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Alternative Spiroketalization Methods toward Purpuromycin: A Diketone Approach To Prevent Benzofuran Formation

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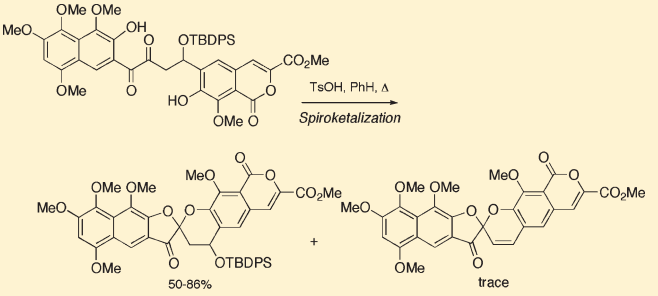
Supporting Information

ABSTRACT: The central portion of purpuromycin has been assembled via a classical spiroketalization reaction. Key to promoting this reaction mode versus benzofuran formation was the oxidation state of the spiroketal core. With a higher oxidation state, even the electron-deficient isocoumarin found in purpuromycin could be employed directly in the spiroketalization. The two halves of the spiroketalization precursor were joined via a nitrile oxide/styrene 1,3-dipolar cycloaddition. A very mild selenium dioxide oxidation was used to introduce the required oxidation state of the spiroketal core.



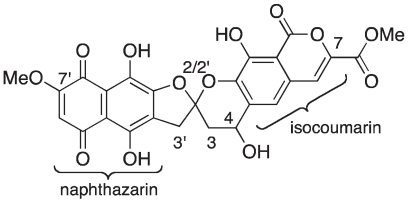
INTRODUCTION

The spiroketal purpuromycin (**1**, Figure 1),[1,2] a member of a unique class of highly oxidized aromatic polyketides, has been the subject of much inquiry.[3] In particular, the inability to directly form the central portion of the molecule by conventional spiroketalization has driven several innovative alternative approaches.[4−6] Nonetheless, the central question remains as to why spiroketalization fails.

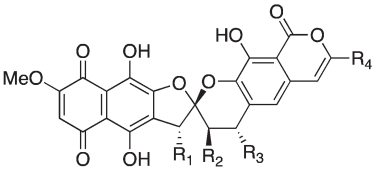
The lack of spiroketalization reaction in the rubromycin family of compounds has been previously attributed primarily to the nucleophilicity of the two phenols (Figure 2).[3,7,8] Namely, the electron-poor isocoumarin phenol was hypothesized to be a poor partner in the spiroketalization, rendering the first step of path b unlikely and also impeding the third step of path a.

Our recent work toward the total synthesis of purpuromycin (see companion paper, DOI 10.1021/jo200398v),[9] however, produced some new insight into the activity of the two phenols and other intermediates involved in spiroketalization. Specifically, we discovered that the more nucleophilic phenol of the naphthalene does not hemiketalize (top, Figure 3) as judged by NMR spectroscopy. The less nucleophilic phenol on an isocoumarin model, however, readily forms the hemiketal (bottom, Figure 3).[9] This result implies that the six-membered hemiketal ring from the isocoumarin phenol (i.e., intermediate **4** in Figure 2) forms easily, while the five-membered hemiketal ring from the naphthalene (i.e., intermediate **3** in Figure 2) is difficult to achieve. As a consequence, it is clear that the nucleophilicities of the phenols are not the sole factor controlling the spiroketalization.

Furthermore, calculations showed that the pyran oxocarbenium (**6**) was 11.6 kcal/mol lower in energy than the furan oxocarbenium (**5**). These results are in accord with the NMR observations illustrated in Figure 3 and indicate that the five-membered ring



Purpuromycin 1



Compound	R_1	R_2	R_3	R_4
γ-Rubromycin	H	H	H	CO_2Me
Heliquinomycinone	OH	OH	H	CO_2Me
Griseorhodin C	OH	OH	OH	CH_3

Figure 1. Rubromycin family.

compounds (i.e., **3**, **5**, **10**) are generally less stable than the six-membered ring compounds (i.e., **4**, **6**, **12**), primarily due to ring strain. However, this finding is not consistent with the observed preference for formation of naphthofurans similar to **7** in other systems.[7] The controlling factor for the cyclization appears to be the energy of activation required to convert the oxocarbenium into a spiroketal or naphthofuran. The transition state from favored

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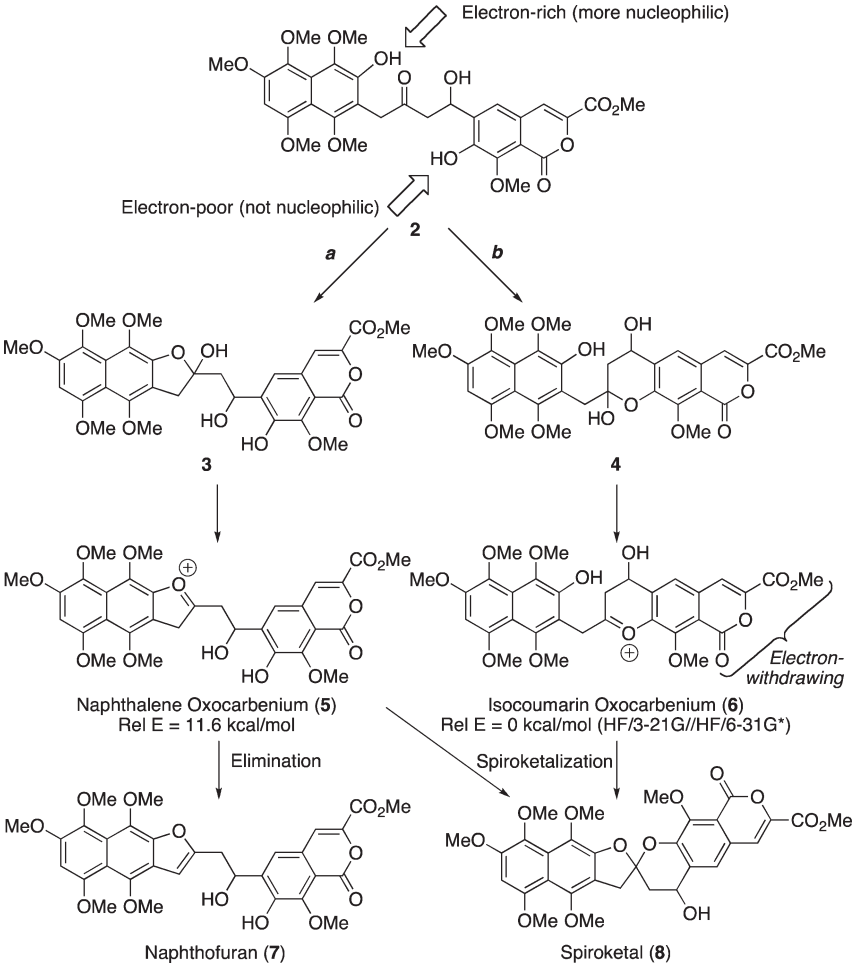

Figure 2. Potential spiroketalization pathways.

oxocarbenium **6** to spiroketal **8** is likely high in energy because significant steric hindrance and strain evolves as the phenol aligns for the S_N1 closure. If the formation of oxocarbenium **5** is energetically competitive with this transition state, then the E1 elimination pathway to naphthofuran **7**, which avoids a loss of rotational freedom, will predominate over the S_N1 closure to spiroketal **8**.

Assuming that the manifold in Figure 2 is under equilibrium, it should be possible to convert naphthofuran **7** into spiroketal **8**. Indeed, Brockmann[3] showed that benzofurans are capable of entering into a spiroketalization with a phenolic group in simple model systems. The work of Danishefsky, however, showed that the complete isocoumarin of purpuromycin would not directly add to a naphthofuran (i.e., **7** to **8** in Figure 2).[4] This inability to spiroketalize is not due to the inability of the isocoumarin phenol to attack the naphthalene oxocarbenium (**5**, Figure 2), but rather because the electron-rich naphthalene is unstable, either decomposing or oxidatively demethylating to the naphthoquinone under strenuous conditions.' The spiroketal isolated by Reissig and co-workers supports this argument, as the isolated product has also undergone oxidation to the quinone.[3,8] This tempering of the inherent electron-rich nature of the naphthalene is likely what allowed this compound to be formed and isolated. Supporting this electronic argument, Brimble and co-workers show that an electron-poor phenol is a competent spiroketalizing partner to a naphthalene phenol under mild conditions.[10]

Thus, our goals were to stabilize the naphthalene unit by decreasing its electron-rich character and to prevent benzofuran formation while using the intact isocoumarin unit to facilitate a convergent assembly. Using a diketone strategy to prevent elimination to the benzofuran, a method complementary to our other approaches,[9] we intend to show that the isocoumarin of purpuromycin can function as a competent nucleophile in a spiroketalization.

RESULTS AND DISCUSSION

Diketone Rationale. To prevent elimination of the naphthalene oxocarbenium to naphthofuran (i.e., **7** in Figure 2), we hypothesized that removal of the acidic protons on the methylene adjacent to the naphthalene ring would suppress the unwanted reaction pathway. The group used to replace the protons had to be easy to install and remove as well as being compatible with extant functionality. We chose a carbonyl group as we believed it would meet these requirements and not deleteriously alter the properties or size of the molecule (**13**, Figure 4). In fact, the electron-withdrawing carbonyl group would temper the electron-rich naphthalene, which is typically very reactive, as well as enhance the reactivity of the existing carbonyl group.

While the work of Danishesky and co-workers[4] indicated that the neutral form of **13** (i.e., **16**, Figure 5A) was accessible, two concerns remained. First, the indirect route employed by

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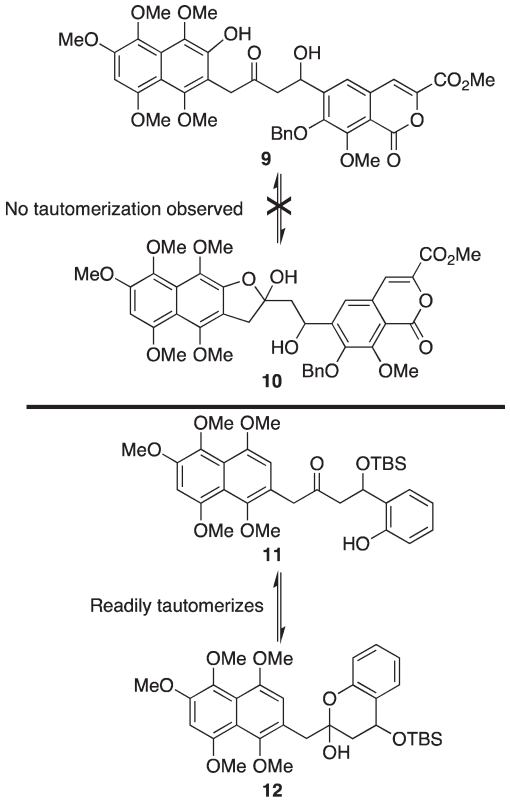


Figure 3. Comparison of hemiketalization from the different phenols.

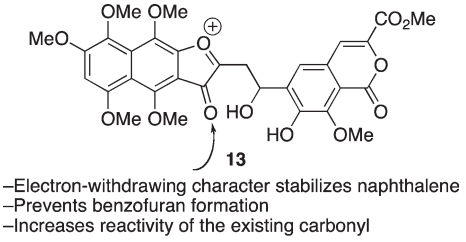


Figure 4. Diketone to prevent benzofuran formation.

Danishefsky and co-workers using a Mitsunobu reaction to establish the final spirocyclic bond raised questions as to whether similar intermediates could be achieved via conventional acidic spirocyclization protocols. As far as we can determine, no reports directly support the proposed transformation of diketone **18** (Figure 5B) in this type of system. In addition, the placement of the alkoxy substituent on the central core differs in the purpuromycin series, raising the possibility of *ortho*-quinone methide generation from intermediates such as **18** (Figure 5B). With the goal of examining if a diketone could facilitate the spiroketalization of the intact naphthalene and isocoumarin units of purpuromycin, and keeping in mind the considerations outlined above, the synthesis of **19** was undertaken from penultimate intermediate **18** (Figure 5B). Strategically, however, it was unclear whether it was better to install the requisite oxygen functionality on the naphthalene prior to or after 1,3-dipolar cycloaddition.

Diketone Generation after Fragment Union. With advanced intermediates in hand, it seemed most logical to introduce the diketone group at a late stage. Accordingly, oxidations of

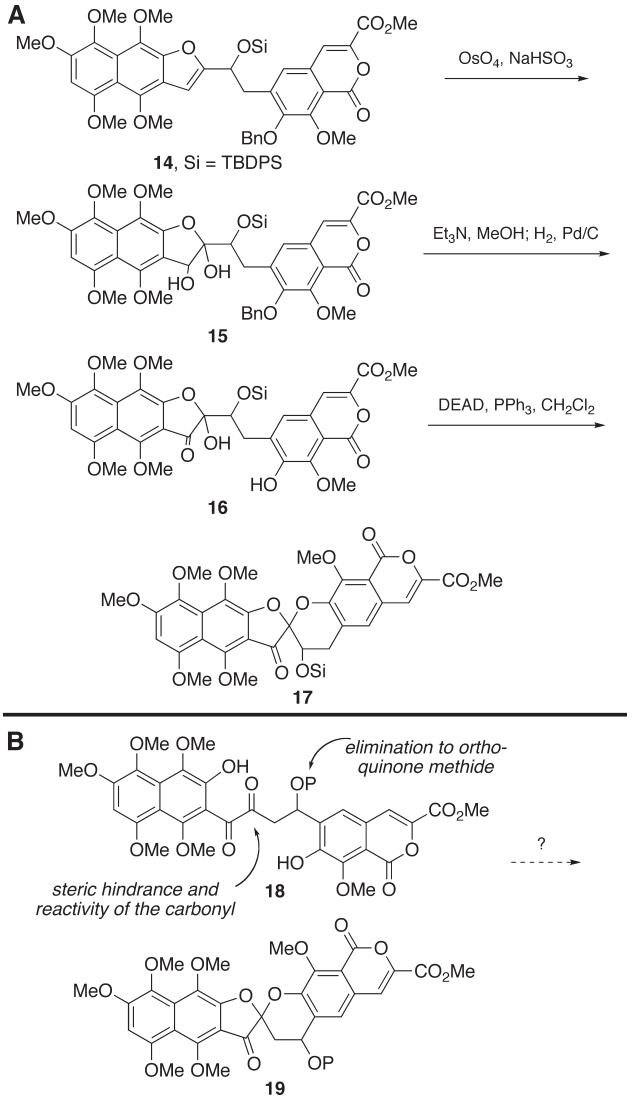


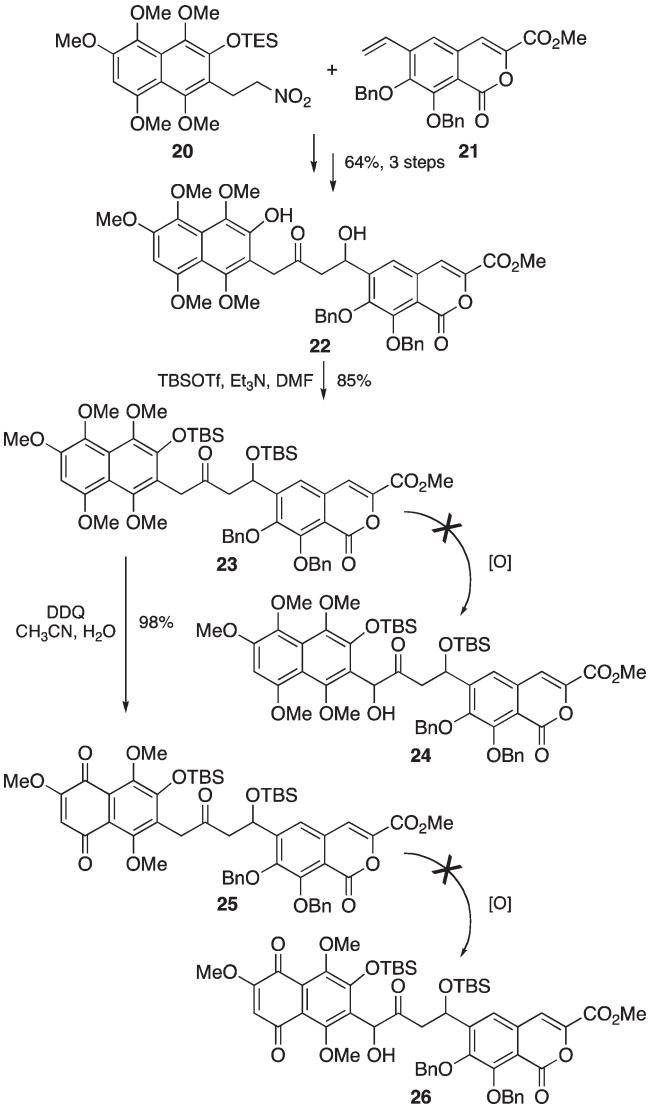
Figure 5. Comparison of strategies using a ketone blocking group.

protected intermediate **23** from our original 1,3-dipolar cycloaddition pathway,[7] as outlined in Scheme 1, were explored with the aim of generating benzyl alcohol **24**. Despite extensive experimentation with a variety of oxidants (including Oxone, PhNO, O_2, OsO_4, and *m*-CPBA), both pentamethoxy naphthalene **23** and its oxidized counterpart naphthoquinone **25**[7] failed to undergo the requisite benzylic oxidation.

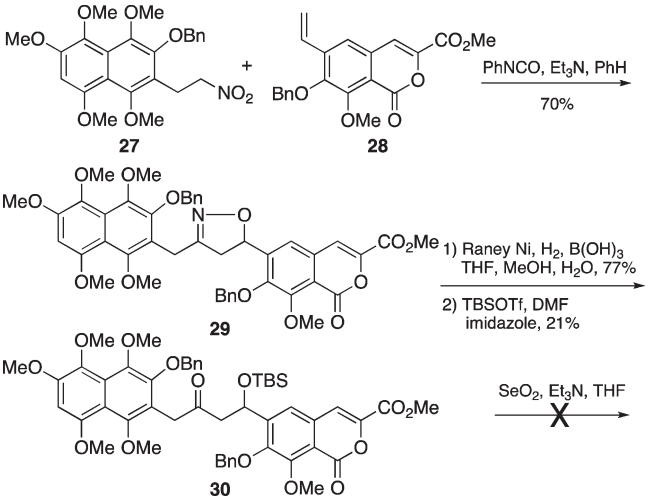
Encouraged by the discovery of a modification to the Riley reaction (vide infra Scheme 8),[11] compound **30** (differing from the successful candidate **63** in Scheme 11 by only an additional C4 methoxy group) was targeted for oxidation. Thus, isoxazoline **29** (Scheme 2) was synthesized via 1,3-dipolar cycloaddition and subjected to nickel cleavage and silylation. However, application of these new conditions to **30** failed to produce the 1,2-diketone.

Diketone Generation Prior to Fragment Union. We next attempted to introduce the requisite keto group, or a surrogate thereof, prior to fragment assembly (Scheme 3). Nitro alcohol **31**, which was available from our improved naphthalene synthesis,[12] failed to undergo cycloaddition and instead resulted in decomposition. All attempts to silylate **31** were unsuccessful.[12] Ketone **33** would cyclize with isocoumarin **21** to form isoxazoline

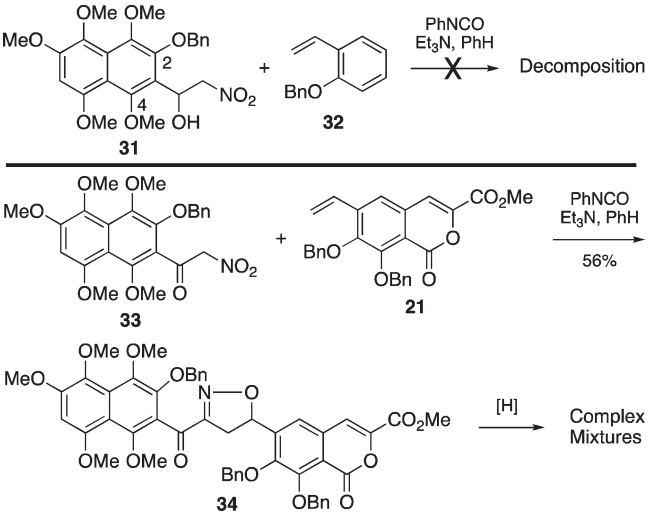
Scheme 1. Attempted Oxidation after Fragment Union of Existing Compounds



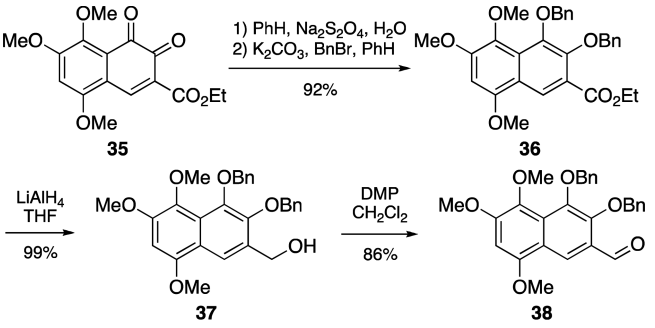
Scheme 2. Attempted Oxidation of the Di-*ortho* Substituted System with Selenium Dioxide



Scheme 3. Diketone Generation Prior to Fragment Union



Scheme 4. Synthesis of Mono-*ortho* Aldehyde 38



34 in moderate yield, but **34** proved highly resistant to selective reduction, yielding complex mixtures.

Construction of Diketones Lacking Naphthazarin C4-Substitution Prior to Fragment Union. From the above syntheses (Scheme 3), we concluded that reduction of the isoxazoline was impossible in the presence of an α-ketone. This seemed to be a significant setback, as other forms of oxygen functionality on the nitroethane were incompatible with 1,3-dipolar cycloaddition. For example, hydroxy nitro **31** would not cyclize, and it could not be protected.[12] We reasoned that our inability to protect **31** arose from the dense functionality of the naphthalene itself; the seven substituents prevented silylation of the benzylic alcohol **31**, specifically the C2 and C4 ethers flanking the C3 nitroethane. Further support for the steric hindrance can be found in the reluctance of **30** (Scheme 2) to undergo α-oxygenation. To test this hypothesis, we undertook the synthesis of a naphthalene without substitution at the C4 position.

Toward the construction of a C4 unsubstituted naphthalene, *ortho*-quinone **35**[12] (Scheme 4) was reduced and benzylated to produce **36**. Further reduction to alcohol **37** followed by oxidation with Dess–Martin periodinane (DMP)[13] proved to be the most efficient pathway to **38**. From aldehyde **38** (Scheme 5),

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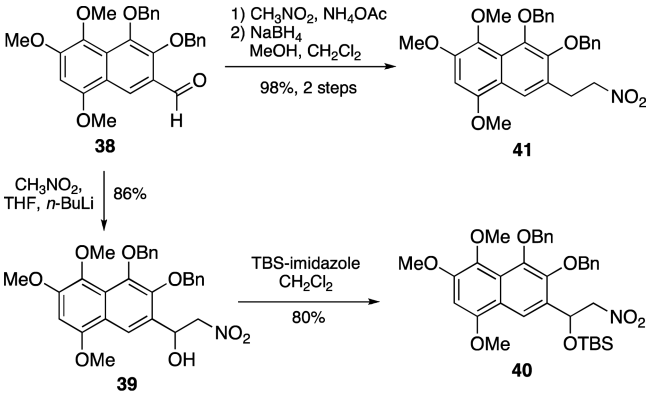
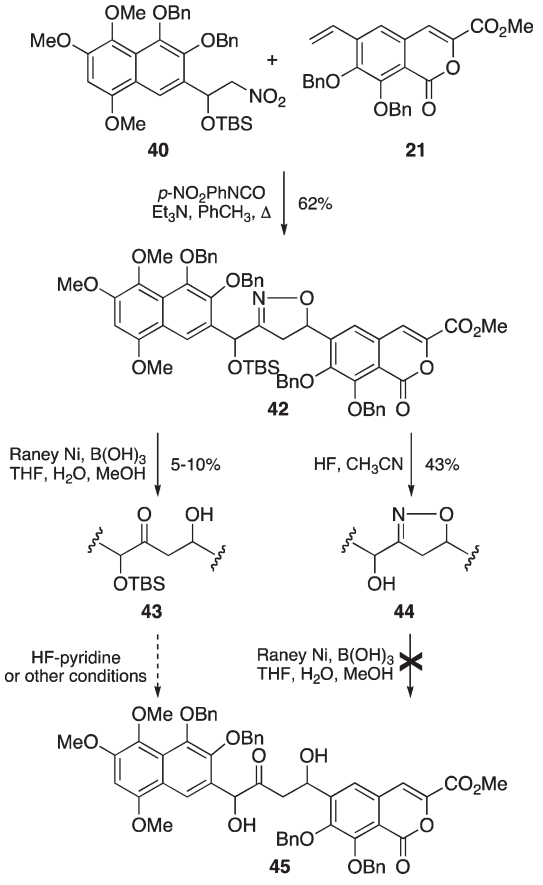
Scheme 5. Mono-*ortho* Naphthalene Elaboration



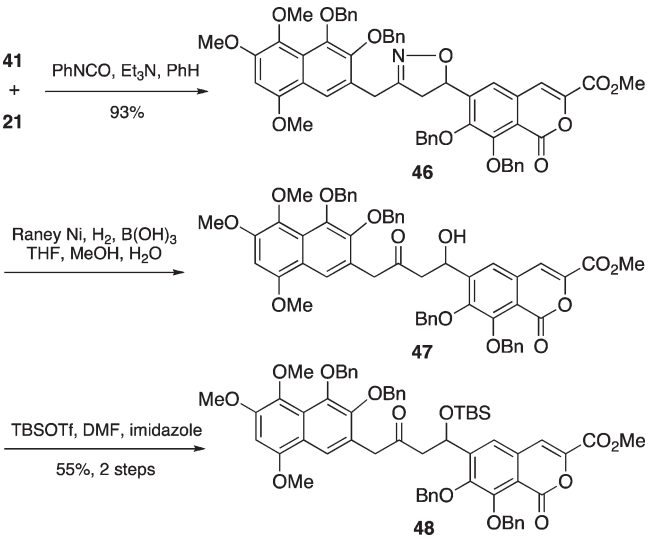
Scheme 6. Reduction with Existing Oxygen Functionality on the Mono-*ortho* Naphthalene



hydroxy nitro **39** could be readily produced by means of the Henry reaction. The highly reactive silylating agent *tert*-butyldimethylsilyl imidazole was effective in generating **40**, lending support to our steric hindrance hypothesis. The unsubstituted nitroalkane (**41**) could be synthesized as well via the eliminative Henry reaction and subsequent reduction.

Our first attempt to incorporate a mono-*ortho* substituted naphthalene involved **40** (Scheme 6), with the oxidized functionality present prior to cycloaddition. Cycloaddition was successful

Scheme 7. Cycloaddition and Elaboration of the Unoxidized, Mono-*ortho* Naphthalene



when a stronger dehydrating agent (*para*-nitro phenylisocyanate versus phenylisocyanate) was used along with more strenuous reaction conditions (toluene, reflux). With **42** in hand, we again attempted to reductively cleave the isoxazoline with Raney nickel. Unfortunately, this material still proved resistant to reduction. While trace amounts of **43** could be detected, the major product of this reaction was decomposition. Isoxazoline **42** could be desilylated, but **44** was likewise incompatible with reduction. All other reductants such as molybdenum hexacarbonyl also failed to effect reduction. From the results of this sequence combined with that described in Scheme 3, we concluded that any oxygen functionality α to the isoxazoline prohibited selective reduction.

Diketone Generation after Fragment Union from C4-Unsubstituted Naphthazarin. With the possibility of including the oxygen functionality to prevent benzofuran formation prior to 1,3-dipolar cycloaddition precluded, we again turned to oxidation of the naphthalene benzylic position after isoxazoline formation and subsequent cleavage. Reasoning that oxidation would be more facile with a less hindered benzylic position, compound **48**, which lacks C4 substitution, became a target of interest. As depicted in Scheme 7, naphthalene **41** and isocoumarin **21** were combined to form isoxazoline **46**. Raney nickel catalyzed cleavage gave **47** which was protected as silyl ether **48**.

Treatment of **48** (Scheme 8) with triethylamine and methanol-d_4 showed complete deuterium incorporation at the α positions of the ketone as well as transesterification of the isocoumarin methyl ester (**49**). Satisfied that enolization readily occurred, our attention turned to identifying a suitable oxidant. Our first approach was to generate the diketone via the benzylic alcohol (**50**). As treatment with sodium hexamethyldisilazane (NaHMDS) and the Davis oxaziridine caused decomposition instead of forming the requisite molecule, the search for oxidants broadened. Screening of oxidation conditions revealed a slight conversion to desired product **51** with selenium dioxide. Hypothesizing that the reaction would be more rapid with the enolate, we added triethylamine. Not only did this modification enable direct production of the diketone, but also the base allowed for much milder conditions than are typical for this reaction.[11]

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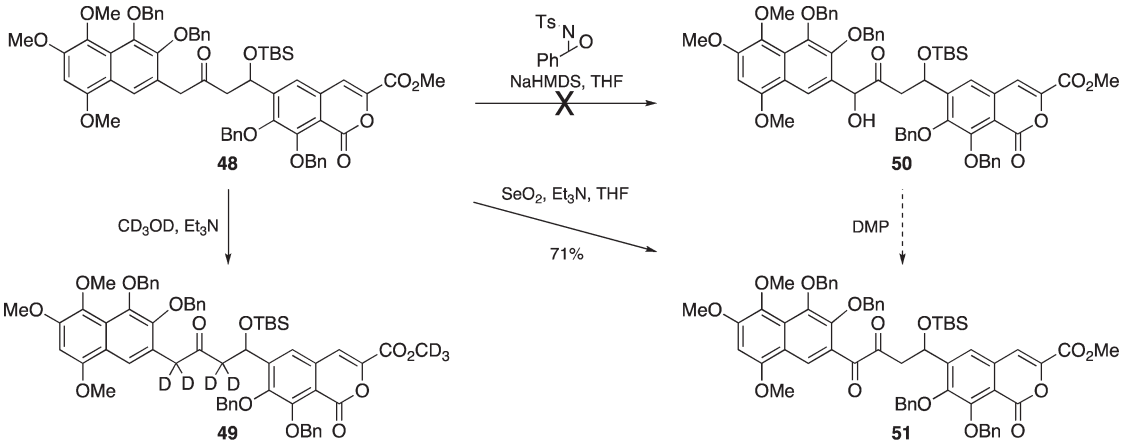
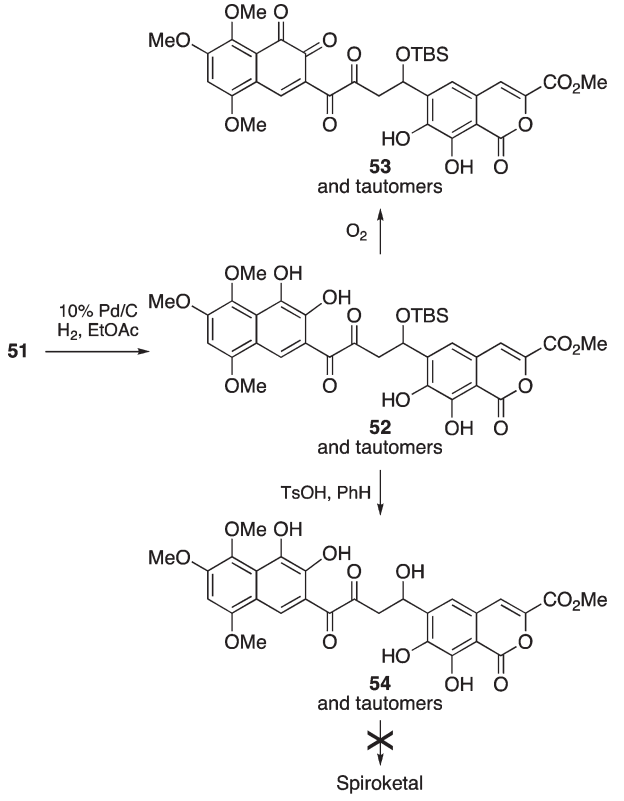
Scheme 8. Oxidation to the Diketone



Scheme 9. Hydrogenolysis and Attempted Spiroketalization of Symmetrically Protected 51



With **51** in hand, the stage was set for spirocyclization from the diketone (Scheme 9). Hydrogenolysis furnished **52**, which existed as a mixture of tautomers preventing full characterization. Further supporting the hypothesis of instability in the electron-rich naphthalene,[4,8] **52** spontaneously oxidized to *ortho*-quinone **53** upon exposure to air. Further, the silyl ether of **52** was labile under the vigorous conditions needed to effect spiroketalization, adding additional tautomers (**54**) to the mixture and opening a pathway for a retro-Claisen reaction. This combination of problems from the symmetrically protected system stymied spiroketal formation by this route.

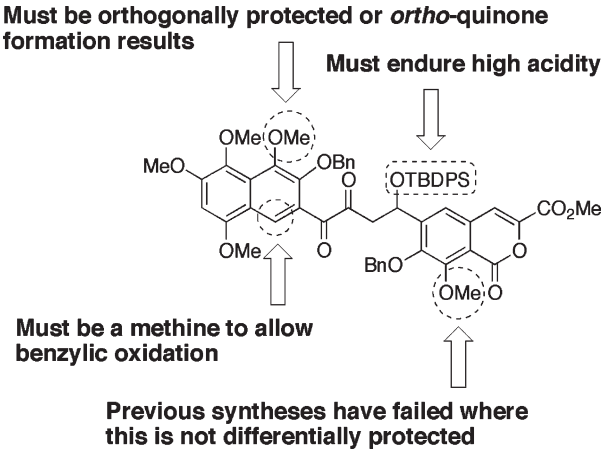


Figure 6. Requirements for a spiroketal precursor.

Second Generation Synthesis with Orthogonal Phenol Protection. The knowledge gained from our earlier routes is summarized in Figure 6. Orthogonal protection is needed on the naphthalene to prevent the catechol from oxidizing to the *ortho*-quinone. Only one substituent is tolerated adjacent to the naphthalene benzylic position if diketone formation is to occur. The protecting group for the central chain alcohol must be sufficiently robust to withstand the spiroketalization conditions. Orthogonal protection of the isocoumarin catechol is preferable.

With these requirements in mind, a new naphthalene synthesis was undertaken (Scheme 10). Reduction and selective benzylation of the more acidic position of the catechol found in *ortho*-quinone **35**[12] with potassium bicarbonate furnished **55**, which could be easily methylated to give **56**. Following a protocol similar to that outlined in Scheme 4 and Scheme 5, **56** was transformed into **60**.

Following our standard protocol (see Scheme 7), orthogonally protected naphthalene **60** (Scheme 11) was combined with an orthogonally protected isocoumarin (**28**)[14] and transformed into **63**. Fresh selenium dioxide failed to give clean conversion to diketone **64**, but after the addition of 1 equiv of water to the reaction mixture, high yields of pure product were again obtained. The likely role of water is to assist in hydrolysis of a selenine intermediate or to generate a reactive selenous acid species.[15] Hydrogenolysis of the benzyl ethers yielded **65** as a mixture of

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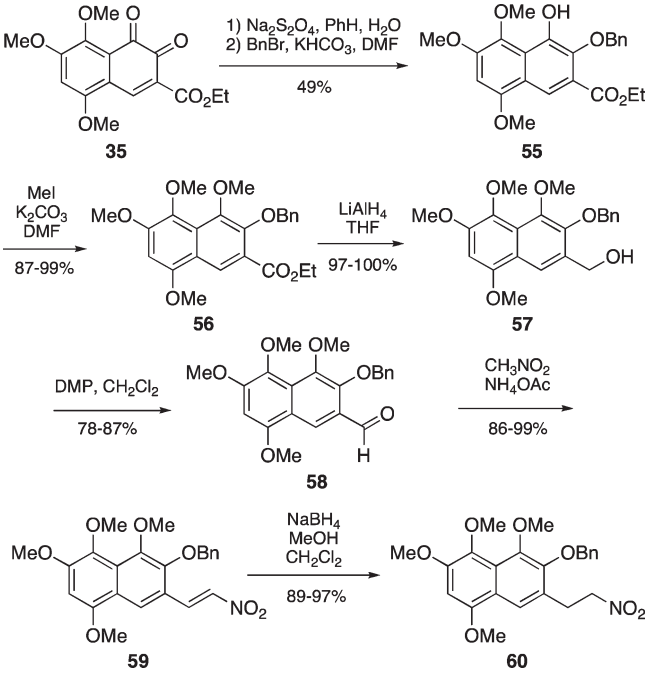
Scheme 10. Differentially Protected Naphthalene

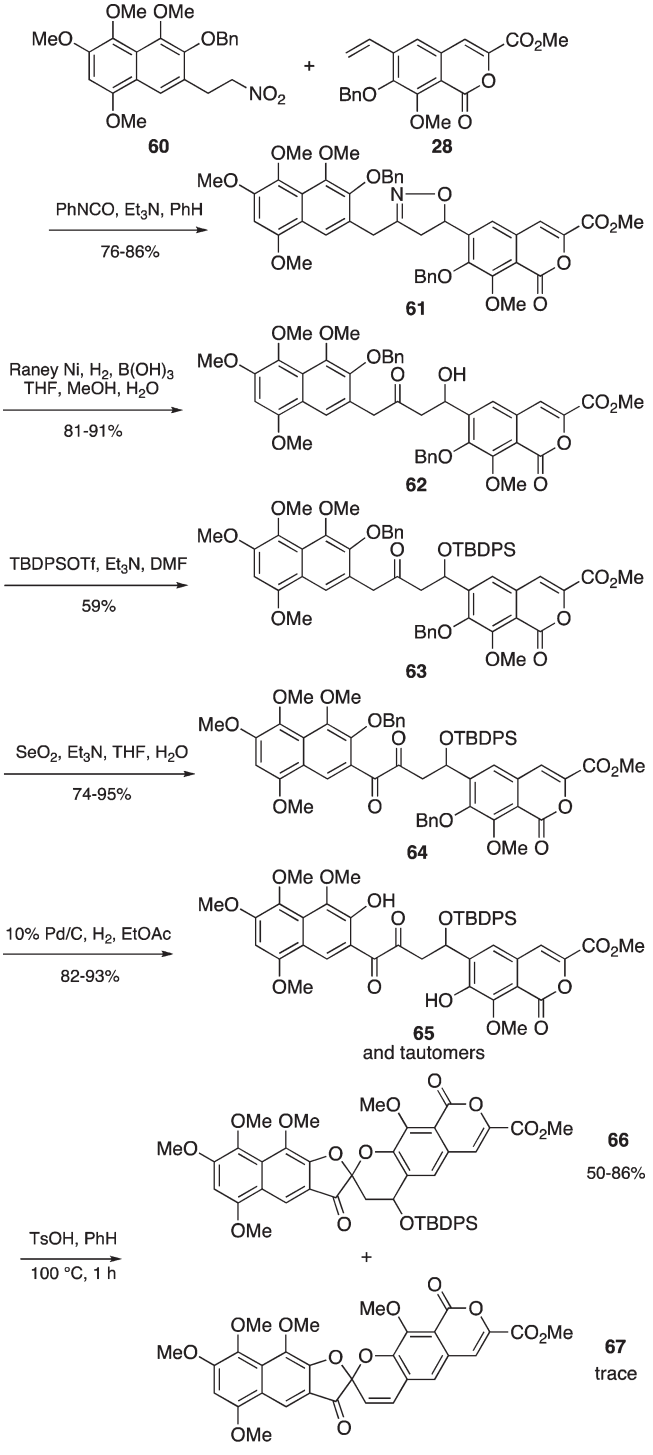


tautomers. Addition of a small amount of DABCO to the NMR sample coalesced the tautomers to one signal for easier visualization.[16] Treatment of **65** with *p*-toluenesulfonic acid in benzene at 100−105 °C for 1 h gave a diastereomeric mixture of spiroketal **66** in 50−86% and a small amount of the eliminated product **67**. This result constitutes the first example of direct ketalization of two hemispheres to yield the complete carbon skeleton of a member of the rubromycin family.

Reactions of the Spiroketal. While we were able to introduce the carbon skeleton necessary for the rubromycin family using a complete isocoumarin that proved stable under strongly acidic conditions, two major challenges remain in converting spiroketal **66** (Figure 7) into purpuromycin (**1**). The challenges are (1) reduction of the 3′ carbonyl, a functionality introduced to prevent competitive elimination of the oxocarbenium intermediate, and (2) oxidation of the 4′ methine, a functionality needed to allow installation of the 3′ ketone.

We began by attempting the reduction of the ketone (Scheme 12). Spiroketal **66** could be reduced to alcohol **68** using sodium borohydride. Alcohol **68** proved resistant to further reduction under a variety of conditions including hydridic, hydrogenolysis, trimethylsilyl chloride, trimethylsilyl ioide, and dithionite. In addition to the stepwise reduction of **66**, we attempted a more direct reduction in two ways: (1) by forming a dithiane and reducing with Raney nickel and (2) by using trifluoroacetic acid and triethylsilane. Both of these methods resulted in the reduction of the ketone but surprisingly also substituted or reduced the methoxy group conjugated to the isocoumarin lactone (**70a** and **70b**, respectively). We hypothesize that the isocoumarin ring system is capable of undergoing a conjugate addition and elimination type reaction, which accounts for the formation of these products. Additionally, ketone **66** and alcohol **68** were subjected to oxidation conditions in the hope of installing oxygen functionality at the 4′ position (Figure 7). Both of these substrates failed to oxidize, instead resulting in complex mixtures.

Scheme 11. Cycloaddition and Elaboration to the Spiroketal



Besides reduction and direct oxidation onto the naphthalene ring, manipulations of the naphthoquinone were also investigated (Scheme 13). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) readily oxidized **66** to quinone **71**. This material, however, showed the same resistance to oxidation even via nucleophilic addition into the aromatic ring at the doubly activated 4′ position. Light-induced selective demethylation[17] cleaved the 7′-methyl ether, but this did not lend itself to furthering the goals of Figure 7. Boron trichloride-mediated demethylation gave **72**, regardless of the

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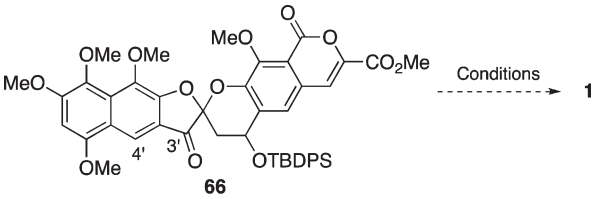
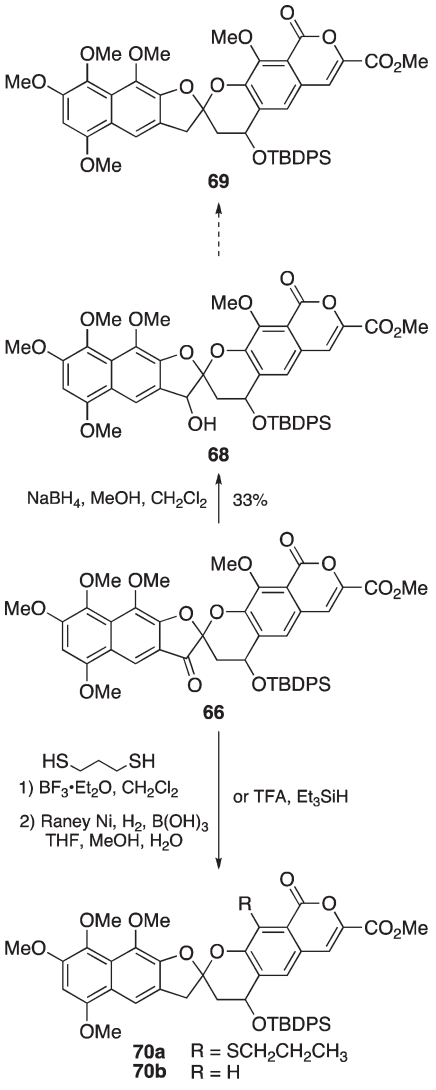


Figure 7. Oxidation changes needed to achieve **1**.

Scheme 12. Reduction of the 3′ Carbonyl

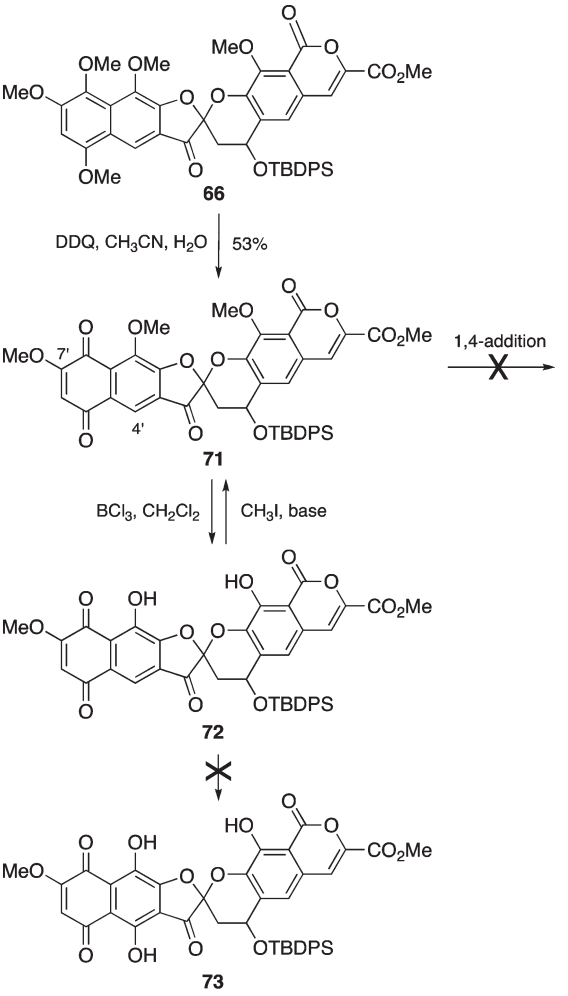


oxidation state of **71** (quinone or quinol), prior to exposure to Lewis acid. Diphenol **72** could be reverted to **71** by treatment with methyl iodide and base. Oxidation of diphenol **72** to **73** also proved impossible, probably due to the very electron-poor nature of the ring systems.

CONCLUSION

We have shown that the spiroketal skeleton of the rubromycin family can be synthesized in a convergent manner using classical ketalization conditions. The synthesis centers on a 1,3-dipolar

Scheme 13. Formation of the Naphthoquinone and Its Chemistry



cycloaddition strategy providing a convergent method to easily couple naphthalene and isocoumarin hemispheres. Here, five different isoxazolines were constructed allowing us to test hypotheses and to produce an array of analogs to probe biological function (e.g., spiroketal compounds **66**, **67**, **68**, **70**, **71**, **72**) in a straightforward and reliable manner. A key step in this endeavor was the discovery that water facilitates a mild late-stage selenium dioxide oxidation to generate a 1,2-diketone. We have unequivocally shown that the complete isocoumarin is indeed a sufficiently powerful nucleophile to attack the oxocarbenium intermediate so long as the competing elimination pathway to the naphthofuran is suppressed. NMR experiments and calculations showed that the primary consideration in spiroketalization of phenolic groups is the ring strain, due to the phenol sp^2 centers, generated in the hemiketal and oxocarbenium intermediates. Extensive experimentation has given us insight into the properties of the completed spiroketal, which will be useful in the generation of analogs and other members of this class of natural products. In particular, the isocoumarin unit is quite electrophilic, undergoing conjugate additions at the unsaturated ester with thiols and hydride nucleophiles. Also of interest is product **67** arising from spiroketalization and elimination, which could offer easy entry to the griseorhodin structural type if a different isocoumarin were employed.

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EXPERIMENTAL SECTION

7-Benzyloxy-8-methoxy-1-oxo-6-{3-[1,4,5,6,8-pentamethoxy-3-(triethyl-silanyloxy)-naphthalen-2-ylmethyl]-4,5-dihydro-isoxazol-5-yl}-1*H*-isochromene-3-carboxylic Acid Methyl Ester (9tes). To triethyl-[1,4,5,7,8-pentamethoxy-3-(2-nitro-ethyl)-naphthalen-2-yloxy]-silane[7] (0.0079 g, 0.016 mmol) and **28**[14] (0.008 g, 0.02 mmol) dissolved in PhH (5 mL) were added PhNCO (0.05 mL, 0.46 mmol) and Et_3N (0.01 mL, 0.07 mmol). The mixture was heated (oil bath, 55 °C) and stirred for 40 h when it was cooled and concentrated to an orange oil containing a white solid. This residue was purified by flash chromatography[18] (33−50% EtOAc/hexanes, SiO_2) to give **9tes** as an off-white solid (0.0095 g, 70%): R_f = 0.55 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.31−7.34 (m, 3H), 7.25−7.29 (m, 3H), 6.60 (s, 1H), 5.60 (dd, J = 7.2, 11.2 Hz, 1H), 5.17 (d, J = 11.2 Hz, 1H), 5.14 (d, J = 11.1 Hz, 1H), 3.99 (s, 3H), 3.950 (s, 3H), 3.947 (s, 3H), 3.94 (s, 3H), 3.85 (d, J = 15.3 Hz, 1H), 3.79 (d, J = 15.3 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.62 (s, 3H), 3.24 (dd, J = 11.3, 17.5 Hz, 1H), 2.65 (dd, J = 7.2, 17.5 Hz, 1H), 0.91 (t, J = 7.8 Hz, 9H), 0.76 (q, J = 7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 158.4, 157.2, 155.0, 153.4, 151.7, 150.8, 150.2, 146.4, 145.1, 142.7, 140.4, 136.7, 136.1, 132.6, 128.8, 128.7, 128.5, 125.7, 121.2, 119.1, 116.6, 113.1, 112.5, 95.4, 76.5, 75.8, 62.4, 62.3, 62.2, 61.8, 57.0, 56.8, 53.0, 45.3, 23.5, 7.0, 5.4; IR (film) 3092, 3065, 2953, 2880, 2845, 1741, 1602, 1455, 1413, 1355, 1058 cm^{-1}; HRMS (ES) calcd for $C_{44}H_{52}NO_{13}Si$ (MH^+) 830.3208, found 830.3185.

7-Benzyloxy-6-[3-(3-hydroxy-1,4,5,6,8-pentamethoxy-naphthalen-2-ylmethyl)-4,5-dihydro-isoxazol-5-yl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (9isox). To a stirring solution of **9tes** (0.103 g, 0.124 mmol) in MeOH (10 mL) was added concentrated HCl (0.10 mL). After stirring at rt for 4.5 h, the mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic fractions were washed with brine (100 mL), dried with Na_2SO_4, and concentrated to a yellow oil. The residue was taken up in PhH and eluted through a plug of SiO_2 (CH_2Cl_2, Et_2O, 15 mm, 1 in.) to give **9isox** (0.074 g, 83%) from the Et_2O fraction as a yellow oil: R_f = 0.25 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.35 (s, 1H), 7.20−7.22 (m, 2H), 7.07−7.12 (m, 3H), 6.90 (s, 1H), 6.34 (s, 1H), 6.33 (s, 1H), 5.65 (dd, J = 7.4, 11.2 Hz, 1H), 4.93 (d, J = 11.1 Hz, 1H), 4.89 (d, J = 11.1 Hz, 1H), 4.04 (d, J = 14.9 Hz, 1H), 4.00 (d, J = 17 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 3.56 (s, 3H), 3.54 (s, 3H), 3.45 (s, 3H), 3.42 (s, 3H), 3.14 (dd, J = 11.5, 17.6 Hz, 1H), 2.70 (dd, J = 7.4, 17.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 161.1, 157.8, 156.9, 155.5, 154.4, 153.4, 151.4, 151.2, 147.3, 145.3, 143.3, 137.8, 136.8, 136.1, 133.3, 129.1, 129.0, 128.9, 125.9, 121.7, 117.3, 115.7, 113.3, 112.7, 77.2, 75.9, 62.8, 62.6, 62.11, 62.07, 57.1, 57.0, 52.4, 45.8, 23.5; IR (film) 3381, 3092, 3034, 2937, 2841, 1741, 1606, 1451, 1359, 1050 cm^{-1}; HRMS (ES) calcd for $C_{38}H_{37}NO_{13}Na$ (MNa^+) 738.2162, found 738.2189.

7-Benzyloxy-6-[1-hydroxy-4-(3-hydroxy-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-3-oxo-butyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (9). Isoxazoline **9isox** (0.074 g, 0.103 mmol) was dissolved in THF (3 mL) and MeOH (3 mL). $B(OH)_3$ (0.0335 g, 0.542 mmol) was dissolved in water (1 mL), and the solution was added to the stirring mixture along with Raney Ni (12 drops). The system was purged and stirred rapidly under an atmosphere of H_2 for 5.5 h. The mixture was diluted with EtOAc (10 mL) and filtered through a plug of Celite (EtOAc). The eluant was washed with water (25 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated to give **9** (0.071 g, 96%) as a yellow oil: R_f = 0.13 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.40 (s, 1H), 7.37 (d, J = 7.6 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.7 Hz, 1H), 7.05 (s, 1H), 6.51 (s, 1H), 6.34 (s, 1H), 5.68 (dd, J = 1.4, 9.1 Hz, 1H), 5.10 (d, J = 11.0 Hz, 1H), 4.92 (d, J = 10.9 Hz, 1H), 3.93 (s, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.61 (s, 3H), 3.59 (s, 3H), 3.56 (s, 3H), 3.46 (s, 6H), 3.02 (dd, J = 2.2, 17.2 Hz, 1H), 2.80 (dd, J = 9.3, 17.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.3, 160.9, 156.8, 155.1, 153.9, 152.7, 151.0, 150.8, 146.8, 146.3, 142.9, 137.6, 136.6, 135.9, 132.8, 128.9, 128.7, 128.5, 125.7, 121.8, 116.5, 114.8, 112.9, 112.5, 75.6, 65.8, 62.4, 62.0, 61.8, 61.7, 56.8, 56.6, 52.1, 49.2, 39.8; IR (film) 3405, 3092, 3073, 3034, 2934, 2841, 1737, 1606, 1451, 1359, 1050 cm^{-1}; HRMS (ES) calcd for $C_{38}H_{39}O_{14}$ (MH^+) 719.2340, found 719.2334.

4-(*tert*-Butyl-dimethyl-silanyloxy)-4-(2-hydroxy-phenyl)-1-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-butan-2-one (11). Benzyl ether **11benz**[14] (0.046 g, 0.070 mmol) was dissolved in EtOAc (8 mL), and the solution was combined with 10% Pd/C (0.040 g), purged with H_2, placed under a H_2 atmosphere, and stirred for 14 h. The mixture was filtered through a plug of Celite (EtOAc) and concentrated to give **11** (0.040 g, 99%) as a yellow oil: R_f = 0.55 (50% EtOAc/hexanes). The material exists as a 1:0.66:0.2 mixture of inseparable tautomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.37 (d, J = 7.6 Hz, 0.2H), 7.22 (dt, J = 1.5, 7.8 Hz, 0.66H), 7.13 (s, 1H), 7.13 (dt, J = 1.6, 7.7 Hz, 1H), 7.09 (dd, J = 1.4, 7.5 Hz, 0.66H), 6.97 (dd, J = 1.4, 7.5 Hz, 1H), 6.94 (d, J = 8.3 Hz, 0.66H), 6.93 (t, J = 7.7 Hz, 0.2H), 6.88 (dt, J = 0.9, 7.4 Hz, 0.66H), 6.82 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 7, 0.2H), 6.77 (dt, J = 1.0, 7.2 Hz, 1H), 6.77 (s, 0.2H), 6.75 (t, J = 7 Hz, 0.2H), 6.75 (s, 0.66H), 6.75 (s, 0.2H), 6.73 (s, 1H), 6.72 (s, 1H), 5.33 (dd, J = 5.6, 7.6 Hz, 1H), 5.07 (dd, J = 5.9, 10.5 Hz, 0.2H), 4.83 (dd, J = 2.9, 2.9 Hz, 0.66H), 3.99 (s, 0.6H), 3.98 (s, 2H), 3.97 (coincidental s, 5H), 3.95 (s, 0.6H), 3.94 (s, 3H), 3.91 (s, 2H), 3.88 (s, 3H), 3.83 (s, 0.6H), 3.81 (s, 0.6H), 3.80 (s, 3H), 3.79 (s, 2H), 3.76 (s, 2H), 3.74 (d, J = 16.0 Hz, 1H), 3.68 (d, J = 16.0 Hz, 1H), 3.62 (s, 3H), 3.43 (d, J = 14.0 Hz, 0.2H), 3.40 (d, J = 13.7 Hz, 0.66H), 3.32 (d, J = 13.6 Hz, 0.66H), 3.21 (dd, J = 7.7, 16.4 Hz, 1H), 3.16 (d, J = 13.9 Hz, 0.2H), 2.87 (dd, J = 5.6, 16.4 Hz, 1H), 2.33 (dd, J = 6.0, 12.5 Hz, 0.2H), 2.26 (dd, J = 2.6, 14.6 Hz, 0.66H), 1.99 (dd, J = 3.5, 14.6 Hz, 0.66H), 1.94 (dd, J = 10.7, 12.4 Hz, 0.2H), 0.94 (s, 1.8H), 0.85 (s, 9H), 0.83 (s, 4H), 0.18 (s, 0.6H), 0.14 (s, 2H), 0.12 (s, 3H), 0.11 (s, 0.6H), 0.09 (s, 2H), −0.2 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 155.7, 152.8, 152.3, 152.2, 152.1, 152.0, 151.4, 150.2 (2), 149.9, 148.7, 148.5, 148.2, 138.9 (2), 138.8, 130.2, 129.9, 129.2, 128.5, 127.5, 127.1, 127.0, 126.6, 124.0, 123.9, 123.5, 122.5, 121.5, 120.9, 120.6, 120.0, 117.8, 117.6, 117.4, 116.6, 115.0, 114.3, 111.9, 111.8, 110.1, 110.0, 100.0, 99.9, 99.7, 99.4, 99.3, 98.8, 73.1, 66.4, 63.8, 62.5, 62.1, 62.00, 61.97, 57.8, 57.7, 57.5, 57.3, 57.2, 57.1, 57.04, 56.97, 50.1, 46.0, 42.3, 40.9, 39.8, 36.5, 26.1, 25.80, 25.75, 18.3, 18.2, 18.0, −4.0, −4.1, −4.5, −4.6, −5.08, −5.09; IR (film) 3389, 2953, 2934, 2903, 2856, 1714, 1602, 1459 cm^{-1}; HRMS (ES) calcd for $C_{31}H_{42}O_8SiNa$ (MNa^+) 593.2547, found 593.2525.

7,8-Dibenzyloxy-6-[3-(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-ylmethyl)-4,5-dihydro-isoxazol-5-yl]-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (29). To **27**[12] (0.0149 g, 0.033 mmol) and **28**[14] (0.012 g, 0.033 mmol) dissolved in PhH (4 mL) were added PhNCO (0.04 mL, 0.37 mmol) and Et_3N (0.030 mL, 0.22 mmol). The mixture was heated (oil bath, 70 °C) and stirred for 16 h, after which it was cooled, filtered through Celite (PhH), and concentrated to a brown oil. The residue was purified by flash chromatography (60% EtOAc/hexanes, SiO_2) to give **29** (0.0213 g, 70%) as a yellow oil: R_f = 0.30 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.43 (m, 2H), 7.26−7.35 (m, 9H), 7.22 (s, 1H), 6.67 (s, 1H), 5.57 (dd, J = 7.0, 11.2 Hz, 1H), 5.17 (d, J = 10.9 Hz, 1H), 5.14 (s, 2H), 5.12 (d, J = 11.0 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 9H), 3.86 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 3.16 (dd, J = 11.3, 17.5 Hz, 1H), 2.57 (dd, J = 7.0, 17.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 158.6, 157.2, 154.9, 153.2, 151.4, 150.8, 150.3, 149.0, 145.0, 143.9, 142.6, 137.8, 137.0, 136.8, 132.6, 128.8, 128.7, 128.6, 128.53, 128.51, 128.2, 126.4, 121.2, 120.3, 116.5, 114.6, 112.5, 96.6, 76.4, 75.7, 75.2, 62.5, 62.2, 62.1, 61.0, 57.1, 57.0, 53.0, 45.5, 23.4; IR (film) 3034, 2934, 2841, 1737, 1602, 1455, 1359, 1328 cm^{-1}; HRMS (ES) calcd for $C_{45}H_{43}NO_{13}Na$ (MNa^+) 828.2632, found 828.2627.

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7-Benzyloxy-6-[4-(3-benzyloxy-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-1-(*tert*-butyl-dimethyl-silanyloxy)-3-oxo-butyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (30). Isoxazoline **29** (0.0213 g, 0.026 mmol) was dissolved in THF (3 mL) and MeOH (3 mL). $B(OH)_3$ (0.0322 g, 0.521 mmol) was dissolved in water (1 mL), and the solution was added to the stirring mixture along with Raney Ni (12 drops, 50% in water). The system was purged and stirred rapidly under an atmosphere of H_2 for 3 h. The mixture was diluted with EtOAc (10 mL), and the solution was filtered through a plug of Celite (EtOAc). The eluant was washed with water (25 mL), washed with brine (25 mL), dried with Na_2SO_4, and concentrated, yielding **30alc** (0.0165 g, 77%) as a yellow-black oil which was used immediately in the next reaction.

Alcohol **30alc** (0.0165 g, 0.0204 mmol) and imidazole (0.012 g, 0.176 mmol) were dissolved in DMF (2 mL). *tert*-Butyldimethylsilyl triflate (TBSOTf) (0.030 mL, 0.131 mmol) was added and the mixture was stirred under an inert atmosphere (N_2) for 4 h, after which the mixture was diluted with EtOAc (10 mL) and poured into saturated NH_4Cl (10 mL). The aqueous layer was washed with EtOAc (10 mL). The combined organic layers were washed with saturated NH_4Cl (10 mL), washed with brine (2 × 10 mL), dried with Na_2SO_4, and concentrated to an orange-red oil. The residue was purified by flash chromatography (35% EtOAc/hexanes SiO_2) to give **30** (0.0040 g, 21%) as a yellow oil: R_f = 0.62 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.44 (m, 2H), 7.41 (s, 1H), 7.27−7.37 (m, 9H), 6.64 (s, 1H), 5.57 (dd, J = 2.8, 8.3 Hz, 1H), 5.17 (d, J = 10.9 Hz, 1H), 5.13 (m, 2H), 5.08 (d, J = 11.1 Hz, 1H), 3.99 (s, 3H), 3.955 (s, 3H), 3.946 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78 (d, J = 16.7 Hz, 1H), 3.71 (d, J = 16.7 Hz, 1H), 3.62 (s, 3H), 2.79 (dd, J = 8.4, 16.6 Hz, 1H), 2.60 (dd, J = 2.9, 16.6 Hz, 1H), 0.84 (s, 9H), 0.00 (s, 3H), −0.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 161.1, 157.3, 155.1, 153.2, 151.4, 150.3, 150.2, 149.0, 148.3, 143.6, 142.6, 138.0, 137.1, 136.8, 132.2, 129.0, 128.9, 128.7, 128.6, 128.4, 128.1, 126.4, 122.0, 120.1, 116.0, 114.7, 112.6, 96.7, 75.6, 75.1, 65.8, 62.3, 62.1, 62.05, 62.00, 57.12, 57.07, 53.0, 51.3, 40.5, 26.0, 18.3, −4.7, −4.9; IR (film) 3034, 2934, 2895, 2860, 1741, 1602, 1455 cm^{-1}; HRMS (ES) calcd for $C_{51}H_{58}O_{14}SiNa$ (MNa^+) 945.3494, found 945.3455.

Methyl 7,8-Bis(benzyloxy)-6-(3-(3-(benzyloxy)-1,4,5,6,8-pentamethoxy-2-naphthoyl)-4,5-dihydroisoxazol-5-yl)-1-oxo-1*H*-isochromene-3-carboxylate (34). A solution of α-nitro-ketone **33**[12] (0.070 g, 0.15 mmol) and styrene **21**[14] (0.10 g, 0.23) in PhH (6 mL) was treated with phenylisocyanate (0.065 g, 0.60 mmol) followed by Et_3N (0.006 g, 0.03 mmol) and heated at 70 °C for 48 h. The mixture was cooled, diluted with PhH and hexanes, filtered, and concentrated. Chromatography (25−40% EtOAc/hexanes) afforded **34** (0.075 g, 56%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.38 (m, 6H), 7.29 (m, 4H), 7.21 (m, 4H), 7.15 (s, 1H), 6.69 (s, 1H), 5.65 (dd, J = 8.1, 11.7 Hz, 1H), 5.28−5.11 (m, 6H), 4.02 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 3.35 (dd, J = 11.7, 16.2 Hz, 1H), 2.91 (dd, J = 8.1, 16.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7, 160.5, 159.0, 156.9, 153.8, 153.3, 151.2, 150.5, 146.7, 143.1, 142.8, 142.5, 137.6, 136.7, 136.2, 135.8, 132.5, 129.4 (2), 128.7 (2), 128.7, 128.6, 128.4 (2), 128.4 (2), 128.1 (2), 127.8, 127.7, 127.5 (2), 124.7, 120.5, 120.1, 117.1, 113.9, 112.1, 96.0, 79.8, 76.9, 75.7, 75.2, 64.2, 62.0, 61.9, 56.7, 56.6, 52.8, 40.1; IR (film) 3034, 2937, 2845, 1741, 1679, 1602 cm^{-1}; HRMS (ES) calcd for $C_{51}H_{45}NO_{14}Na$ (MNa^+) 918.2747, found 918.2737.

Ethyl 3,4-Bis(benzyloxy)-5,6,8-trimethoxynaphthalene-2-carboxylate (36). A solution of **35**[12] (1.33 g, 4.15 mmol) in PhH (100 mL) was treated with a saturated solution of $Na_2S_2O_4$ in H_2O (100 mL). After stirring for 5 min, the mixture was extracted with PhH, dried (Na_2SO_4), and concentrated. The resultant oil was dissolved in acetone (65 mL), and the solution was treated with BnBr (2.4 mL, 19.5 mmol) and K_2CO_3 (4.5 g, 32.5 mmol). After heating at reflux for 6 h, the mixture was filtered, concentrated, and chromatographed (10−25% EtOAc/hexanes) to afford **36** (1.92 g, 92%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.55 (m, 4H), 7.33 (m, 6H), 6.65 (s, 1H), 5.24 (s, 2H), 5.06 (s, 2H), 4.39 (q, J = 7.8 Hz, 2H), 4.04 (s, 3H), 4.01 (s, 3H), 3.79 (s, 3H), 1.35 (t, J = 7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 153.6, 152.0, 149.4, 147.0, 137.9, 137.6, 136.0, 129.0 (2), 128.4 (2), 128.1 (2), 128.1 (2), 127.7, 127.6, 127.3, 123.2, 122.5, 118.8, 94.3, 76.7, 76.0, 62.1, 61.0, 56.8, 55.8, 14.3; IR (film) 2980, 2937, 2845, 1718, 1613 cm^{-1}; HRMS (ES) calcd for $C_{30}H_{31}O_7$ (MH^+) 503.2075, found 503.2069.

(7,8-Bis(benzyloxy)-1,2,4-trimethoxynaphthalen-6-yl)-methanol (37). A solution of **36** (1.92 g, 3.82 mmol) in THF (40 mL) at 0 °C was treated with $LiAlH_4$ (0.850 g, 22.4 mmol). After stirring for 2 h, the mixture was treated with 0.85 mL of H_2O, 0.85 mL of 15% $NaOH/H_2O$, and then 2.55 mL of H_2O. After stirring for 10 min, the mixture was filtered and concentrated to afford **37** (1.76 g, 99%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.61 (m, 2H), 7.35 (m, 8H), 6.64 (s, 1H), 5.27 (s, 2H), 5.06 (s, 2H), 4.70 (q, J = 6.3 Hz, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.81 (s, 3H), 2.10 (t, J = 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 150.2, 149.5, 145.6, 137.9, 137.4, 136.4, 131.8, 128.9 (2), 128.5 (2), 128.3, 128.2 (2), 128.2 (2), 127.7, 125.1, 119.7, 118.0, 94.4, 76.7, 75.6, 62.5, 62.1, 57.1, 55.8 ; IR (film) 3439, 2937, 2845, 1602 cm^{-1}; HRMS (ES) calcd for $C_{28}H_{29}O_6$ (MH^+), 461.1974, found 461.1964.

3,4-Bis(benzyloxy)-5,6,8-trimethoxynaphthalene-2-carbaldehyde (38). A solution of **37** (1.76 g, 3.82 mmol) in CH_2Cl_2 (50 mL) was treated with a Dess−Martin periodinane (2 g, 4.7 mmol).[13] After stirring for 1 h, the mixture was diluted with H_2O, extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, and chromatographed (25% EtOAc/hexanes) to afford **38** (1.5 g, 86%) as a yellow resin: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.57 (s, 1H), 7.59 (m, 2H), 7.31 (m, 8H), 6.64 (s, 1H), 5.29 (s, 2H), 5.09 (s, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 154.9, 153.1, 151.0, 146.0, 137.7, 136.6, 136.0, 129.0 (2), 128.7 (2), 128.5 (2), 128.3, 128.3 (2), 127.9, 127.8, 126.6, 121.6, 119.0, 94.1, 76.8, 76.7, 62.2, 56.7, 55.9 ; IR (film) 2937, 2849, 1687, 1610 cm^{-1}; HRMS (ES) calcd for $C_{28}H_{27}O_6$ (MH^+) 459.1796, found 459.1807.

1-(3,4-Dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-yl)-2-nitro-ethanol (39). THF (10 mL) and CH_3NO_2 (2.3 mL, 42.5 mmol) were combined and cooled in an ice bath. *n*-BuLi (6.0 mL, 6.6 mmol) was added dropwise over 15 min. After stirring for an additional 15 min, **38** (0.292 g, 0.637 mmol) dissolved in THF (10 mL) was added and the mixture was allowed to warm to rt over 26 h. The reaction was quenched by the addition of saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated. The resultant orange oil was purified by flash chromatography (25% EtOAc/hexanes, SiO_2) to give **39** (0.286 g, 86%) as a yellow oil or orange foam: R_f = 0.64 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.32−7.41 (m, 8H), 6.65 (s, 1H), 5.62 (dd, J = 2.7, 9.3 Hz, 1H), 5.39 (d, J = 11.2 Hz, 1H), 5.21 (d, J = 11.2 Hz, 1H), 5.06 (d, J = 9.8 Hz, 1H), 4.99 (d, J = 9.8 Hz, 1H), 4.49 (dd, J = 9.4, 13.2 Hz, 1H), 4.43 (dd, J = 3.0, 13.2 Hz, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.83 (s, 3H), 2.86 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 150.8, 147.8, 145.7, 137.7, 137.1, 136.1, 129.3, 128.9 (2), 128.8, 128.7, 128.5, 128.1, 125.5, 119.6, 117.0, 94.4, 80.3, 77.0, 75.8, 67.6, 62.4, 57.1, 56.0; IR (film) 3432 (br), 3034, 2937, 2883, 2845, 2250, 1718, 1621, 1602, 1552, 1498, 1455, 1420 cm^{-1}; HRMS (ES) calcd for $C_{29}H_{29}NO_8Na$ (MNa^+) 542.1791, found 542.1799.

***tert*-Butyl-[1-(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-yl)-2-nitro-ethoxy]-dimethyl-silane (40).** Alcohol **39** (0.047 g, 0.090 mmol) was dissolved in CH_2Cl_2 (5 mL), and TBS−imidazole (0.070 mL, 0.361 mmol) was added in one portion. The mixture was heated to reflux (oil bath, 50 °C) and stirred for 16 h, after which additional TBS−imidazole (0.15 mL, 0.773 mmol) was added. After stirring at reflux (oil bath, 55 °C) for an additional 24 h, the mixture was partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The organic

layer was dried with Na_2SO_4 and concentrated. The residual orange oil was purified by flash chromatography (20% EtOAc/hexanes, SiO_2) to give **40** as a clear, faintly yellow oil contaminated with TBS_2O. This material was eluted through a plug of SiO_2 (hexanes, CH_2Cl_2) to give **40** (0.049 g, 86%) as a clear, faintly yellow oil, still with a small amount of TBS_2O: R_f = 0.69 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.58 (d, J = 6.7 Hz, 2H), 7.33−7.42 (m, 8H), 6.65 (s, 1H), 5.66 (dd, J = 2.4, 9.6 Hz, 1H), 5.40 (d, J = 11.3 Hz, 1H), 5.26 (d, J = 11.3 Hz, 1H), 5.08 (d, J = 9.8 Hz, 1H), 4.98 (d, J = 9.8, 1H), 4.42 (dd, J = 2.5, 11.9 Hz, 1H), 4.34 (dd, J = 9.6, 11.8 Hz, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.84 (s, 3H), 0.89 (s, 9H), −0.04 (s, 3H), −0.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 150.6, 147.4, 145.4, 137.8, 137.3, 136.2, 130.0, 129.4, 129.1, 128.8, 128.6, 128.5, 128.1, 125.3, 119.7, 117.5, 94.4, 81.7, 77.0, 75.6, 68.6, 62.4, 57.2, 56.1, 25.8, 18.3, −4.7, −5.4; IR (film) 3066, 2935, 2896, 2858, 1730, 1599, 1552, 1460, 1359 cm^{-1}; HRMS (ES) calcd for $C_{35}H_{44}NO_8Si$ (MH^+) 634.2836, found 634.2834.

1,2-Bis(benzyloxy)-5,7,8-trimethoxy-3-(2-nitroethyl)naphthalene (41). A solution of **38** (0.50 g, 1.1 mmol) in $MeNO_2$ (30 mL) was treated with NH_4OAc (0.02 g, 0.4 mmol). After heating at reflux for 30 min, the mixture was diluted with H_2O, extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, and chromatographed (25% EtOAc/hexanes) to afford **41ene** as yellow resin, which was carried directly to the next step: **1,2-Bis(benzyloxy)-5,7,8-trimethoxy-3-((*E*)-2-nitrovinyl)naphthalene (41ene)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.18 (d, J = 13.6 Hz, 1H), 7.82 (d, J = 13.6 Hz, 1H), 7.60 (m, 2H), 7.33 (m, 8H), 6.65 (s, 1H), 5.23 (s, 2H), 5.08 (s, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.8, 149.6, 146.6, 137.9, 137.8, 136.5, 136.4, 135.9, 129.2 (2), 129.1 (2), 128.7 (2), 128.7, 128.5 (2), 128.1, 127.4, 122.5, 122.0, 119.5, 94.6, 76.9, 76.4, 62.4, 57.0, 56.1; IR (film) 2937, 2845, 1606 cm^{-1}; LRMS (ES) calcd for $C_{29}H_{27}NO_7$ (M^+) 501.1788, found 501.1787.

A solution of unpurified **41ene** in MeOH/$CHCl_3$ (30 mL, 1:1) was treated with $NaBH_4$ (0.166 g, 4.39 mmol). After stirring 5 min, the mixture was diluted with H_2O, acidified with 1 M HCl (pH 3), extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, and chromatographed (25% EtOAc/hexanes) to afford **41** (0.54 g, 98%) as a yellow resin; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.57 (m, 2H), 7.35 (m, 8H), 6.64 (s, 1H), 5.27 (s, 2H), 5.06 (s, 2H), 4.54 (t, J = 7.4 Hz, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 3.82 (s, 3H), 3.33 (t, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 150.2, 149.5, 145.7, 137.7, 137.4, 136.3, 128.9 (2), 128.5 (2), 128.3 (2), 128.2 (2), 128.1, 127.8, 126.5, 125.0, 119.6, 119.4, 94.5, 76.7, 75.4, 75.0, 62.1, 57.1, 55.8, 29.6 ; IR (film) 2934, 2849, 1602 cm^{-1}; HRMS (ES) calcd for $C_{29}H_{30}NO_7$ (MH^+) 504.2027, found 504.2022.

7,8-Dibenzyloxy-6-[3-{(*tert*-butyl-dimethyl-silanyloxy)-(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-yl)-methyl}-4,5-dihydro-isoxazol-5-yl]-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (42). To a stirring solution of **40** (0.230 g, 0.363 mmol) and **21**[14] (0.160 g, 0.362 mmol) in $PhCH_3$ (22 mL) were added *p*-NO_2PhNCO (0.319 g, 1.94 mmol) and NEt_3 (0.02 mL, 0.143 mmol). The mixture was heated (oil bath, 130−135 °C) and stirred for 15 h, after which the mixture was cooled, filtered through a plug of Celite (PhH), and concentrated. The residual red oil was purified by flash chromatography (25% EtOAc/hexanes, SiO_2) to give recovered **40** (0.045 g) and **42** (0.237 g, 62%) as a 1:1 mixture of diastereomers: a dark yellow foam; R_f = 0.43 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 0.5H), 8.14 (s, 0.5H), 7.17−7.54 (m, 21.5H), 6.94 (s, 0.5H), 6.67 (s, 0.5H), 6.62 (s, 0.5H), 5.95 (s, 0.5H), 5.89 (s, 0.5H), 5.59 (dd, J = 7.0, 11.3 Hz, 0.5H), 5.53 (dd, J = 5.9, 11.2 Hz, 0.5H), 4.94−5.28 (m, 7H), 4.75 (d, J = 9.6 Hz, 0.5H), 4.61 (d, J = 9.6 Hz, 0.5H), 4.04 (s, 1.5H), 4.00 (s, 1.5H), 3.98 (s, 3H), 3.96 (s, 1.5H), 3.85 (s, 1.5H), 3.83 (s, 1.5H), 3.72 (s, 1.5H), 3.23 (dd, J = 11.3, 17.5 Hz, 0.5H), 2.89 (dd, J = 11.3, 17.4 Hz, 0.5H), 2.57 (dd, J = 6.0, 17.4 Hz, 0.5H), 2.26 (dd, J = 7.0, 17.5 Hz, 0.5H), 0.95 (s, 4.5H), 0.80 (s, 4.5H), 0.09 (s, 1.5H), 0.01 (s, 1.5H), −0.06 (s, 1.5H), −0.07 (s, 1.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 160.5, 160.14, 160.11, 157.4, 157.2, 153.5, 153.2, 153.02, 152.95, 150.9, 150.8, 150.51, 150.47, 148.3, 148.1, 145.8, 145.6, 145.1, 144.7, 142.7, 142.5, 137.8, 137.7 (2), 137.6, 136.6, 136.5, 136.4, 136.3, 136.2, 136.1, 132.7, 132.6, 131.3, 131.1, 129.7, 129.6, 129.3, 129.0, 128.93, 128.87, 128.83, 128.77 (6), 128.7 (3), 128.6, 128.5, 128.4 (2), 128.3, 128.2, 128.0, 127.9, 125.4, 125.3, 121.20, 121.17, 119.70, 119.69, 117.2, 117.0, 116.9, 116.8, 112.4, 112.2, 94.5, 94.4, 77.1, 76.9, 76.8, 76.7, 76.6 (2), 75.91, 75.87, 75.3, 75.1, 65.9, 65.8, 62.5, 62.4, 57.3, 57.2, 56.1 (2), 53.1, 52.8, 41.7, 41.5, 25.9, 25.7, 18.5, 18.3, −4.7 (2), −4.8, −4.9; IR (film) 3092, 3065, 3034, 2953, 2934, 2887, 2856, 1741, 1602, 1498, 1455 cm^{-1}; HRMS (ES) calcd for $C_{62}H_{63}NO_{13}SiNa$ (MNa^+) 1080.3966, found 1080.3926.

7,8-Dibenzyloxy-6-[3-{(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-yl)-hydroxy-methyl}-4,5-dihydro-isoxazol-5-yl]-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (44). To **42** (0.0235 g, 0.022 mmol) dissolved in CH_3CN (2.5 mL) in a plastic container was added 49% HF (0.60 mL). The mixture was stirred at rt for 2.5 h, after which it was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated. The residual brown oil was purified by flash chromatography (50% EtOAc/hexanes after treatment with 1% water in 50% EtOAc/hexanes, SiO_2) to give **44** (0.009 g, 43%) as a 1:1 mixture of diastereomers: a light yellow oil; R_f = 0.43 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 0.5H), 7.95 (s, 0.5H), 7.21−7.52 (m, 21.5H), 7.17 (s, 0.5H), 6.66 (s, 0.5H), 6.65 (s, 0.5H), 5.76 (d, J = 5.9 Hz, 0.5H), 5.67 (d, J = 6.3 Hz, 0.5H), 5.62 (dd, J = 7.2, 11.4 Hz, 0.5H), 5.59 (dd, J = 6.9, 11.4 Hz, 0.5H), 5.40 (d, J = 10.8 Hz, 0.5H), 5.27 (d, J = 10.8 Hz, 0.5H), 5.20 (d, J = 10.8 Hz, 0.5H), 4.97−5.17 (m, 6H), 4.03 (coincidental s, 3H), 3.98 (s, 1.5H), 3.97 (s, 1.5H), 3.95 (s, 1.5H), 3.80 (s, 1.5H), 3.79 (s, 1.5H), 3.16 (dd, J = 11.4, 17.7 Hz, 0.5H), 3.10 (dd, J = 11.6, 17.8 Hz, 0.5H), 3.06 (d J = 6.5 Hz, 0.5H), 3.01 (d, J = 6.0 Hz, 0.5H), 2.57 (coincidental dd, J = 7.1, 17.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 160.72 (2), 160.68, 157.2 (2), 153.6, 153.5, 153.0 (2), 151.1, 151.0, 150.91, 150.86, 148.6 (2), 146.09, 146.07, 144.5, 144.3, 142.7 (2), 137.72, 137.67, 137.5, 137.3, 136.58, 136.55, 136.2, 136.1, 132.8, 132.7, 129.9 (2), 129.6 (2), 129.14, 129.10, 128.8 (3), 128.74 (2, 128.72, 128.71, 128.68, 128.64 (3), 128.60, 128.48, 128.47, 128.4 (2), 128.1 (2), 126.2 (2), 125.7, 125.6, 121.2, 121.1, 119.7, 119.6, 118.0 (2), 117.5 (2), 117.08, 117.05, 112.5, 112.4, 94.54, 94.47, 77.5, 77.4, 77.1, 77.04, 76.95 (2), 75.9 (2), 75.6 (2), 68.1, 67.5, 62.4 (2), 57.2 (2), 56.1, 56.0, 53.0 (2), 42.9 (2); IR (film) 3486, 3092, 3065, 3034, 2941, 2883, 2845, 1741, 1602, 1498 cm^{-1}; HRMS (ES) calcd for $C_{56}H_{49}NO_{13}Na$ (MNa^+) 966.3102, found 966.3093.

7,8-Dibenzyloxy-6-[3-(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-ylmethyl)-4,5-dihydro-isoxazol-5-yl]-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (46). To **41** (0.272 g, 0.540 mmol) and **21**[14] (0.207 g, 0.468 mmol) dissolved in PhH (22 mL) were added PhNCO (0.26 mL, 2.4 mmol) and Et_3N (0.020 mL, 0.14 mmol). The mixture was heated (oil bath, 65−70 °C) and stirred for 17 h, after which it was cooled, filtered through Celite (PhH), and concentrated to a dark red oil/foam. The residue was purified by flash chromatography (20−33% EtOAc/hexanes then 15% MeOH/CH_2Cl_2, SiO_2) to give **46** (0.218 g, 50%) as a dark orange foam. The highly colored impure fractions were taken up in CH_2Cl_2 (~30 mL), decolorized with charcoal, dried with $MgSO_4$, filtered through a plug of Celite, and concentrated to give **46** (0.184 g, 42%) as an orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.50 (m, 4H), 7.29 (m, 18H), 6.64 (s, 1H), 5.60 (dd, J = 6.7, 11.2 Hz, 1H), 5.14 (m, 8H), 4.01 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.79 (s, 3H), 3.74 (m, 2H), 3.09 (dd, J = 11.2, 17.8 Hz, 1H), 2.48 (dd, J = 6.7, 17.8 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.5, 157.7, 156.9, 153.3, 152.2, 150.8, 150.1, 149.4, 146.0, 144.6, 142.4, 137.6, 137.3, 136.4, 136.3, 136.0, 132.5, 129.3 (2), 128.8 (2), 128.5 (2), 128.4 (4), 128.4 (2), 128.3 (4), 128.2 (2), 128.0, 127.7, 126.6, 124.9, 121.0, 119.7, 119.3, 116.2, 112.2, 94.6, 76.8, 76.6, 76.3, 75.6, 75.3, 62.1,

57.1, 55.8, 52.7, 44.6, 28.9 ; IR (film) 3034, 2934, 1741, 1598 cm^{-1}; HRMS (ES) calcd for $C_{56}H_{50}NO_{12}$ (MH^+) 928.3305, found 928.3333.

7,8-Dibenzyloxy-6-[4-(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-yl)-1-hydroxy-3-oxo-butyl]-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (47). Isoxazoline **46** (0.218 g, 0.235 mmol) was dissolved in THF (12 mL) and MeOH (11 mL). $B(OH)_3$ (0.284 g, 4.59 mmol) was dissolved in water (6 mL), and the solution was added to the stirring mixture along with Raney Ni (~1.5 mL, 50% in water). The system was purged and stirred rapidly under an atmosphere of H_2 for 8 h. The mixture was diluted with EtOAc (40 mL) and filtered through a plug of Celite (EtOAc). The eluant was washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated to yield **47** as a brown oil, which was carried on directly without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.57 (m, 5H), 7.32 (m, 1H), 7.26 (s, 1H), 7.17 (m, 14H), 6.99 (s, 1H), 6.37 (s, 1H), 5.49 (dd, J = 3.3, 8.5 Hz, 1H), 5.12 (m, 8H), 3.86 (s, 3H), 3.63 (s, 3H), 3.54 (m, 2H), 3.44 (s, 3H), 3.43 (s, 3H), 3.38 (s, 1H), 2.81 (dd, J = 3.3, 17.5 Hz, 1H), 2.62 (dd, J = 8.5, 17.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 160.7, 156.8, 153.7, 152.5, 150.9, 150.9, 150.0, 146.5, 146.1, 142.9, 138.4, 138.1, 137.8, 137.2, 137.1, 132.8, 129.4 (2), 129.0 (2), 128.7 (2), 128.7 (2), 128.6 (2), 128.5 (2), 128.5 (2), 128.4, 128.3, 128.2 (2), 128.0, 127.7, 126.0, 125.9, 121.8, 120.7, 120.6, 116.8, 112.2, 96.1, 76.9, 76.5, 75.6, 75.4, 65.6, 61.9, 57.4, 55.3, 52.0, 48.8, 46.3; IR (film) 3462, 3034, 2930, 1737, 1602 cm^{-1}; HRMS (ES) calcd for $C_{56}H_{51}O_{13}$ (MH^+) 931.3353, found 931.3329.

7,8-Dibenzyloxy-6-[1-(*tert*-butyl-dimethyl-silanyloxy)-4-(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-yl)-3-oxo-butyl]-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (48). Alcohol **47** (0.219 g, 0.235 mmol) and imidazole (0.099 g, 1.45 mmol) were dissolved in DMF (21 mL). TBSOTf (0.31 mL, 1.35 mmol) was added, and the mixture was stirred under an inert atmosphere (N_2) for 18 h, after which the mixture was diluted with EtOAc (75 mL) and poured into saturated NH_4Cl (75 mL) and water (50 mL). The aqueous layer was washed with EtOAc (75 mL). The combined organic layers were washed with saturated NH_4Cl (75 mL) and brine (2 × 75 mL), dried with Na_2SO_4, and concentrated to a brown solid. The residue was purified by flash chromatography (1% Et_2O/CH_2Cl_2, SiO_2) to give **48** (0.134 g, 55%) as a dark yellow oil or a yellow foam: R_f = 0.66 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.51−7.54 (m, 4H), 7.39 (s, 1H), 7.24−7.35 (m, 17H), 6.62 (s, 1H), 5.54 (dd, J = 2.8, 8.5 Hz, 1H), 5.20 (d, J = 11.2 Hz, 1H), 5.16 (d, J = 10.9 Hz, 1H), 5.13 (d, J = 10.9 Hz, 1H), 5.12 (d, J = 11.4 Hz, 1H), 5.09 (d, J = 10.1 Hz, 1H), 5.03, (d, J = 9.9 Hz, 1H), 5.02 (d, J = 9.7 Hz, 1H), 4.99 (d, J = 9.7 Hz, 1H), 4.01 (s, 3H, 3.97 (s, 3H), 3.95 (s, 3H), 3.79 (s, 3H), 3.74 (d, J = 16.3 Hz, 1H), 3.64 (d, J = 16.3 Hz, 1H), 2.75 (dd, J = 8.6, 16.0 Hz, 1H), 2.45 (dd, J = 3.0, 16.0 Hz), 0.85 (s, 9H), 0.00 (s, 3H), −0.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 161.0, 157.4, 153.6, 152.5, 150.4, 150.2, 149.8, 148.1, 146.0, 142.6, 138.0, 137.8, 136.6, 136.4, 136.2, 132.3, 129.7, 129.2, 129.0, 128.8, 128.7, 128.6, 128.52, 128.47 (2), 128.4, 128.1, 127.9, 125.8, 125.2, 122.0, 120.5, 119.8, 116.4, 112.5, 94.4, 76.9, 76.8, 75.7, 75.3, 66.1, 62.4, 57.2, 56.0, 53.0, 50.9, 46.8, 26.0, 18.3, −4.7, −5.0; IR (film) 3092, 3065, 3034, 2953, 2934, 2887, 2856, 1745, 1602, 1455, 1440, 1351 cm^{-1}; HRMS (ES) calcd for $C_{62}H_{64}O_{13}SiNa$ (MNa^+) 1067.4014, found 1067.4020.

7,8-Dibenzyloxy-6-[1-(*tert*-butyl-dimethyl-silanyloxy)-4-(3,4-dibenzyloxy-5,6,8-trimethoxy-naphthalen-2-yl)-3,4-dioxo-butyl]-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (51). To **48** (0.0928 g, 0.0888 mmol) in THF (9 mL) were added Et_3N (0.25 mL, 1.79 mmol) and SeO_2 (0.0972 g, 0.876 mmol). The mixture was heated (65−70 °C, oil bath) for 2.5 h. The mixture was cooled, diluted with CH_2Cl_2 (10 mL), eluted through a plug of SiO_2 (CH_2Cl_2, 0.5 in.), and concentrated to an orange solid. The residue was taken up in CH_2Cl_2 and eluted through a plug of SiO_2 (0−50% Et_2O/CH_2Cl_2), which upon concentration yielded **51** (0.0672 g, 71%) as a yellow oil: R_f = 0.54 (50% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.52−7.53 (m, 2H), 7.45−7.47 (m, 2H), 7.42 (s, 1H), 7.25−7.34 (m, 14H), 7.18−7.19 (m, 3H), 6.64 (s, 1H), 5.53 (dd, J = 3.6, 7.7 Hz, 1H), 5.12−5.17 (m, 4H), 4.97−5.04 (m, 4H), 4.04 (s, 3H), 4.00 (s, 3H), 3.96 (s, 3H), 3.74 (s, 3H), 3.11 (dd, J = 7.8, 16.0 Hz, 1H), 2.82 (dd, J = 3.6, 16.0 Hz, 1H), 0.85 (s, 9H), 0.03 (s, 3H), −0.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 192.9, 161.0, 157.3, 154.7, 153.6, 153.3, 150.7, 149.2, 147.3, 145.7, 142.6, 137.6, 136.9, 136.7, 136.3, 136.2, 132.3, 129.6, 129.1, 129.0, 128.81, 128.78, 128.7 (2), 128.6, 128.51, 128.47, 128.4, 128.2, 128.0, 125.7, 123.5, 122.4, 119.2, 116.7, 112.6, 94.3, 77.1, 76.7, 76.1, 75.7, 65.9, 62.4, 57.0, 56.1, 53.0, 47.0, 26.0, 18.3, −4.7, −5.0; IR (film) 3092, 3065, 3034, 2953, 2934, 2887, 2856, 1745, 1671, 1606, 1459, 1351, 1258, 1058 cm^{-1}; HRMS (ES) calcd for $C_{62}H_{63}O_{14}Si$ (MH^+) 1059.3987, found 1059.3967.

3-Benzyloxy-4-hydroxy-5,6,8-trimethoxy-naphthalene-2-carboxylic Acid Ethyl Ester (55). *ortho*-Quinone **35** (1.56 g, 4.87 mmol) was dissolved in PhH (250 mL) and combined with 10% $Na_2S_2O_4$ (250 mL). The mixture was stirred overnight, changing from red to bright yellow. The layers were separated, and the aqueous layer was washed with PhH (100 mL). The combined organic layers were concentrated to a yellow solid that was used immediately.

The residue was dissolved in thoroughly deoxygenated DMF (75 mL), and $KHCO_3$ (3.10 g, 31.0 mmol) and BnBr (1.0 mL, 8.4 mmol) were added. After stirring for 5 d, the mixture was filtered through a plug of Celite (EtOAc) and poured into 1 N HCl (250 mL). The layers were separated, and the aqueous layer was washed with EtOAc (3 × 200 mL). The combined organic layers were washed with saturated NH_4Cl (2 × 250 mL), washed with brine (250 mL), dried with Na_2SO_4, and concentrated to an oily red solid. This residue was taken up in CH_2Cl_2 and eluted through a plug of SiO_2 (CH_2Cl_2 then EtOAc, 65 mm, 1 in.) to give a yellow solid and a red solid, respectively.

The yellow CH_2Cl_2 fraction was purified by flash chromatography (33% EtOAc/hexanes, SiO_2) to give **55** as a yellow crystalline solid. The red EtOAc fraction was purified by flash chromatography (33% EtOAc/hexanes, SiO_2) to give **55** as a yellow solid. The impure fractions were combined and resubjected to flash chromatography (33% EtOAc/hexanes, SiO_2) to give further **55** as an orange solid. The spectral data of **55** (0.982 g, 49%) were in accord with those reported.[12] A small amount of the isomeric phenol **55iso** was isolated as well: **4-Benzyloxy-3-hydroxy-5,6,8-trimethoxy-naphthalene-2-carboxylic acid ethyl ester**, a white crystalline or yellow solid; R_f = 0.48 (33% EtOAc/hexanes); mp 187−190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.7, (s, 1H), 8.65 (s, 1H), 7.70 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.52 (s, 1H), 5.06 (s, 2H), 4.49 (q, J = 7.1 Hz, 2H), 4.03 (s, 3H), 4.01 (s, 3H), 3.76 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 154.3, 152.9, 151.2, 139.2, 138.4, 135.3, 129.3, 128.9, 128.4, 127.9, 122.4, 115.9, 112.2, 92.4, 76.2, 62.5, 61.8, 56.8, 56.0, 14.5; IR (film) 3113, 2981, 2935, 2889, 2850, 1676, 1607, 1460, 1336, 1058, 1012 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{25}O_7$ (MH^+) 413.1600, found 413.1601.

3-Benzyloxy-4,5,6,8-tetramethoxy-naphthalene-2-carboxylic Acid Ethyl Ester (56). To a stirring solution of **55** (0.227 g, 0.549 mmol) in DMF (24 mL) was added K_2CO_3 (0.943 g, 6.82 mmol) and CH_3I (0.35 mL, 5.6 mmol). The mixture was stirred at rt for 22 h, after which it was diluted with EtOAc (75 mL) and filtered through a plug of Celite. The eluant was washed with 1 N HCl (100 mL), saturated NH_4Cl (100 mL), and brine (100 mL), dried with Na_2SO_4, and concentrated to a red oil. This oil was azeotroped with EtOAc (3 × 50 mL) which upon concentration resulted in **56** (0.233 g, 99%) as amorphous red solid to a light yellow powder: R_f = 0.44 (33% EtOAc/hexanes); mp 82−85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.59 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 6.62 (s, 1H), 5.22 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 166.4, 153.8, 152.2, 149.3, 148.5, 138.1, 136.2, 128.6, 128.5, 128.0, 127.4, 123.3, 122.4, 119.0, 94.6, 76.1, 62.3, 62.2, 61.2, 57.2, 56.0, 14.5; IR (film) 2980, 2937, 2883, 2841, 1718, 1613, 1594, 1455, 1355 cm^{-1}; HRMS (ES) calcd for $C_{24}H_{27}O_7$ (MH^+) 427.1757, found 427.1750.

(3-Benzyloxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-methanol (57). To a stirring solution of **56** (0.233 g, 0.546 mmol) in THF (5 mL) in an ice bath was added $LiAlH_4$ (0.106 g, 2.79 mmol). After stirring cold for 2 h, the mixture was quenched by the addition of water (10 mL). The resultant mixture was diluted with 1 N HCl (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to a yellow oil. The residue was eluted through a plug of SiO_2 (Et_2O) to give **57** (0.209 g, 100%) as a yellow oil: R_f = 0.21 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.49 (dm, J = 7.1 Hz, 2H), 7.39 (tm, J = 7.2 Hz, 2H), 7.34 (tm, J = 7.2 Hz, 1H), 6.61 (s, 1H), 5.28 (s, 2H), 4.69 (d, J = 4.8 Hz, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H), 2.18 (t, J = 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 150.3, 149.3, 147.0, 137.8, 136.6, 131.9, 128.8, 128.6, 128.4, 125.2, 119.8, 117.8, 94.7, 75.6, 62.7, 62.2, 62.1, 57.4, 56.0; IR (film) 3447, 3065, 3030, 2934, 2841, 1062, 1498, 1455, cm^{-1}; HRMS (ES) calcd for $C_{22}H_{24}O_6Na$ (MNa^+) 407.1471, found 407.1475.

3-Benzyloxy-4,5,6,8-tetramethoxy-naphthalene-2-carbaldehyde (58). To a stirring solution of **57** (0.209 g, 0.544 mmol) in CH_2Cl_2 (5 mL) in an ice bath was added DMP (0.246 g, 0.580 mmol) in one portion. The mixture was stirred cold for 1.1 h, after which it was filtered through a plug of Celite (CH_2Cl_2) and concentrated to a red oil. The residue was suspended in 30% EtOAc/hexanes (5 mL) and sonicated for 5 min. The resulting suspension was eluted through a plug of SiO_2 (30% EtOAc/hexanes) to give **58** (0.180 g, 87%) as a yellow crystalline solid: R_f = 0.37 (33% EtOAc/hexanes); mp 120−124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.53 (s, 1H), 7.47 (dm, J = 6.9 Hz, 2H), 7.38 (tm, J = 7.1 Hz, 2H), 7.33 (tm, J = 7.0 Hz, 1H), 6.62 (s, 1H), 5.29 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 155.1, 153.3, 150.8, 147.4, 137.1, 136.1, 128.83, 128.77 (2), 128.6, 126.7, 121.5, 119.1, 94.3, 76.7, 62.3, 62.2, 57.0, 56.1; IR (film) 3065, 3030, 2937, 2845, 1683, 1606, 1498, 1455, 1351 cm^{-1}; HRMS (ES) calcd for $C_{22}H_{22}O_6Na$ (MNa^+) 405.1314, found 405.1319.

2-Benzyloxy-1,5,7,8-tetramethoxy-3-(2-nitro-vinyl)-naphthalene (59). To a solution of **58** (5.1 g, 13.3 mmol) in CH_3NO_2 (350 mL) was added NH_4OAc (0.381 g, 4.94 mmol). The mixture was heated to reflux (oil bath, 120 °C) and stirred for 8 h. The mixture was cooled, and additional NH_4OAc (4.22 g, 5.47 mmol) was added. The mixture was heated to reflux (oil bath, 120 °C) and stirred for 5 h. The mixture was cooled and partitioned between CH_2Cl_2 (1.2 L) and water (1.2 L). The aqueous layer was further extracted with CH_2Cl_2 (2 × 600 mL). The combined organic layers were dried with Na_2SO_4 and concentrated to give **59** (5.6 g, 99%) as a red oil: R_f = 0.37 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.15 (d, J = 13.6, 1H), 7.46 (dm, J = 6.9 Hz, 2H), 7.38 (tm, J = 7.1 Hz, 2H), 7.34 (tm, J = 7.0 Hz, 1H), 6.63 (s, 1H), 5.23 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.8, 149.2, 147.8, 137.9, 136.7, 136.3, 136.0, 129.0, 128.8, 128.7, 127.2, 122.6, 121.8, 119.4, 94.6, 76.0, 62.23, 62.20, 57.0, 56.1; IR (film) 3150, 3107, 3065, 3034, 2937, 2845, 1606, 1509, 1455 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{24}NO_7$ (MH^+) 426.1553, found 426.1598.

2-Benzyloxy-1,5,7,8-tetramethoxy-3-(2-nitro-ethyl)-naphthalene (60). To a stirring solution of **59** (0.390 g, 0.917 mmol) in CH_2Cl_2 (10 mL) and MeOH (10 mL) in an ice bath, was added $NaBH_4$ (0.0816 g, 2.16 mmol) in one portion. After stirring for 15 min, the now-yellow mixture was quenched by the addition of 1 N HCl (5 mL) and partitioned between CH_2Cl_2 (50 mL) and 1 N HCl (50 mL). The aqueous layer was washed once with CH_2Cl_2 (25 mL). The combined organic layers were dried with Na_2SO_4 and concentrated to a red-orange oil. The residue was eluted through a plug of SiO_2 (25% Et_2O/CH_2Cl_2) to give **60** (0.380 g, 97%) as a yellow-orange foam: R_f = 0.45 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.47 (dm, J = 7.1 Hz, 2H), 7.39 (tm, J = 7.2 Hz, 2H), 7.35 (tm, J = 7.1 Hz, 1H), 6.61 (s, 1H), 5.27 (s, 2H), 4.55 (t, J = 7.5 Hz, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 3.32 (t, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 150.4, 149.3, 147.2, 137.8, 136.5, 128.8, 128.5, 128.4, 126.6, 125.1, 119.7, 119.3. 94.8, 75.4, 75.3, 62.2, 62.1, 57.4, 56.0, 29.8; IR (film) 3065, 3030, 2934, 2845, 1621, 1602, 1552, 1498, 1455 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{26}NO_7$ (MH^+) 428.1709, found 428.1707.

7-Benzyloxy-6-[3-(3-benzyloxy-4,5,6,8-tetramethoxy-naphthalen-2-ylmethyl)-4,5-dihydro-isoxazol-5-yl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (61). To **60** (1.3 g, 3.0 mmol) and **28**[14] (1.101 g, 3.005 mmol) dissolved in PhH (80 mL) were added PhNCO (1.40 mL, 12.9 mmol) and Et_3N (0.060 mL, 0.43 mmol). The mixture was heated (oil bath, 45−50 °C) and stirred for 20 h, whereupon additional PhNCO (0.40 mL, 3.68 mmol) was added to the mixture. After stirring an additional 20 h, the mixture was cooled, filtered through Celite (PhH), and concentrated to a dark yellow oil. The residue was purified by flash chromatography (45% EtOAc/hexanes, SiO_2) to give **61** (2.026 g, 86%) as a yellow oil or foam: R_f = 0.42 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.44 (d, J = 6.9 Hz, 2H), 7.25−7.34 (m, 10H), 6.61 (s, 1H), 5.60 (dd, J = 7.0, 11.3 Hz, 1H), 5.17 (d, J = 11.0 Hz, 1H), 5.15 (d, J = 10.9 Hz, 1H), 5.14 (d, J = 10.9 Hz, 1H), 5.12 (d, J = 11.1 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.944 (s, 3H), 3.942 (s, 3H), 3.874 (s, 3H), 3.867 (s, 3H), 3.72 (s, 2H), 3.10 (dd, J = 11.3, 17.6 Hz, 1H), 2.49 (dd, J = 7.1, 17.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 158.0, 157.1, 154.9, 152.4, 150.7, 150.3, 149.3, 147.4, 144.8, 142.6, 137.7, 136.7, 136.5, 132.6, 128.8, 128.7, 128.65, 128.59, 128.5, 128.3, 126.7, 125.0, 121.1, 119.8, 119.2, 116.6, 112.5, 94.9, 76.6, 75.8, 75.3, 62.2, 62.1, 62.0, 57.4, 56.0, 53.0, 44.9, 29.1; IR (film) 3065, 3034, 2937, 2907, 2841, 2250, 1737, 1621, 1598, 1455 cm^{-1}; HRMS (ES) calcd for $C_{44}H_{41}NO_{12}Na$ (MNa^+) 798.2526, found 798.2544.

7-Benzyloxy-6-[4-(3-benzyloxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-1-hydroxy-3-oxo-butyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (62). Isoxazoline **61** (0.226 g, 0.291 mmol) was dissolved in THF (9 mL) and MeOH (9 mL). $B(OH)_3$ (0.0811 g, 1.31 mmol) was dissolved in water (3 mL), and the solution was added to the stirring mixture along with Raney Ni (~1 mL, 50% in water). The system was purged and stirred rapidly under an atmosphere of H_2 for 21 h. The mixture was diluted with EtOAc (25 mL) and filtered through a plug of Celite (EtOAc). The eluant was washed with water (70 mL), washed with brine (70 mL), dried with Na_2SO_4, and concentrated to give **62** (0.206 g, 91%) as a yellow oil: R_f = 0.30 (50% EtOAc/hexanes) UV/CAM; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.39−7.40 (m, 4H), 7.28−7.35 (m, 8H), 6.60 (s, 1H), 5.29 (dd, J = 2.1, 9.6 Hz, 1H), 5.18 (d, J = 10.9 Hz, 1H), 5.17 (d, J = 11.1 Hz, 1H), 5.13 (d, J = 11.0 Hz, 1H), 5.09 (d, J = 11.1 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.63 (d, J = 16.3 Hz, 1H), 3.57 (d, J = 16.4 Hz, 1H), 3.53 (s, 1H), 2.76 (dd, J = 2.6, 17.7 Hz, 1H), 2.55 (dd, J = 9.1, 17.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 160.9, 157.2, 154.8, 152.4, 150.6, 150.3, 149.2, 147.1, 145.8, 142.5, 137.8, 136.7, 136.5, 132.5, 128.9, 128.72, 128.65, 128.6, 128.5, 128.2, 125.3, 125.2, 121.5, 120.1, 119.7, 116.2, 112.6, 94.8, 75.8, 75.1, 65.3, 62.14, 62.08, 62.05, 57.4, 56.0, 53.0, 48.5, 46.3; IR (film) 3478, 3092, 3065, 3034, 2937, 2845, 1733, 1602, 1455 cm^{-1}; HRMS (ES) calcd for $C_{44}H_{42}O_{13}Na$ (MNa^+) 801.2523, found 801.2555.

7-Benzyloxy-6-[4-(3-benzyloxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-1-(*tert*-butyl-diphenyl-silanyloxy)-3-oxo-butyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (63). Alcohol **62** (0.206 g, 0.265 mmol) and imidazole (0.258 g,

3.79 mmol) were dissolved in CH_2Cl_2 (20 mL). *tert*-Butyldiphenylsilyl triflate (6.3 mL, 2.5 mmol) in CH_2Cl_2 and Et_3N (0.25 mL, 1.8 mmol) were added, and the mixture was stirred under an inert atmosphere (N_2) and excluded from light for 21 h. The mixture was filtered through a plug of Celite (CH_2Cl_2), washed with 1 N HCl (75 mL) and brine (75 mL), dried with Na_2SO_4, and concentrated to a dark orange oil. The residue was purified by flash chromatography (35% EtOAc/hexanes, SiO_2) to give **63** (0.158 g, 59%) as a yellow oil or yellow foam: R_f = 0.61 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.56 (m, 3H), 7.13−7.42 (m, 20H), 6.57 (s, 1H), 5.62 (dd, J = 5.6, 5.6 Hz, 1H), 5.07 (d, J = 11.0 Hz, 1H), 5.03 (d, J = 11.1 Hz, 1H), 4.99 (d, J = 10.8 Hz, 1H), 4.54 (d, J = 10.9 Hz, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.62 (d, J = 16.2 Hz, 1H), 3.50 (d, J = 16.1 Hz, 1H), 2.84 (dd, J = 6.5, 15.6 Hz, 1H), 2.57 (dd, J = 4.5, 15.9 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 161.0, 157.2, 154.9, 152.4, 150.5, 150.2, 149.4, 147.1, 146.5, 142.2, 137.9, 136.9, 136.5, 136.1, 136.0, 133.3, 133.0, 131.9, 130.0, 129.9, 128.6, 128.5, 128.43, 128.37, 128.3, 128.1, 127.8, 127.7, 125.6, 125.0, 122.7, 120.0, 119.7, 115.9, 112.6, 94.6, 75.2, 75.1, 67.1, 62.1, 62.0, 61.9, 57.4, 55.9, 53.0, 50.6, 46.5, 27.2, 19.5; IR (film) 3073, 3034, 2999, 2934, 2895, 2860, 1741, 1602, 1455, 1355, 1073 cm^{-1}; HRMS (ES) calcd for $C_{60}H_{60}O_{13}SiNa$ (MNa^+) 1039.3701, found 1039.3651.

7-Benzyloxy-6-[4-(3-benzyloxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-1-(*tert*-butyl-diphenyl-silanyloxy)-3,4-dioxo-butyl]-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (64). To **63** (0.482 g, 0.474 mmol) in THF (100 mL) were added water (0.0847 mL, 4.70 mmol), Et_3N (1.30 mL, 9.33 mmol), and SeO_2 (0.519 g, 4.68 mmol). The mixture was heated (55−60 °C, oil bath) and stirred for 3 h. The mixture was cooled, diluted with CH_2Cl_2 (100 mL), eluted through a plug of SiO_2 (50% CH_2Cl_2/Et_2O), and concentrated to a dark yellow oil. The residue was eluted through a plug of SiO_2 (50% Et_2O/CH_2Cl_2) to give **64** (0.466 g, 95%) as a clear yellow oil: R_f = 0.46 (50% EtOAc/hexanes) UV/CAM; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.58−7.60 (m, 2H), 7.37−7.43 (m, 6H), 7.27−7.29 (m, 4H), 7.13−7.23 (m, 10H), 6.60 (s, 1H), 5.56 (dd, J = 5.4, 5.4 Hz, 1H), 5.00 (d, J = 10.7 Hz, 1H), 4.96 (d, J = 10.8 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 4.48 (d, J = 10.9 Hz, 1H), 4.03 (s, 3H), 3.970 (s, 3H), 3.967 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.63 (s, 3H), 3.27 (dd, J = 5.5, 15.4 Hz, 1H), 2.87 (dd, J = 5.3, 15.4 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 193.1, 161.0, 157.2, 154.7, 153.4, 150.7, 148.8, 146.8, 145.6, 142.2, 136.9, 136.2, 136.0, 135.0, 133.3, 132.8, 131.8, 130.1, 129.9, 129.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.25, 128.21, 127.9, 127.8, 127.7, 125.3, 123.3, 122.9, 119.0, 116.1, 112.8, 94.3, 76.0, 75.2, 67.3, 62.3, 62.2, 61.7, 56.9, 56.0, 53.0, 46.7, 27.2, 19.5; IR (film) 3069, 3034, 2999, 2937, 2891, 2860, 1745, 1606, 1455, 1355, 1069 cm^{-1}; HRMS (ES) calcd for $C_{60}H_{58}O_{14}SiNa$ (MNa^+) 1053.3494, found 1053.3517.

6-[1-(*tert*-Butyl-diphenyl-silanyloxy)-4-(3-hydroxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-3,4-dioxo-butyl]-7-hydroxy-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic Acid Methyl Ester (65). To a stirring solution of **64** (0.0955 g, 0.0926 mmol) in EtOAc (11 mL) was added 10% Pd/C (0.0963 g, 0.0905 mmol). The system was evacuated and purged with H_2 and stirred under an atmosphere of the same for 1 h, after which it was eluted through a plug of packed Celite (EtOAc) and concentrated to yield **65** (0.079 g, 100%) as an oily yellow-orange foam or a yellow oil: R_f = 0.19 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$ with DABCO[17]) δ 8.28 (br s, 1H), 7.72 (d, J = 6.7 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.41 (br s, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.27 (br t, 1H), 7.17 (br t, J = 6.8 Hz, 2H), 6.92 (s, 1H), 6.47 (s, 1H), 5.70 (br s, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 2.85 (br s, 1H), 2.77 (DABCO), 2.62 (br s, 1H), 1.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$ with DABCO[17]) δ 196.8, 160.9, 157.3, 155.6, 154.1, 149.2, 147.9, 140.8, 138.1, 137.8, 136.2, 135.9, 135.8, 135.0, 132.7, 132.4, 130.4, 130.1, 128.0, 127.9, 127.7, 123.3, 118.1, 116.5, 114.7, 112.9, two aromatic carbons and the hemiketal signal could not be resolved from the baseline, 92.8, 68.1, 62.4, 62.1, 61.7, 56.8, 56.1, 52.8, 45.4 (DABCO), 42.6, 27.2, 19.5; IR (film) 3383, 3074, 2943, 2866, 1738, 1622, 1460, 1352, 1074 cm^{-1}; HRMS (ES) calcd for $C_{46}H_{46}O_{14}SiNa$ (MNa^+) 873.2555, found 873.2545.

Tetramethylnaphthyl Spiroketal Ketone (66). To **65** (0.0064 g, 0.0075 mmol) in PhH (3.8 mL) was added TsOH (0.0183 g, 0.096 mmol). The mixture was heated (oil bath, 100−105 °C) and stirred for 1 h. The mixture was cooled and partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated to a brown solid. The residue was eluted through a plug of SiO_2 (25% Et_2O/CH_2Cl_2) to give **66** (0.0054 g, 86%) as a dark yellow oil or resin: R_f = 0.45 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6 as a 4:1 mixture of diastereomers) δ 8.72 (s, 0.25H), 8.65 (s, 1H), 7.80−7.82 (m, 0.5H), 7.77−7.79 (m, 2.5H), 7.69−7.71 (m, 2H), 7.47 (s, 1H), 7.18−7.23 (m, 6 H), 7.11−7.14 (m, 2.5H), 7.02 (s, 0.25H), 6.77 (s, 0.25H), 6.09 (s, 0.25H), 6.07 (s, 1H), 5.60 (dd, J = 5.2, 11.7 Hz, 1H), 5.34 (dd, J = 5.5, 5.5 Hz, 0.25H), 3.94 (s, 0.75H), 3.87 (s, 3.75H), 3.81 (s, 3H), 3.80 (s, 0.75H), 3.70 (s, 3H), 3.46 (s, 0.75H), 3.45 (s, 3H), 3.42 (s, 3.75H), 3.29 (s, 0.75H), 3.27 (s, 3H), 2.66 (dd, J = 12.3, 12.9 Hz, 1H), 2.42 (dd, J = 6.0, 14.2 Hz, 0.25H), 2.39 (dd, J = 5.1, 14.3 Hz, 0.25H), 2.26 (dd, J = 5.5, 13.1 Hz, 1H), 1.22 (s, 2.25H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6 for the major diastereomer) δ 193.1, 161.0, 156.4, 155.82, 155.78, 154.6, 150.8, 147.6, 142.8, 138.3, 137.5, 136.41, 136.37, 136.3, 136.2, 135.6, 133.6, 133.1, 131.6, 130.7, 130.6, 130.55, 130.50, 128.6, 128.5, 120.4, 118.5, 112.1, 103.7, 94.1, 64.7, 61.95, 61.90, 61.7, 56.5, 55.4, 52.1, 35.1, 27.3, 19.7; IR (film) 3073, 2934, 2860, 1741, 1625, 1590, 1459 cm^{-1}; HRMS (ES) calcd for $C_{46}H_{44}O_{13}SiNa$ (MNa^+) 855.2449, found 855.2424.

Tetramethylnaphthyl Spiroketal Ketone Alkene (67). Isolated as a yellow or orange oil in trace amounts (<5%) from the above protocol: R_f = 0.22 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.38 (s, 1H), 7.22 (s, 1H), 7.14 (d, J = 9.8 Hz, 1H), 6.59 (s, 1H), 6.06 (d, J = 9.8 Hz, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 1.53 (water), 1.26 (grease); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 161.0, 156.9, 156.2, 155.7, 154.7, 150.4, 145.7, 142.5, 137.3, 136.3, 131.3, 130.9, 128.7, 126.7, 121.2, 121.0, 119.9, 119.4, 117.0, 116.0, 112.1, 101.0, 93.3, 62.6, 62.4, 62.2, 56.8, 56.2, 53.1, 29.9 (grease); IR (film) 2957, 2918, 2853, 1733, 1625, 1586, 1459 cm^{-1}; HRMS (ES) calcd for $C_{30}H_{24}O_{12}Na$ (MNa^+) 599.1165, found 599.1160.

Hydroxyl Spiroketal (68). To a stirring solution of **66** (0.0096 g, 0.0115 mmol) in MeOH (1.5 mL) and CH_2Cl_2 (2 mL) in an ice bath was added $NaBH_4$ (0.0040 g, 0.106 mmol) dissolved in MeOH (0.5 mL). After stirring for 10 min, the mixture was quenched by the addition of 1 N HCl (10 mL) and partitioned with CH_2Cl_2 (10 mL). The organic layer was dried with Na_2SO_4 and concentrated to a yellow film. This residue was purified by flash chromatography (50% EtOAc/hexanes, SiO_2) to give **68** (0.0032 g, 33%) as a faintly yellow film: R_f = 0.77 (2.5% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$ for the major diastereomer) δ 8.12 (s, 1H), 7.74−7.79 (m, 4 H), 7.40−7.49 (m, 6H), 7.27−7.29 (m, 2H), 6.58 (s, 1H), 5.45 (dd, J = 6.4, 10.1 Hz, 1H), 5.18 (s, 1H), 3.98 (coincidental s, 6H), 3.95 (s, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 2.46 (dd, J = 10.2, 13.2 Hz, 1H), 2.41 (dd, J = 6.5, 13.3 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 157.1, 152.9, 150.9, 150.1, 146.94, 146.85, 142.0, 136.83, 136.80, 136.2, 136.1 (2C), 133.3, 132.5, 130.6, 130.5, 129.8, 128.3, 128.2, 127.0, 126.1, 121.0, 119.8, 116.1, 114.6, 112.7, 109.0, 93.7, 64.7, 62.1, 62.03, 61.96, 57.1, 56.0, 53.0, 36.7, 29.9, 27.3, 19.7; IR (film) 3429, 2935, 2858, 1746, 1614, 1460, 1336, 1251, 1112 cm^{-1}; HRMS (ES) calcd for $C_{46}H_{47}O_{13}Si$ (MH^+) 835.2786, found 835.2772.

Spiroketal Thiopropane (70a). To a stirring solution of **66** (0.0062 g, 0.0074 mmol) in CH_2Cl_2 (2.5 mL) in an ice bath were added propanedithiol (0.0120 mL, 0.120 mmol) and BF_3 Et_2O (0.0150 mL, 0.118 mmol). The mixture was slowly warmed to rt. After stirring for 1 d, additional dithiane (0.0120 mL, 0.120 mmol) and BF_3 etherate

(0.0300 mL, 0.237 mmol) were added. After another 1 d, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried overnight with Na_2SO_4 and concentrated to a yellow oil.

This residue was dissolved in THF (1 mL) and MeOH (1 mL) to which was added $B(OH)_3$ (0.0112 g, 0.181 mmol) dissolved in water (0.33 mL), followed by Raney Ni (6 drops, ~0.3 mL). The system was evacuated and purged with H_2 and stirred under an atmosphere of the same for 18 h. Additional Raney Ni (3 drops, ~0.15 mL) was added, and stirring under H_2 was continued for 7 h. The mixture was diluted with EtOAc (5 mL) and eluted through a plug of Celite (EtOAc). The eluant was washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated to a yellow oil. This residue was purified by flash chromatography (SiO_2, 33% EtOAc/hexanes) to give a single diastereomer of **70a** (0.001 g) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.56 (d, J = 6.8 Hz, 2H), 7.46 (d, J = 7.3 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.14−7.22 (m, 6H), 7.10 (d, J = 2.0 Hz, 1H), 6.46 (d, J = 2.2 Hz, 1H), 5.58 (t, J = 6.2 Hz, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 3.89−4.00 (m, 2H), 3.84 (s, 3H), 3.51 (dd, J = 6.1, 14.1 Hz, 1H), 3.34 (dd, J = 6.3, 14.1 Hz, 1H), 2.55 (t, J = 7.3 Hz, 2H), 1.40 (sextet, J = 7.3 Hz, 2H), 1.08 (s, 9H), 0.86 (t, J = 7.3 Hz, 2H); IR (film) 3074, 2927, 2858, 1738, 1622, 1460 cm^{-1}; HRMS (ES) calcd for $C_{48}H_{51}O_{11}SSi$ (MH^+) 863.2921, found 863.2906.

Spiroketal Ketone Quinone (71). To a stirring solution of 77 (0.0360 g, 0.0432 mmol) in CH_3CN (7 mL) and water (0.7 mL) in an ice bath was added DDQ (0.0110 g, 0.0485 mmol). The mixture was warmed to rt over 18 h. Additional DDQ (0.0096 g, 0.0423 mmol) was added, and after 3 h the mixture was poured into saturated $NaHCO_3$ (25 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and concentrated to a red oil. The residue was purified by flash chromatography (60% EtOAc/hexanes, SiO_2) to give **71** (0.0184 g, 53%) as a dark yellow oil: R_f = 0.29 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6 as a 4:1 mixture of diastereomers) δ 8.32 (s, 0.25H), 8.19 (s, 1H), 7.65−7.76 (m, 5H), 7.50 (s, 1H), 7.12−7.23 (m, 8.5H), 7.00 (s, 0.25H), 6.66 (s, 0.25H), 5.694 (s, 0.25 H), 5.689 (s, 1H), 5.41 (dd, J = 5.4, 11.9 Hz, 1H), 5.14 (dd, J = 4.9, 5.2 Hz, 0.25H), 3.83 (s, 3H), 3.80 (s, 0.75H), 3.78 (s, 0.75H), 3.53 (s, 3H), 3.43 (s, 3H), 3.42 (s, 0.75H), 2.90 (s, 3H), 2.89 (s, 0.75H), 2.45 (dd, J = 12.7, 12.7 Hz, 1H), 2.23 (dd, J = 5.4, 14.6 Hz, 0.25H), 2.18 (dd, J = 4.7, 14.5 Hz, 0.25H), 2.11 (dd, J = 5.4, 13.3 Hz, 1H), 1.17 (s, 11.25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 182.3, 178.1, 166.0, 161.7, 161.4, 156.7, 151.2, 147.3, 147.1, 143.7, 136.81, 136.80, 136.7, 136.6, 135.8, 133.8, 133.1, 131.6, 131.4, 131.2, 130.7, 130.3, 123.1, 120.7, 119.3, 112.3, 109.4, 104.4, 64.7, 62.4, 61.6, 56.1, 52.7, 35.1, 27.7. 20.2; IR (film) 3074, 3012, 2943, 2896, 2858, 1746, 1692, 1653, 1607, 1468, 1205, 1112 cm^{-1}; HRMS (ES) calcd for $C_{44}H_{38}O_{13}SiNa$ (MNa^+) 825.1979, found 825.1999.

■ ASSOCIATED CONTENT

Supporting Information. Characterization data including ^{1}H and ^{13}C NMR spectra. Coordinates of calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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