] calcd for $C_{14}H_{14}O_5$ 262.0841, found 262.0844.

*Methyl (E)-4-Methoxy-5-(methoxymethoxy)-3-(6H-naphtho[1,2-b]pyran-6-on-5-yl)acrylate (**7**).* To a solution of **9** (0.78 g, 3.0 mmol) and dimethyl glutaconate (**10**) (0.94 g, 5.9 mmol) in THF (15 mL) was added piperidine (0.26 g, 3.0 mmol), and the resulting mixture was stirred at room temperature for 1 h and then heated at 70 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with $CHCl_3$ (350 mL), and washed with cold aqueous 1.0 M HCl solution (1×). The layers were separated, and the organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was slurried with diethyl ether (20 mL), stirred for 10 min, and vacuum filtered. This process (ether addition, stirring, and filtration) was repeated to afford **7** (0.96 g, 87%) as a yellow solid. R_f = 0.30 (50% ethyl acetate/hexanes); mp 184−187 °C; IR (neat) ν = 1714 (m), 1697 (s), 998 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.26 (d, J = 8.3 Hz, 1H), 7.90 (s, 1H), 7.62 (d, J = 15.9 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 15.8 Hz, 1H), 6.74 (s, 1H), 5.29 (s, 2H), 4.01 (s, 3H), 3.83 (s, 3H), 3.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6, 159.2, 154.3, 153.9, 145.8, 144.0, 138.3, 128.3, 126.2, 122.9, 122.2, 120.5, 117.2, 117.1, 114.5, 101.4, 96.8, 56.6, 56.6, 51.9; APCI-(+)-MS m/z (%) 371 (50, $[M + H]^+$, 50), 339 (100); HRMS [CI-(+)] calcd for $C_{20}H_{19}O_7$ 371.1131, found 371.1136.

*10,12-Dimethoxy-1-(methoxymethoxy)-6H-benzo[d]-naphtho[1,2-b]pyran-6-one-8-carboxylic Acid Methyl Ester (**6**).* A mixture of dimethoxyacetaldehyde (2.35 g, 13.5 mmol, 60% solution in water) and piperidine (0.92 g, 11 mmol) in benzene (40 mL) was heated at reflux for 1 h using a Dean−Stark apparatus. Approximately 30 mL of solvent was removed from the reaction flask through the Dean−Stark apparatus. The reaction mixture was cooled to room temperature, and **7** (0.50 g, 1.4 mmol) was added in one portion. The resulting mixture was then heated at reflux for 48 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (400 mL) and washed with water (1×). The organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (5% methanol/$CHCl_3$). Diethyl ether (20 mL) was added to the residue, and the mixture was stirred well for 10 min and vacuum filtered. This process (ether addition to the solids, stirring, and filtration) was repeated to afford **6** (0.51 g, 89%) as an orange solid. R_f = 0.30 (50% ethyl acetate/hexanes); mp 222−225 °C; IR (neat) ν = 1735 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.76 (d, J = 1.7 Hz, 1H), 8.41 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 1.7 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.26−7.24 (m, 1H), 5.30 (s, 2H), 4.15 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 160.8, 157.6, 153.9, 152.9, 142.2, 130.7, 128.4, 127.6, 126.8, 124.5, 123.5, 119.6, 117.3, 116.9, 116.1, 113.0, 104.3, 97.1, 56.80, 56.76, 56.7, 52.8; APCI-(+)-MS m/z (%) 425 (58, $[M + H]^+$), 393 (100); HRMS [CI-(+)] calcd for $C_{23}H_{21}O_8$ 425.1236, found 425.1248.

*10,12-Dimethoxy-1-(methoxymethoxy)-6H-benzo[d]-naphtho[1,2-b]pyran-6-one-8-carboxylic Acid (**26**).* A suspension of **6** (0.11 g, 0.26 mmol) in 10% KOH/methanol (3.0 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, and a majority of the solvent was removed under reduced pressure. The residue was cooled to 0 °C, and cold water (1 mL) was added dropwise to dissolve the residue. The pH was adjusted to ∼4.0 using cold aqueous 1.0 M HCl solution. The yellow precipitate that formed was isolated by suction filtration. The solids were vacuum-dried for 2 h and then dried under air in an oven at 90−100 °C for 12 h to afford **26** (91 mg, 86%) as a pale yellow solid. R_f = 0.20 (ethyl acetate); mp 197−200 °C; IR (neat) ν = 3300−2400 (br, w), 1733 (m), 1689 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 8.41 (d, J = 1.6 Hz, 1H), 8.34 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 1.7 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.24 (d, J = 7.7 Hz, 1H), 5.29 (s, 2H), 4.14 (s, 3H), 3.95 (s, 3H), 3.52 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.9, 159.6, 157.1, 153.5, 152.2, 140.7, 131.7, 127.7, 126.5, 125.7, 122.7, 118.2, 116.8, 115.4, 114.7, 112.5, 103.2, 95.9, 56.6, 56.1, 56.0; ESI-(−)-MS m/z (%) 409 (100, $[M - 1]^-$); MALDI-TOF HRMS calcd for $C_{22}H_{18}O_8$ 410.1002, found 410.0991.

*8-(Hydroxymethyl)-10,12-dimethoxy-1-(methoxymethoxy)-6H-benzo[d]naphtho[1,2-b]pyran-6-one-8-carboxylic Acid (**27**).* To a 0 °C suspension of **26** (80 mg, 0.20 mmol) in THF (8.0 mL) was added $H_3B{\cdot}SMe_2$ (0.60 mL, 1.2 mmol) dropwise over a period of 5 min, and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was cooled to 0 °C, methanol (1 mL) was added dropwise, and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL), and the resulting solution was washed with aqueous $NaHCO_3$ solution (1×), dried over Na_2SO_4, and gravity filtered. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (2% methanol/$CHCl_3$). The product was triturated with ether (2 × 1 mL) to afford **27** (40 mg, 51%) as a pale yellow solid. R_f = 0.50 (ethyl acetate); mp 165−168 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, J = 8.7 Hz, 1H), 8.10 (s, 1H), 7.88 (s, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.06 (s, 1H), 5.30 (s, 2H), 4.69 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.67 (s, 3H), 2.55 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.1, 157.1, 153.4, 151.8, 142.8, 140.5, 126.9, 126.5, 122.9, 122.8, 119.5, 118.6, 117.1, 116.0, 114.5, 113.3, 103.8, 97.2, 64.4, 56.6, 56.1, 55.9; APCI-(+)-MS m/z (%) 397 (95, $[M + H]^+$), 214 (100); HRMS [EI-(+)] calcd for $C_{22}H_{20}O_7$ 396.1209, found 396.1222.

*10,12-Dimethoxy-1-(methoxymethoxy)-6H-benzo[d]-naphtho[1,2-b]pyran-6-one-8-carbaldehyde (**28**).* To a mixture of **27** (60 mg, 0.15 mmol) and celite (100 mg) in CH_2Cl_2 (8.0 mL) was added PCC (65 mg, 0.30 mmol) in three portions, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was gravity filtered, and the filter cake was washed thoroughly with $CHCl_3$. The solvent was removed under reduced pressure, and the residue

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was subjected to column chromatography (2% methanol/$CHCl_3$). The residue was triturated with diethyl ether (2 × 1 mL) to afford **28** (44 mg, 73%) as a yellow solid. R_f = 0.40 (50% ethyl acetate/hexanes); mp 200−203 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.10 (s, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.44 (s, 1H), 8.33 (d, J = 8.9 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.55 (t, J = 8.5 Hz, 1H), 7.29−7.28 (m, 1H), 5.31 (s, 2H), 4.18 (s, 3H), 4.05 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 160.2, 157.9, 153.6, 152.7, 142.3, 136.1, 129.8, 127.5, 127.1, 126.5, 123.6, 119.5, 117.0, 116.0, 112.6, 103.8, 96.7, 56.51, 56.45, 56.4; APCI-(+)-MS m/z (%) 395 (52, $[M + H]^+$), 394 (100), 363 (99); HRMS [EI-(+)] calcd for $C_{22}H_{18}O_7$ 394.1053, found 394.1067.

*10,12-Dimethoxy-1-(methoxymethoxy)-8-vinyl-6H-benzo-[d]naphtho[1,2-b]pyran-6-one (**29**).* A mixture of PPh_3MeBr (135 mg, 0.38 mmol) and DBU (68 mg, 0.45 mmol) in CH_2Cl_2 (2.5 mL) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, and **28** (25 mg, 0.06 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 16 h and then heated at reflux for 2 h. The reaction mixture was cooled to room temperature and diluted with $CHCl_3$ (20 mL). The resulting mixture was washed with aqueous 1.0 M HCl solution (1×), and the layers were separated. The organic layer was dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was triturated with ether (2 × 0.5 mL). ^{1}H NMR analysis of the residue showed the presence of starting material (ca. 10%), so the material was resubjected to the original reaction conditions using freshly prepared ylide. This time, the reaction mixture was refluxed first for 3 h and then stirred at room temperature for 12 h. The workup was performed as before. The residue was subjected to column chromatography (2% methanol/$CHCl_3$), and the product was triturated with ether (2 × 1 mL) to afford **29** (19 mg, 76%) as a yellow solid. R_f = 0.60 (50% ethyl acetate/hexanes); mp 184−187 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.44 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.38 (s, 1H), 7.25−7.22 (m, 1H), 6.82 (dd, J = 17.6, 11.1 Hz, 1H), 5.96 (d, J = 18.4 Hz, 1H), 5.45 (d, J = 11.0 Hz, 1H), 5.31 (s, 2H), 4.13 (s, 3H), 4.04 (s, 3H), 3.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 157.5, 153.6, 152.5, 141.0, 138.6, 135.4, 127.2, 126.7, 123.9, 123.5, 120.7, 118.8, 117.0, 116.4, 115.5, 114.1, 113.4, 104.3, 96.9, 56.6, 56.5, 56.3; APCI-(+)-MS m/z (%) 393 (100, $[M + H]^+$); HRMS [EI-(+)] calcd for $C_{23}H_{20}O_6$ 392.1260, found 392.1272.

*N-10,12-Trimethoxy-1-(methoxymethoxy)-N-methyl-6H-benzo[d]naphtho[1,2-b]pyran-6-one-8-carboxamide (**30**).* To a solution of EDCI·HCl (23 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added DIPEA (47 mg, 0.36 mmol), and the resulting mixture was stirred at room temperature for 15 min. Carboxylic acid **26** (25 mg, 0.061 mmol) was added, and the resulting mixture was stirred for 30 min. *N,O*-Dimethylhydroxylamine hydrochloride (18 mg, 0.18 mmol) was then added in three portions, and the reaction mixture was stirred for a further 16 h. The reaction mixture was diluted with $CHCl_3$ (15 mL) and washed with aqueous 1.0 M HCl solution (1×). The layers were separated, and the aqueous layer was washed with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (1% methanol/$CHCl_3$). The product was triturated with ether (2 × 0.5 mL) to afford **30** (11 mg, 40%) as a pale yellow solid. R_f = 0.40 (ethyl acetate); mp 134−137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, J = 1.7 Hz, 1H), 8.47 (s, 1H), 8.34 (dd, J = 8.5, 1.1 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.53 (t, J = 8.1 Hz, 1H), 7.27−7.24 (m, 1H), 5.31 (s, 2H), 4.15 (s, 3H), 4.05 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9, 160.8, 157.2, 153.6, 152.6, 141.7, 134.4, 127.4, 126.7, 126.5, 123.0, 122.6, 119.2, 117.0, 116.9, 115.7, 112.9, 104.3, 96.9, 61.5, 56.63, 56.55, 56.5, 33.8; APCI-(+)-MS m/z (%) 454 (96, $[M + H]^+$), 422 (100); HRMS [EI-(+)] calcd for $C_{24}H_{23}NO_8$ 453.1424, found 453.1421.

*1-Hydroxy-10,12-dimethoxy-6H-benzo[d]naphtho[1,2-b]-pyran-6-one-8-carboxylic Acid Methyl Ester (**31**).* To a −78 °C solution of **6** (100 mg, 0.24 mmol) in CH_2Cl_2 (20 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 1.2 mL, 1.2 mmol) dropwise, and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred for an additional 30 min. To this mixture was added cold water (15 mL) and then $CHCl_3$ (25 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (2% methanol/$CHCl_3$). The product was triturated with ether (2 × 2 mL) to afford **31** (81 mg, 87%) as a yellow solid. R_f = 0.30 (50% ethyl acetate/hexanes); mp 258−261 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.28 (s, 1H), 8.69 (d, J = 1.6 Hz, 1H), 8.26 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 4.12 (s, 3H), 4.11 (s, 3H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 160.4, 157.1, 154.2, 152.0, 142.7, 130.5, 128.8, 127.9, 126.0, 124.2, 123.1, 116.6, 115.3, 113.7, 113.4, 112.1, 101.4, 56.6, 56.1, 52.6; APCI-(+)-MS m/z (%) 381 (70, $[M + H]^+$), 214 (100); HRMS [EI-(+)] calcd for $C_{21}H_{16}O_7$ 380.0896, found 380.0905.

*1-Hydroxy-10,12-dimethoxy-6H-benzo[d]naphtho[1,2-b]-pyran-6-one-8-carboxaldehyde (**32**).* To a −78 °C solution of **28** (11 mg, 0.028 mmol) in CH_2Cl_2 (3.0 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 0.25 mL, 0.25 mmol) dropwise, and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred for an additional period of 30 min. To this mixture was added cold water (10 mL) and then $CHCl_3$ (15 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (2% methanol/$CHCl_3$); the product was triturated with ether (2 × 1 mL) to afford **32** (8 mg, 82%) as a yellow solid. R_f = 0.45 (50% ethyl acetate/hexanes); mp 269−271 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.11 (s, 1H), 9.35 (s, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 4.19 (s, 3H), 4.17 (s, 3H); APCI-(+)-MS m/z (%) 351 (16, $[M + H]^+$), 214 (100); HRMS [EI-(+)] calcd for $C_{20}H_{14}O_6$ 350.0790, found 350.0799.

*1-Hydroxy-10,12-dimethoxy-8-vinyl-6H-benzo[d]naphtho-[1,2-b]pyran-6-one (Defucogilvocarcin V) (**5c**).* To a −78 °C solution of **29** (14 mg, 0.035 mmol) in CH_2Cl_2 (4.0 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 0.30 mL, 0.30 mmol) dropwise, and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred for an additional min. To this mixture was added cold water (10 mL) and then $CHCl_3$ (15 mL). The layers were separated, and the aqueous layer was

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extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (2% methanol/$CHCl_3$). The product was triturated with ether (2 × 1 mL) to afford **5c** (10 mg, 83%) as a yellow solid. R_f = 0.65 (50% ethyl acetate/hexanes); mp 240−245 °C (lit. mp[15] 253−257 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.30 (s, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.27 (s, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.76 (dd, J = 17.7, 10.7 Hz, 1H), 5.92 (d, J = 17.5 Hz, 1H), 5.43 (d, J = 10.9 Hz, 1H), 4.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.1, 157.2, 154.2, 151.8, 141.5, 138.6, 135.3, 128.5, 126.0, 123.5, 123.2, 120.5, 116.4, 114.7, 113.9, 113.4, 112.7, 101.4, 56.1, 55.9; APCI-(+)-MS m/z (%) 349 (100, $[M + H]^+$); HRMS [EI-(+)] calcd for $C_{21}H_{16}O_5$ 348.0998, found 348.1013.

*1-Hydroxy-N-10,12-trimethoxy-N-methyl-6H-benzo[d]-naphtho[1,2-b]pyran-6-one-8-carboxamide (**33**).* To a −78 °C solution of **30** (9 mg, 0.02 mmol) in CH_2Cl_2 (2.0 mL) was added BCl_3 (1.0 M solution in CH_2Cl_2, 0.20 mL, 0.20 mmol) dropwise, and the resulting mixture was stirred at this temperature for 1 h. The reaction mixture was cooled to room temperature and stirred for an additional 30 min. To this mixture was added cold water (10 mL) and then $CHCl_3$ (15 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic layers were dried over Na_2SO_4 and gravity filtered. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (1% methanol/$CHCl_3$). The product was triturated with hexanes (2 × 1 mL) to afford **33** (5 mg, 63%) as a pale yellow solid. R_f = 0.40 (ethyl acetate); mp 178−181 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 (s, 1H), 8.51 (d, J = 1.7 Hz, 1H), 8.38 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 4.15 (s, 3H), 3.67 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 160.6, 157.0, 154.2, 152.0, 142.4, 134.4, 128.7, 126.3, 126.1, 122.9, 122.7, 116.9, 115.2, 113.7, 113.2, 112.3, 101.6, 100.0, 61.5, 56.6, 56.1, 33.8; APCI-(+)-MS m/z (%) 410 (100, $[M + H]^+$); HRMS [EI-(+)] calcd for $C_{22}H_{19}NO_7$ 409.1162, found 409.1153.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for compounds **5c**, **6**, **7**, **9**, **11**, and **13**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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