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Alternative Spiroketalization Methods toward Purpuromycin: A Hemiketal Conjugate Addition Strategy and Use of an Electron-Rich Isocoumarin Precursor

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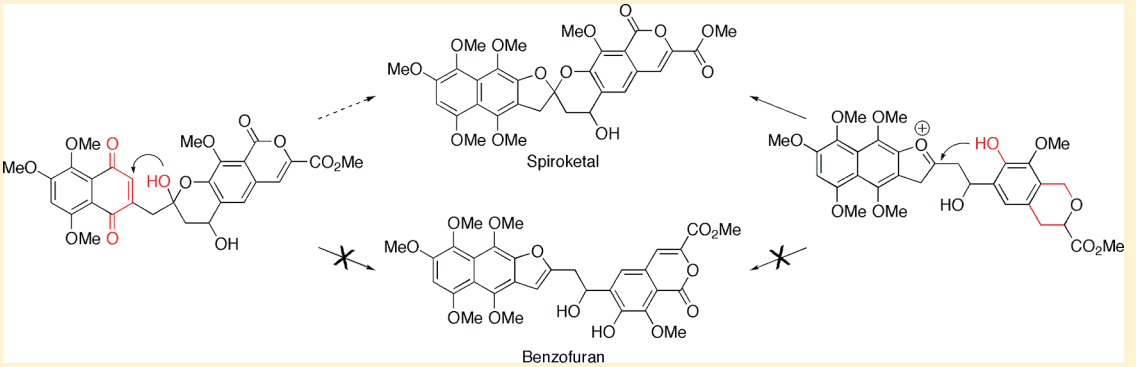
Supporting Information

ABSTRACT:



Two methods are presented that were designed to circumvent the persistent problem of benzofuran formation and instead yield a spiroketal of the rubromycin family type. First, using an alternative disconnection, a hemiketal conjugate addition to a naphthaquinone electrophile was investigated. Synthesis of the requisite electrophile provided insight into the selective oxidation and functionalization of the naphthalene portion. Second, the electronic features of the isocoumarin ring system were adjusted, and the corresponding reactivity further supports the hypothesis that electron-rich isocoumarins are capable of spiroketalization. Robust, flexible syntheses from simple precursors were developed that allowed multiple reduced isocoumarins to be generated. Combined, the data presented herein give insight into the sensitivities of this family and illuminate other potential methods of spiroketalization. In addition, the convergent assembly of substrates containing different naphthaquinone and isocoumarin subunits highlights the utility of our 1,3-dipolar cycloaddition approach to generate analogs of these structures for SAR, as well as chemical reactivity studies.

INTRODUCTION

The rubromycin family of compounds, including purpuromycin,[1,2] are interesting from both a structural standpoint and because of their medicinal activity. In addition to the usual properties of soil bacterial secondary metabolites, this family shows activity against cancer,[3] DNA helicase,[4] reverse transcriptase,[5] DNA polymerase,[6] and human telomerase.[7] Known since 1953,[8] but structurally undefined for nearly twenty years,[9] the rubromycins were determined with respect to their structure[3] and some stereochemistry,[3] and they finally succumbed to total synthesis in the early 21st century.[10−12] While the relative stereochemistry of purpuromycin has been proposed,[13] the absolute configuration remains unknown.

The rubromycin family of compounds, including purpuromycin (**1**), is shown in Figure 1.[14,15] As shown by the labeling, the molecule can be architecturally divided into three portions, the naphthazarin, spiroketal, and isocoumarin. Previously, we described our investigations into the naphthazarin[16] where the naphthalene oxidation state was used as a synthon, a method common to this type of carbocycle.[11,17] We have also built variably substituted isocoumarins.[18] While combination of the hemispheres has proceeded well using 1,3-dipolar cycloaddition methodology,[19] spiroketalization of this family has posed a great challenge.[19,20]

As we have previously reported,[19] elimination of penultimate spiroketal intermediates to form benzofurans has been the major obstacle in the production of this family (Figure 2). The current hypothesis is that the electronic differences between the naphthalene and isocoumarin portions are the root of the problem.[19,21,22] Specifically, if the isocoumarin phenol is electron-poor it is a poor nucleophile, and elimination to benzofuran is competitive.[19] The stability of the isocoumarin is also an issue.[19,21,23] Some successful approaches by others to synthesize this family have involved

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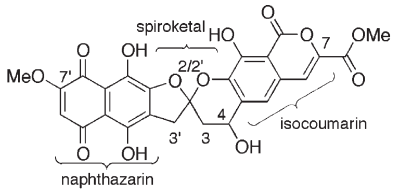
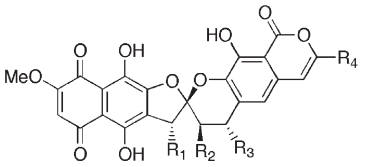




Compound	R_1	R_2	R_3	R_4
γ-Rubromycin	H	H	H	CO_2Me
Heliquinomycinone	OH	OH	H	CO_2Me
Griseorhodin C	OH	OH	OH	CH_3

Figure 1. Rubromycin family of compounds.

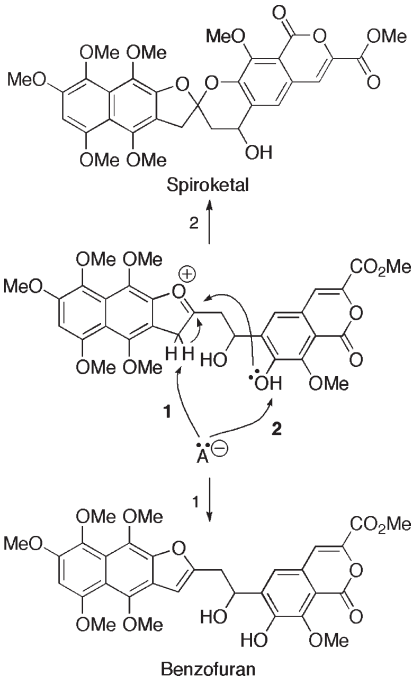


Figure 2. Spiroketal versus benzofuran.

formation of the complete isocoumarin after spiroketalization[10,11] or after coupling of the two hemispheres.[23] Purpuromycin is a continuing challenge in spite of the completion of the parent family member rubromycin[10−12] and the aglycon of heliquinomycin.[24]

Herein, we describe two approaches to circumvent the formation of benzofuran. In the first, the conjugate hemiketal addition approach (Figure 3a), a new disconnection is used wherein the nucleophilic phenol is removed from the naphthalene. This approach prevents benzofuran formation by utilizing a different pathway to the spiroketal instead of traditional ketalization. Similar strategies have been successfully illustrated by Kita[10] and Pettus,[12] where a Pummerer type reaction or an oxidative cycloaddition, respectively, are used to circumvent classical spiroketalization.

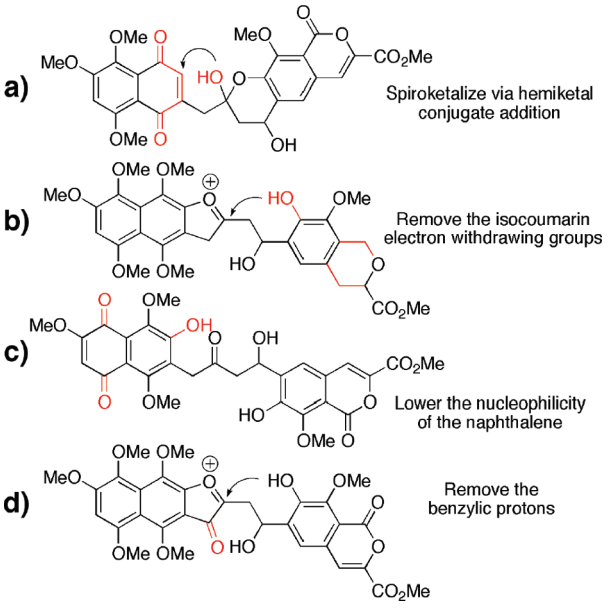


Figure 3. Strategies for preventing formation of benzofuran.

The second approach (Figure 3b) describes modification of the isocoumarin to make it more electron-rich and bring it in line with the nucleophilicity of the naphthalene. Reissig[22] and Brimble[11] have seen success with this type of tactic.

Other reasonable approaches to prevent benzofuran elimination include reducing the nucleophilicity of the naphthalene via a naphthaquinone (Figure 3c). We have shown previously[19] that such an intermediate does not spiroketalize although Reissig has successfully isolated a naphthaquinone spiroketal in low yield.[21] Another alternative, removal of the acidic benzylic protons, completely suppresses the undesired pathway (Figure 3d) and is discussed in a companion paper (DOI 10.1021/jo200399z).[25]

RESULTS AND DISCUSSION

A Conjugate Hemiketal Approach Toward Spiroketals. As shown in the retrosynthesis in Figure 4, with the proper oxidation state adjustment of the naphthalene, disconnection of the hemiketal and its tautomer can be envisaged. This material is easily transformed to an isoxazoline, the product of a 1,3-dipolar cycloaddition between a naphthalene nitrile oxide and an isocoumarin styrene.[18] The nitrile oxide can be produced from naphthaldehydes such as **2** or **3**.

There is precedent for this type of conjugate addition cyclization,[26,27] the most recent by Tamura and co-workers,[28] who were successful in adding a pendant nucleophile to a naphthaquinone electrophile under oxidative conditions (Figure 5). The proposed forward mechanism as catalyzed by base is shown on a model system in Figure 6.

Of concern was the formal closure type being attempted (Figure 7). Baldwin's work[29] shows that a 5-*endo*-trig type cyclization is disfavored but clearly possible according to the precedents above.[26−28] A formal closure of type 5-*exo*-trig may also be possible if the distal quinone acts as a strong electron-withdrawing group, allowing the nucleophilic addition of the hemiketal to the proximal aromatic ring. Our initial work utilized a benzene-based model system, but it soon became evident that this system was inadequate to mimic the reactivity of the

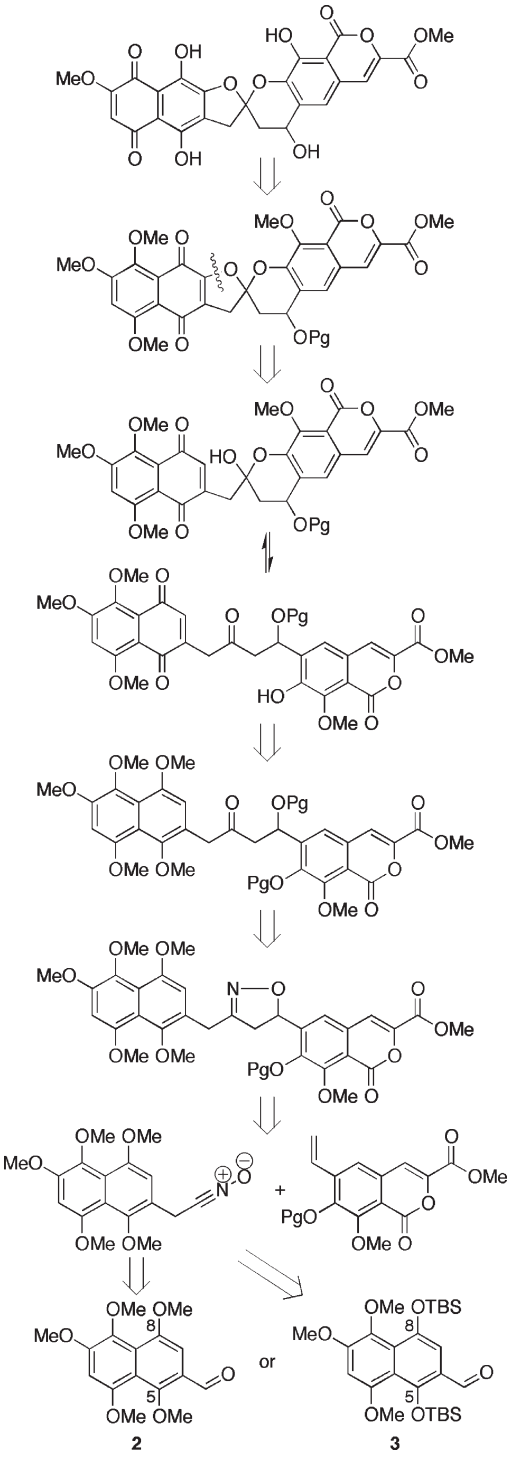


Figure 4. Hemiketal conjugate approach retrosynthetically.

naphthalene/naphthaquinone derivative of the naphthazarin. Instead, we undertook the synthesis of naphthalenes **2** and **3** (Figure 4).

Initial work on the naphthalene focused on orthogonally protecting the C5 and C8 phenols (that is, **3**, Figure 4) to be able to selectively generate both possible quinone isomers (see Scheme 3) via selective deprotection and oxidation. In spite of good precedent,[30] a Hauser type synthesis[31] would not proceed, probably due to the slightly more electron-rich nature of this

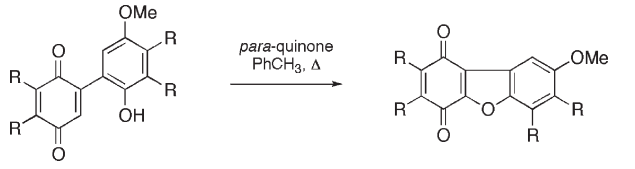


Figure 5. Pendant conjugate addition by Tamura and co-workers.[28]

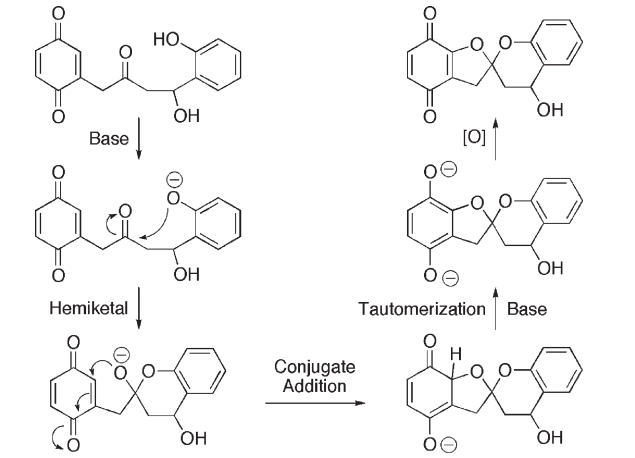


Figure 6. Base catalyzed hemiketal conjugate approach.

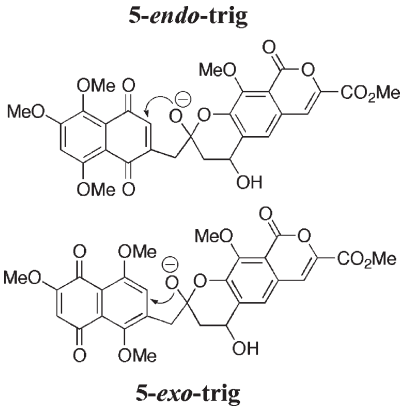
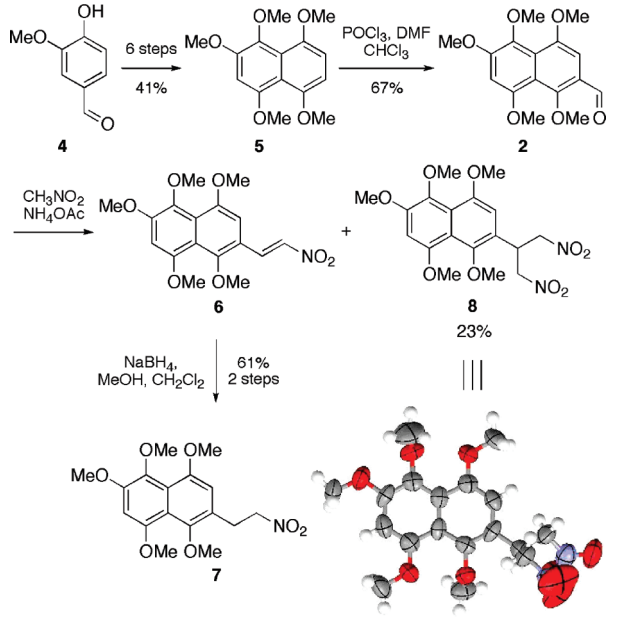


Figure 7. Hemiketal conjugate addition ring closure types.

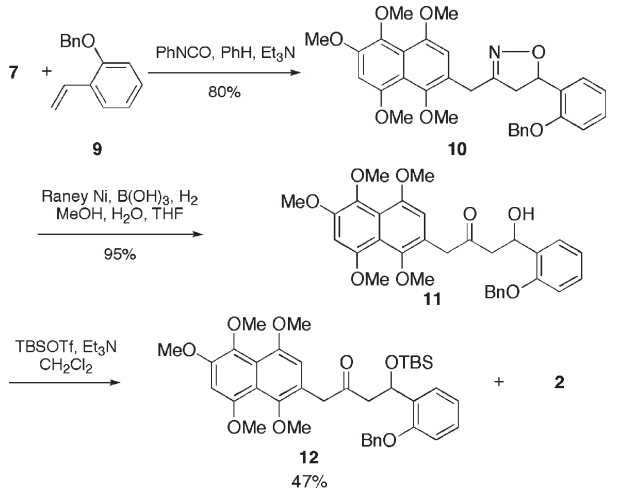
system. Undeterred, attention focused on using benzyne chemistry to synthesize the fully methoxylated naphthalene **5** (Scheme 1).[32] Vilsmeier formylation provided the requisite aldehyde (**2**), validating distal electronic differentiation of naphthalenes as a general strategy for selective functionalization.[16] The Henry reaction allowed installation of the nitro group (**6**) desired for the 1,3-dipolar cycloaddition and subsequent reduction furnished naphthalene **7**. A dinitro side product (**8**) resulting from conjugate addition into the Henry product was isolated and characterized by X-ray crystallography, assuring that the correct regiochemistry had been achieved during the earlier formylation.

Coupling of the new naphthalene with an isocoumarin model (**9**, Scheme 2) gave isoxazoline **10**, which could be reduced to keto alcohol **11** with Raney nickel. Surprisingly, early attempts at silylation resulted in low yields of **12** and a byproduct eventually determined to be aldehyde **2** (Scheme 1). There is scant precedent for this cleavage, the most likely explanation being

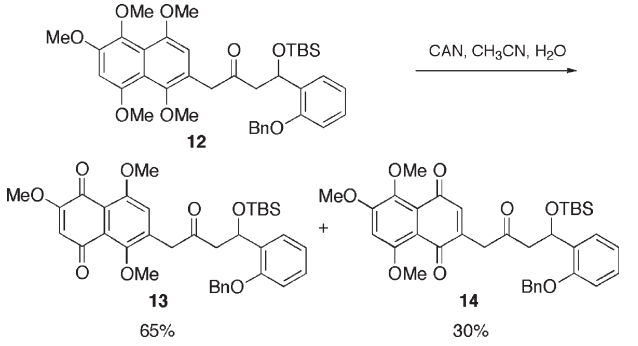
Scheme 1. Synthesis of Naphthalene 7



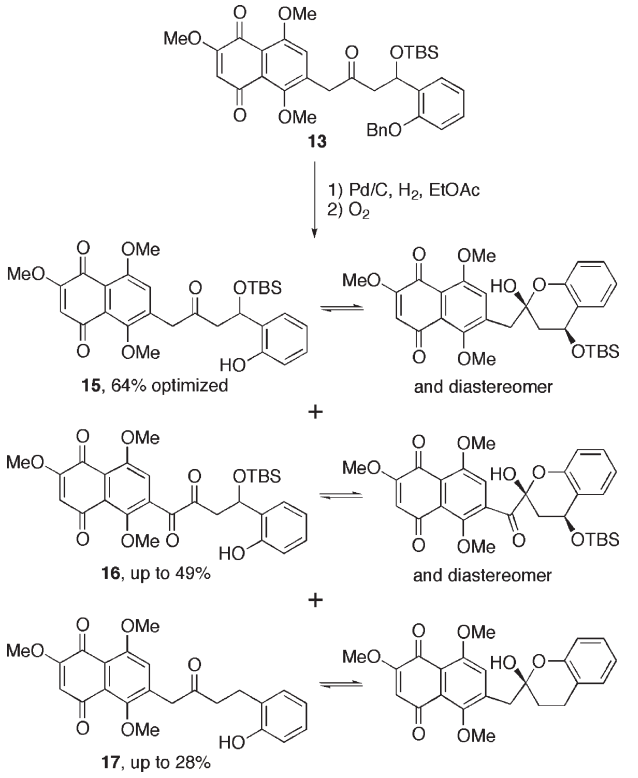
Scheme 2. Central Chain Creation by 1,3-Dipolar Cycloaddition



Scheme 3. CAN Oxidation To Form Quinones



Scheme 4. Variable Hydrogenolysis Products of Benzyl Ether 13



reaction of the enol or silyl enol with singlet oxygen.[33] Singlet oxygen could be produced if the electron-rich naphthalene acts as a photosensitizer. Oxygen oxidation without cleavage at this position is known.[34,35] The byproduct was suppressed by using a single equivalent of silylating reagent and rigorous exclusion of oxygen from the reaction mixture.

With **12** in hand, the next task was to determine oxidative conditions to release the latent quinone (Scheme 3). With 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), only the more electron-rich ring oxidized, resulting in the distal quinone (**13**). Use of ceric ammonium nitrate (CAN) as the oxidant, however, produced both quinone isomers. This result allowed access to both quinones for testing in the spiroketalization reaction.

Penultimate to the testing of a hemiketal conjugate addition strategy of spiroketalization was the cleavage of the benzyl group on the isocoumarin mimic to reveal the phenol nucleophile (Scheme 4). This cleavage was eventually optimized for the expected product **15**, but initially two byproducts were detected. Overreduction where the benzylic silyl ether had been cleaved (**17**) was easily selected against by using a less activating solvent (ethyl acetate instead of methanol). The other byproduct, the unexpected diketone **16**, was isolated when the reaction mixture was not rigorously oxygen free.

A possible mechanism for the formation of **16** is shown in Figure 8. In the hydrogenolysis mixture, the naphthaquinone is first reduced to the naphthaquinol. However, if oxygen is present in the mixture, this process can be reversed; naphthaquinone is still present. Lewis acid complexation allows the formation of a tautomeric extended quinone methide.

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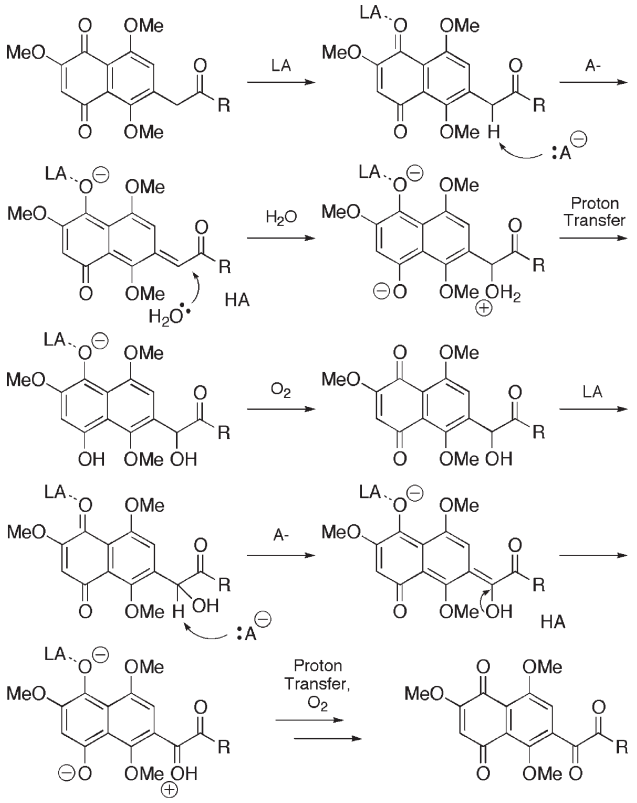
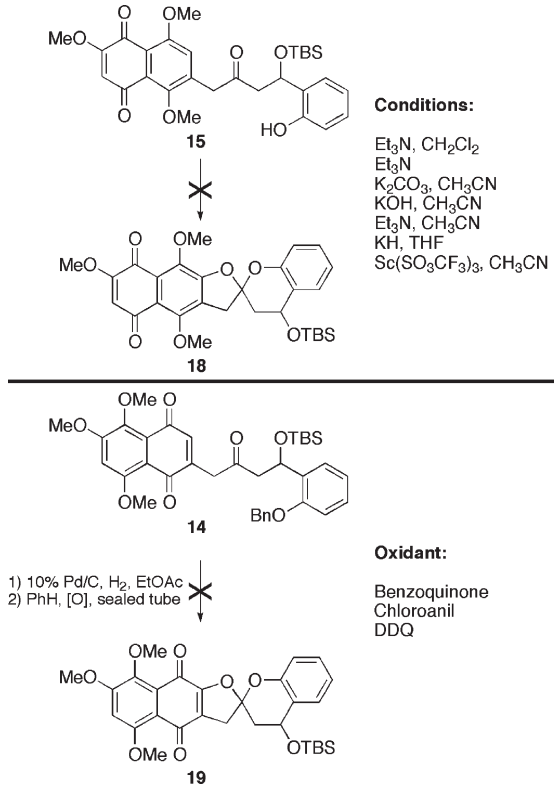


Figure 8. Mechanism for diketone formation.

Scheme 5. Hemiketal Conjugate Addition Attempts



Intermolecular addition of water produces the α-hydroxy ketone. Oxidation returns the molecule to the naphthaquinone.

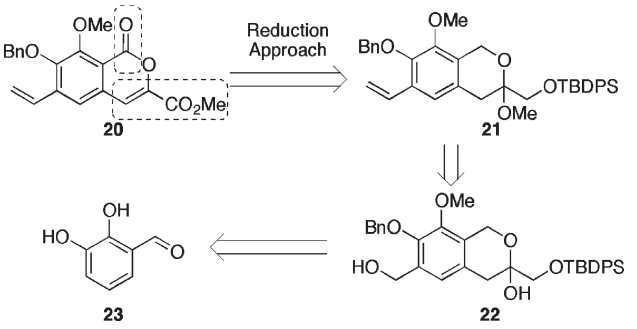


Figure 9. Reduction approach to an electron-rich isocoumarin.

Lewis acid complexation again generates an extended quinone methide, which is a tautomer of the protonated diketone. Oxidation generates the naphthaquinone, terminating the sequence. This discovery points to a facile method for oxidation of benzylic sites in naphthaquinones and anthraquinones using a combination of Pd/C and air.

Once formation of **16** was prevented by scrupulous removal of oxygen, the extended quinone methide was no longer available as an electrophile. All of these products in Scheme 4 (**15**−**17**) were isolated as an interconverting mixture of the hemiketal and the open chain tautomers.

The investigation now turned to the hemiketal addition. The distal quinone **15** was analyzed first (Scheme 5) under a variety of basic conditions. As depicted in Figure 6, the intention was to equilibrate the mixture from the open chain phenolate to the spiroketalized diphenolate or to trap the diphenol as the quinone. None of the conditions screened delivered the desired product **18**; only slow decomposition was observed. Diketone **16** from Scheme 4 also failed to react under basic conditions. Scandium triflate was screened as an acid catalyst but was ineffective. As per the protocol of Tamura and co-workers,[28] the proximal quinone **14** was screened against a variety of oxidants after successful debenzylation. These conditions showed the same pattern as observed with **15**: no reaction and eventual decomposition upon heating except for DDQ, which caused decomposition immediately. It appears either that the basic conditions favor the phenolate form over the hemiketal anion (see Figure 6) or that reoxidation is very slow, such that the cyclic form undergoes retro-conjugate addition more quickly than oxidation. Regardless, these results caution against the design of tandem reactions terminating with an oxidative conjugate addition to a quinone if the initial steps are reversible.

Use of an Electron-Rich Isocoumarin Surrogate. With an oxidative cyclization disconnection having proved ineffective, we next turned to an electron-rich isocoumarin surrogate, with the aim of putting the isocoumarin nucleophilicity on par with the nucleophilicity of the naphthalene. Specifically, we sought to reduce the isocoumarin in such a manner as to disconnect the electron-withdrawing groups from the nucleophilic phenol (Figure 9) while keeping the carbon skeleton intact and readily convertible into the complete isocoumarin.

The synthesis of the first generation isocoumarin surrogate is shown in Scheme 6. Starting from aldehyde **23**, selective methylation[18,36] and bromination produced **24**.[37] Mannich reaction and subsequent displacement of the *N*-acylated species with acetate furnished **25**.[18] After hydrolysis of the acyl groups (**26**), the phenol was chemoselectively benzylated (**27**). Reduction of the aldehyde and bisacylation afforded Stille precursor **28**.

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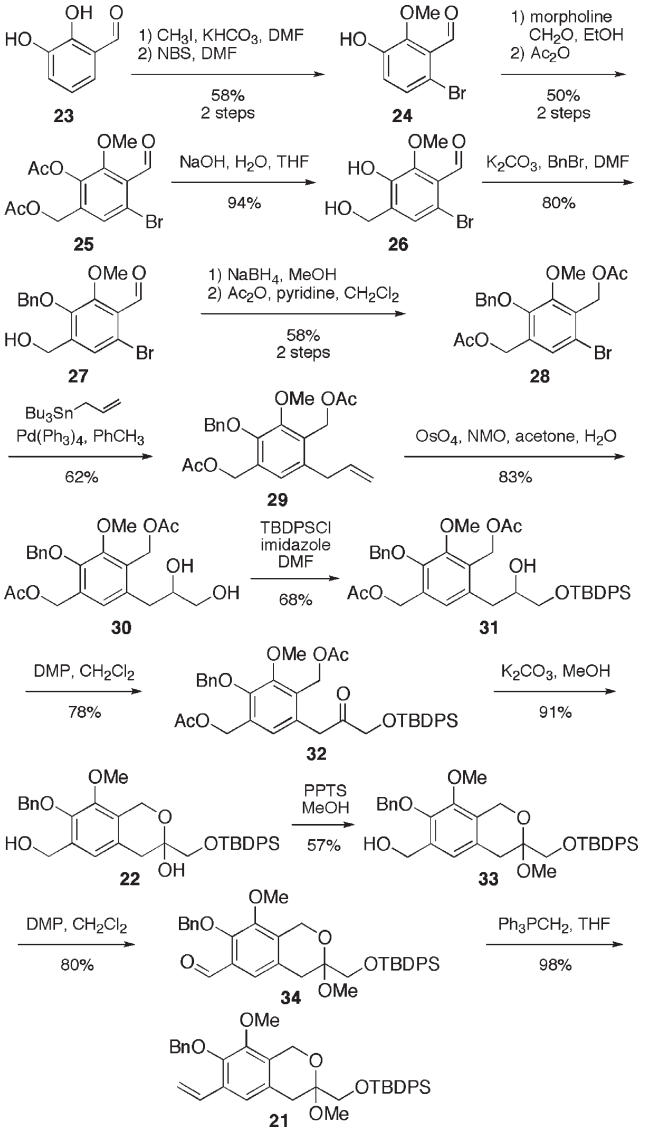
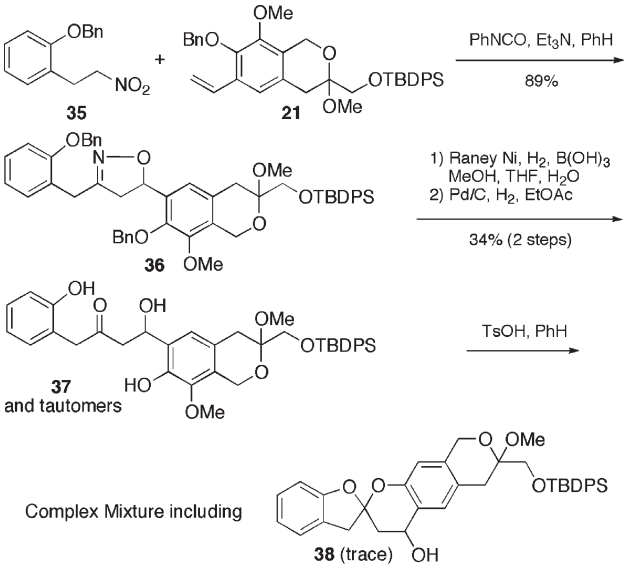
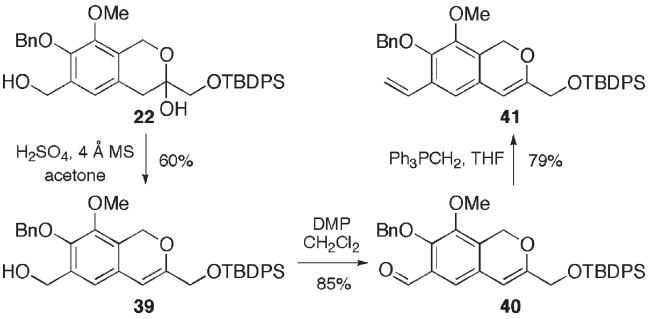
Scheme 6. First Generation Synthesis of an Electron-Rich Isocoumarin Surrogate



Scheme 7. 1,3-Dipolar Cycloaddition and Attempted Spiroketalization of the First Generation Surrogate



Scheme 8. Second Generation Isocoumarin Surrogate



With tributyl allyl tin as the coupling agent, the Stille reaction produced **29**. Oxidation with osmium tetroxide and *N*-methyl morpholine oxide (NMO) generated diol **30**. Attempts to oxidize **30** to the α-ketoacid resulted in decarboxylation. Accordingly, the primary alcohol of diol **30** was selectively silylated with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and **31** was subsequently oxidized with Dess−Martin periodinane (DMP),[38] yielding α-keto silyl ether **32**. Base mediated deacylation gave the diol, which existed predominantly as the hemiketal **22**. Treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol selectively generated the methyl ether by S_N1 displacement of the tertiary alcohol, providing ketal **33**. Finally, oxidation with DMP gave benzaldehyde **34** which could easily be converted to desired styrene **21** via Wittig olefination.

Our attention now turned to utilization of the 1,3-dipolar cycloaddition strategy[19] for the coupling of the isocoumarin surrogate with a model naphthalene (Scheme 7). The previously reported aromatic nitroalkane **35** was selected as the naphthalene mimic.[13] Surrogate **21** and **35** underwent facile cycloaddition, affording **36** in good yield. Reductive cleavage of the isoxazoline ring was accomplished using Raney nickel and of the benzyl ethers using palladium on carbon to provide **37**, predominantly in its hemiketal form. Finally, spiroketalization of the isocoumarin surrogate was attempted by treating **37** with *p*-toluenesulfonic (tosic) acid. While desired spiroketal **38** was detected in the reaction mixture by mass spectroscopy, it could not be separated from the complex reaction mixture that was produced due to the presence of the acid labile methyl ketal.

This encouraging result stimulated us to develop a new surrogate without an acid sensitive group. As shown in Scheme 8, advanced intermediate **22** was readily modified with catalytic sulfuric acid to provide alkene **39**. Oxidation with DMP produced benzaldehyde **40**, which was efficiently converted into styrene **41** through Wittig olefination. With a second generation isocoumarin surrogate in hand, work toward a spiroketal continued.

Coupling of second generation isocoumarin surrogate **41** (Scheme 9) with naphthalene mimic **35** successfully provided isoxazoline **42**. We next employed a sequence analogous to that described in Scheme 7: reductive cleavage of isoxazoline **42** with a buffered Raney nickel solution provided keto alcohol **43**.

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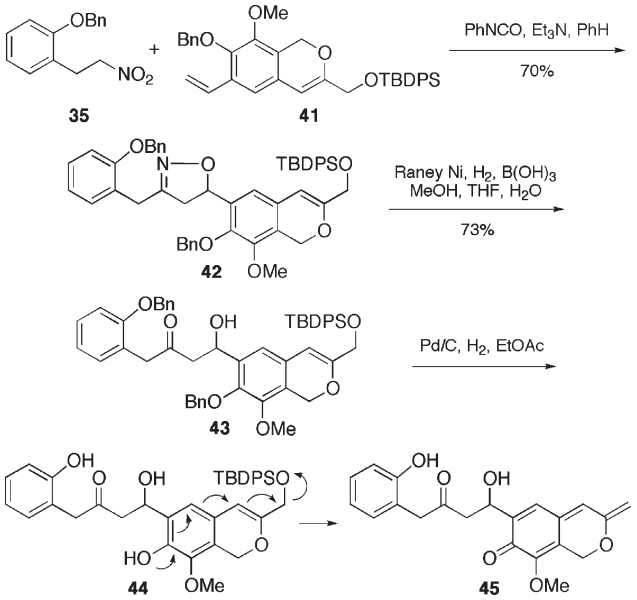
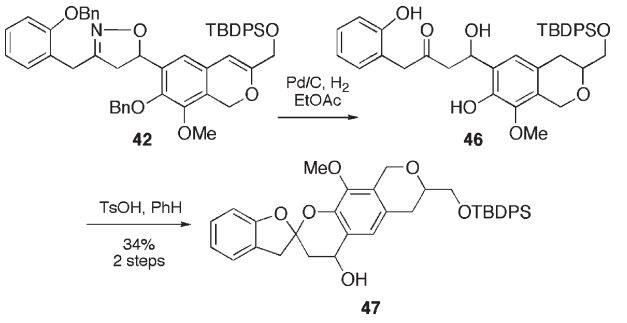
Scheme 9. Cycloadditions of the Second Generation Surrogate



Scheme 10. Successful Creation of a Apiroketal Using an Isocoumarin Surrogate



Unfortunately, the benzyl ether hydrogenolysis resulted in a complex mixture instead of giving rise to phenol **44**. It is likely that the unmasking of the phenol on the isocoumarin surrogate allowed the formation of an extended quinone methide such as **45** by elimination of the *tert*-butyldiphenylsilylether group, which could react further to form a variety of compounds other than the desired spiroketal.

To investigate this hypothesis, isocoumarin **46** (Scheme 10) was targeted because the lack of the enol ether double bond would insulate it from quinone methide formation as outlined in Scheme 9. Thus, a method was sought to first reduce the enol ether double bond without causing hydrogenolysis of the benzyl groups (Scheme 10). While a difficult proposition, treatment of the isoxazoline **42** instead of the β-hydroxy ketone **43** with palladium on carbon under a hydrogen atmosphere was found to result in a different order of reactivity. Under these conditions, enol ether reduction occurred prior to hydrogenolysis of the benzyl ethers. Upon prolonged stirring, hydrogenolysis and isoxazoline ring cleavage occurred. The mixture obtained from hydrogenation of **42** was subjected directly to tosic acid and spirocyclized to a mixture of four diastereomers of **47**, one of which could be separated from the others.

The successful spiroketalization verified our hypothesis and the observations of others[11,22] that increasing the nucleophilicity of the isocoumarin allows competitive spiroketal formation at the expense of benzofuran formation. While providing an expeditious and convergent route to purpuromycin analogs for further study, the removal of double bond functionality to avoid quinone-methide reactivity greatly complicated the conversion of **47** to authentic isocoumarin.

CONCLUSION

We outline two alternative routes to circumvent the propensity for benzofuran formation during spiroketalization in the synthesis of the rubromycin family of compounds. These routes illustrate how our 1,3-dipolar cycloaddition approach permits the rapid and convergent assembly of structures with variable eastern and western hemispheres to probe different hypotheses and ultimately to generate analogs rapidly.[13] While precedent exists for an oxidative conjugate addition to naphthaquinone type systems,[28] a hemiketal conjugate addition did not prove effective. These results caution against the design of tandem reactions terminating with an oxidative conjugate addition if the initial steps are reversible. The discovery of oxidation via quinone-methide type intermediates in this route points to a facile method for oxidation of benzylic sites in naphthaquinones and anthraquinones under conventional hydrogenolysis conditions. In addition, we demonstrate the utility of remote electronic control for the efficient regioselective substitution of naphthalenes (**5** to **7**).

We used an isocoumarin surrogate that lacked the electron-withdrawing groups of the isocoumarin moiety found in the natural product, and thus spiroketalization could be favored over benzofuran formation. Robust, flexible syntheses from simple precursors were developed that allowed multiple reduced isocoumarin analogs to be generated (e.g., **21** and **41**). There was a predilection for formation of extended quinone methides in reduced isocoumarins, indicating that the reactivity of hydroxymethylene groups conjugated to phenols needs to be considered in synthetic ventures. Although the reduced isocoumarin approach was successful and provides an efficient route to many purpuromycin analogs to explore the SAR of the isocoumarin portion, an alternate diketone method under exploration to prevent benzofuran formation[25] became the focus because it permitted introduction of the intact isocoumarin unit.

EXPERIMENTAL SECTION

General procedures can be found in the Supporting Information.

1,2,4,5,8-Pentamethoxy-6-(2-nitro-ethyl)-naphthalene (8). Aldehyde **2** (0.302 g, 0.986 mmol) and NH_4OAc (0.0181 g, 0.231 mmol) were combined in CH_3NO_2 (12.0 mL) and heated in a sealed tube (oil bath, 120 °C) for 21.5 h. The mixture was cooled, poured into water (90 mL), and extracted with CH_2Cl_2 (1 × 90 mL, 1 × 40 mL). Brine (~40 mL) was added to the extraction to clarify an emulsion. The organic layers were combined, dried with Na_2SO_4, and concentrated, giving **6** contaminated with **8** as a dark red solid. A small amount of **6** was purified for characterization purposes: a red-orange solid; mp 178.5−180.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 13.7 Hz, 1H), 7.67 (d, J = 13.7 Hz, 1H), 6.78 (s, 1H), 6.71 (s, 1H), 4.011 (s, 3H), 4.008 (s, 3H), 3.96 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.9, 153.3, 152.8, 138.9, 136.8, 134.8,

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126.6, 117.8, 116.8, 103.8, 98.6, 64.1, 62.1, 57.2, 57.1 (2); IR (film) 3107, 2999, 2937, 2845, 1590, 1498, 1455 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{19}NO_7$ (M^+) 349.1162, found 349.1147.

To a stirring solution of the mixture of **6** and **8** (0.685 g, 1.96 mmol) in MeOH (60 mL) and CH_2Cl_2 (65 mL) was added $NaBH_4$ (0.188 g, 4.97 mmol) in one portion. Stirring was continued for 1 h when the mixture was poured into 0.5 M HCl (260 mL) and partitioned with CH_2Cl_2 (130 mL). The organic layer was dried (Na_2SO_4) and concentrated. The resultant brown oil was purified by flash chromatography[39] (17% hexanes/Et_2O, SiO_2), affording **7** (0.420 g, 61%) and **8** (0.187 g, 23%) as off-white crystalline solids. **7**: mp 115.5−117.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.63 (s, 1H), 4.68 (dd, J = 7.5, 7.7 Hz, 2H), 3.98 (s, 6H), 3.92 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.40 (dd, J = 7.7, 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 152.4, 150.3, 148.5, 138.7, 123.9, 122.8, 117.6, 109.7, 98.9, 75.5, 62.5, 62.0, 57.7, 57.3, 56.9, 29.2; IR (film) 2991, 2934, 2841, 1602, 1548 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{21}NO_7$ (M^+) 351.1318, found 351.1325. **8**: mp 133−136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.53 (s, 1H), 4.89 (m, 4H), 4.80 (m, 1H), 3.98 (s, 6H), 3.91 (s, 3H), 3.803 (s, 3H), 3.798 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 152.8, 151.1, 148.6, 138.7, 124.6, 120.7, 117.3, 105.8, 99.1, 76.5, 63.2, 62.0, 57.5, 57.4, 57.0, 36.8; IR (film) 2934, 2845, 1598, 1556 cm^{-1}; HRMS (ES) calcd for $C_{18}H_{22}N_2O_9Na$ (MNa^+) 433.1223, found 433.1219.

5-(2-Benzyloxy-phenyl)-3-(1,4,5,6,8-pentamethoxy-naphthalen-2-ylmethyl)-4,5-dihydro-isoxazole (10). To a stirring solution of **7** (0.362 g, 1.03 mmol) and **9** (0.249 g 1.18 mmol) in PhH (30 mL) were added PhNCO (0.63 mL, 5.80 mmol) and NEt_3 (3 drops, ∼0.02 mL). The mixture was heated (oil bath, 70−80 °C) and stirred for 44 h. The mixture was cooled, filtered through Celite, and concentrated to a brown oil. This residue was purified by flash chromatography (50% hexanes/EtOAc, SiO_2) to give **10** as an orange oil or a red foam (0.449 g, 80%): R_f = 0.42 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 1.5, 7.6 Hz, 1H), 7.28−7.34 (m, 5H), 7.21 (dt, J = 1.6, 7.8 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 6.56 (s, 1H), 5.84 (dd, J = 7.0, 11.0 Hz, 1H), 5.04 (d, J = 11.7 Hz, 1H), 5.01 (d, J = 11.8 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.88 (d, J = 15.0 Hz, 1H), 3.79, (d, J = 14.4 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 3.30 (dd, J = 11.1, 17.3 Hz, 1H), 2.75 (dd, J = 7.0, 17.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 155.2, 152.8, 152.4, 150.2, 147.9, 138.9, 137.0, 130.3, 128.9, 128.7, 128.1, 127.4, 126.3, 123.6, 123.1, 121.0, 117.8, 111.8, 108.6, 99.2, 77.6, 70.1, 62.5, 62.0, 57.8, 57.1, 57.0, 44.4, 27.5; IR (film) 3065, 3034, 2991, 2930, 2841, 2250, 1745, 1602, 1490, 1451 cm^{-1}; HRMS (ES) calcd for $C_{32}H_{33}NO_7Na$ (MNa^+) 566.2155, found 566.2145.

4-(2-Benzyloxy-phenyl)-4-hydroxy-1-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-butan-2-one (11). To a stirring solution of **10** (0.503 g, 0.925 mmol) in MeOH (45 mL) and THF (25 mL) was added $B(OH)_3$ (0.061 g, 0.987 mmol) dissolved in water (5 mL). Raney Nickel (∼0.5 mL, 50% in water) was added to the mixture, and it was stirred under an atmosphere of H_2 for 13 h and then filtered through Celite (CH_2Cl_2). The filtrate was partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The organic layer was dried (Na_2SO_4) and concentrated giving **11** as a yellow foam (0.481 g, 95%): R_f = 0.32 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 1.5, 7.5 Hz, 1H), 7.29−7.34 (m, 5H), 7.17 (dt, J = 1.6, 7.9 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.72 (s, 1H), 6.50 (s, 1H), 5.49 (dd, J = 3.0, 8.8 Hz, 1H), 5.02 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 2H), 3.61 (s, 3H), 3.06 (dd, J = 3.2, 17.1 Hz, 1H), 2.89 (dd, J = 8.9, 17.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 155.1, 152.8, 152.2, 150.2, 148.2, 138.9, 137.0, 131.4, 128.8, 128.4, 128.1, 127.3, 126.8, 123.9, 121.8, 121.1, 117.8, 111.7, 110.1, 99.2, 70.1, 66.2, 62.1, 62.0, 57.8, 57.2, 57.0, 48.7, 45.4; IR (film) 3447 (br), 3038, 2991, 2934, 2841, 1710, 1602, 1451 cm^{-1}; HRMS (ES) calcd for $C_{32}H_{34}O_8Na$ (MNa^+) 569.2151, found 569.2160.

4-(2-Benzyloxy-phenyl)-4-(*tert*-butyl-dimethyl-silanyloxy)-1-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-butan-2-one (12). Hydroxyketone **11** (0.359 g, 0.657 mmol) was dissolved in CH_2Cl_2 (12 mL) and thoroughly deoxygenated by subjection to three freeze−pump−thaw cycles. The mixture was cooled in an ice bath, and Et_3N (0.20 mL, 1.44 mmol) and *tert*-butyldimethylsilyl triflate (0.15 mL, 0.653 mmol) were added to the mixture, the latter in a dropwise fashion. The mixture was stirred for 1.4 h, at which time it was quenched by the addition of water (2 mL). The mixture was paritioned between water (170 mL) and CH_2Cl_2 (170 mL). The organic layer was dried (Na_2SO_4) and concentrated to a yellow oil. The residue was purified by flash chromatography (33−70% EtOAc/hexanes) to give recovered starting material **11** (0.061 g, 17%) as a yellow oil and **12** as a yellow oil (0.202 g, 47%): R_f = 0.66 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 1.5, 7.6 Hz, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.27 (t, J = 7.2 Hz, 1H), 7.17 (dt, J = 1.5, 8.0 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.72 (s, 1H), 6.54 (s, 1H), 5.74 (dd, J = 2.9, 8.9 Hz, 1H), 5.09 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.89 (d, J = 16.2 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.75 (d, J = 16.2 Hz, 1H), 3.61 (s, 3H), 2.96 (dd, J = 9.0, 15.4 Hz, 1H), 2.73 (dd, J = 3.0, 15.4 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 154.4, 152.8, 152.1, 150.0, 148.2, 138.9, 137.4, 133.3, 128.7, 128.1, 127.8, 127.3, 127.0, 123.7, 122.3, 120.9, 117.9, 111.7, 110.4, 99.3, 69.9, 66.1, 62.2, 62.0, 57.8, 57.2, 57.1, 51.3, 45.8, 26.1, 18.4, −4.6, −4.9; IR (film) 2953, 2930, 2856, 1718, 1602, 1451 cm^{-1}; HRMS (ES) calcd for $C_{38}H_{48}O_8SiNa$ (MNa^+) 683.3016, found 683.3025.

6-[4-(2-Benzyloxy-phenyl)-4-(*tert*-butyl-dimethyl-silanyloxy)-2-oxo-butyl]-2,5,8-trimethoxy-[1,4]naphthaquinone (13) and 2-[4-(2-Benzyloxy-phenyl)-4-(*tert*-butyl-dimethyl-silanyloxy)-2-oxo-butyl]-5,6,8-trimethoxy-[1,4]naphthaquinone (14). To a stirring solution of **12** (0.202 g, 0.306 mmol) in CH_3CN (40 mL) in a salt−ice bath (−10 to −15 °C) was added CAN (0.424 g, 0.773 mmol) dissolved in water (4 mL). The mixture was stirred, still cold, for 10 min when it was diluted with water (160 mL) and extracted with CH_2Cl_2 (1 × 160 mL, 1 × 80 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. The residual red-yellow oil was purified by flash chromatography (50−66% EtOAc/hexanes) to give **13** (0.126 g, 65%) and **14** (0.058 g, 30%) as yellow-red oils. **13**: R_f = 0.27 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 6.99 (s, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 5.98 (s, 1H), 5.70 (dd, J = 2.8, 8.4 Hz, 1H), 5.11 (s, 2H), 3.90 (s, 3H), 3.88 (d, J = 16.8 Hz, 1H), 3.83 (s, 3H), 3.72 (d, J = 16.8 Hz, 1H), 3.64 (s, 3H), 2.99 (dd, J = 8.6, 15.2 Hz, 1H), 2.81 (dd, J = 2.9, 15.2 Hz, 1H), 0.88 (s, 9 H), 0.04 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 184.7, 178.9, 160.0, 156.5, 154.5, 152.1, 139.7, 137.2, 132.8, 128.8, 128.4, 128.0, 127.2, 127.1, 125.1, 121.1 (2C), 119.5, 111.8, 109.7, 70.1, 66.1, 62.1, 56.9, 56.4, 52.0, 45.9, 26.1, 18.4, −4.6, −5.0; IR (film) 3069, 3034, 2953, 2930, 2856, 1722, 1652, 1629, 1590, 1455 cm^{-1}; HRMS (ES) calcd for $C_{36}H_{42}O_8SiNa$ (MNa^+) 653.2547, found 653.2544. **14**: R_f = 0.05 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.35 (t, J = 7.9 Hz, 2H), 7.29 (t, J = 7.1 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.87 (s, 1H), 5.91 (s, 1H), 5.70 (dd, J = 2.9, 8.5 Hz, 1H), 5.11 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.83 (d, J = 16.8 Hz, 1H), 3.70 (d, J = 16.8 Hz, 1H), 3.55 (s, 3H), 2.98 (dd, J = 8.6, 15.2 Hz, 1H), 2.80 (dd, J = 3.1, 15.2 Hz, 1H), 0.88 (s, 9H), 0.04 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 180.2, 179.3, 170.1, 158.5, 154.5, 150.8, 140.5, 137.2, 132.7, 128.7, 128.5, 128.0, 127.2, 127.0, 124.9, 121.1, 119.4, 118.7, 111.8, 103.2, 70.0, 66.1, 62.6, 57.1, 56.7, 51.9, 46.5, 26.0, 18.3, −4.6, −5.0; IR (film) 3069, 3038, 3011, 2953, 2934, 2856, 1722, 1687, 1652, 1602, 1575, 1451 cm^{-1}; HRMS (ES) calcd for $C_{36}H_{42}O_8SiNa$ (MNa^+) 653.2547, found 653.2541.

6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-4-(2-hydroxy-phenyl)-2-oxo-butyl]-2,5,8-trimethoxy-[1,4]naphthaquinone (15). Quinone **13** (0.0167 g, 0.026 mmol) was dissolved in MeOH (5 mL) and combined with 10% Pd/C (0.013 g) in a flask stoppered with a three-way stopcock. House vacuum was attached to one arm of the stopcock and a balloon of hydrogen to the other. The flask was evacuated until the solvent boiled and filled with hydrogen gas. This purging procedure was repeated five times. The mixture was stirred for 1 d before it was filtered through a plug of Celite (MeOH) and concentrated. The residue was taken up in EtOAc (5 mL) and stirred exposed to air for 5 min, after which it was concentrated. The resultant dark yellow oil was purified by flash chromatography (66% EtOAc/hexanes) to give **15** (0.009 g, 63%) as a yellow film: R_f = 0.21 (50% EtOAc/hexanes); the material exists as a 1:0.25:0.25 mixture of inseparable tautomers, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.60 (s, 0.25H), 7.37 (d, J = 7.6 Hz, 0.25H), 7.25 (s, 0.25H), 7.23 (dt, J = 1.6, 7.7 Hz, 0.25H), 7.16 (dt, J = 1.6, 7.7 Hz, 1H), 7.14 (t, J = 7 Hz, 0.25H), 7.12 (dt, J = 1.5, 7.6 Hz, 0.25H), 6.97 (dd, J = 1.5, 7.5 Hz, 1H), 6.95 (t, J = 1.0, 7 Hz, 0.25H), 6.92 (dd, J = 1.0, 7.3 Hz, 0.25H), 6.92 (coincidental s, 1.25H), 6.90 (s, 0.25H), 6.89 (d, J = 8.2 Hz, 0.25H), 6.86 (dd, J = 0.6, 8.1 Hz, 1H), 6.81 (s, 0.25H), 6.79 (dt, J = 1.0, 7.4 Hz, 1H), 6.71 (d, J = 7.5 Hz, 0.25H), 6.01 (s, 0.25H), 6.00 (s, 0.25H), 5.99 (s, 1H), 5.29 (dd, J = 6.3, 7.0 Hz, 1H), 5.06 (dd, J = 5.9, 10.1 Hz, 0.25H), 4.85 (dd, J = 2.8, 2.9 Hz, 0.25H), 4.23 (s, 0.25H), 3.95 (s, 0.75H), 3.94 (s, 0.75H), 3.913 (s, 3H), 3.905 (s, 0.75H), 3.85 (s, 0.75H), 3.831 (coincidental s, 3.75H), 3.828 (s, 0.75H), 3.70 (d, J = 16.6 Hz, 1H), 3.67 (s, 3H), 3.66 (d, J = 16.6 Hz, 1H), 3.45 (d, J = 13.6 Hz, 0.25H), 3.35 (d, J = 13.5 Hz, 0.25H), 3.32 (d, J = 13.5 Hz, 0.25H), 3.21 (dd, J = 7.4, 16.2 Hz, 1H), 3.18 (d, J = 13.6 Hz, 0.25H), 2.98 (dd, J = 6.0, 16.2 Hz, 1H), 2.32 (dd, J = 5.9, 12.6 Hz, 0.25H), 2.23 (dd, J = 2.5, 14.5 Hz, 0.25H), 1.97 (dd, J = 3.4, 14.4 Hz, 0.25H), 1.89 (ddd, J = 1.7, 10.2, 12.2 Hz, 0.25H), 0.94 (s, 2.25H), 0.86 (s, 9H), 0.83 (s, 2.25H), 0.19 (s, 0.75H), 0.16 (s, 0.75H), 0.14 (s, 0.75H), 0.12 (s, 3H), 0.11 (s, 0.75H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 185.0, 184.6, 184.5, 179.1, 179.0, 178.9, 160.0 (2), 159.9, 156.5, 156.2, 155.7, 152.4, 151.94, 151.91, 151.5, 141.0, 140.0, 138.8, 130.4, 130.1, 129.4 (2), 128.8, 127.20, 127.15, 127.1, 126.3, 125.5, 125.2, 125.0, 124.1, 122.7, 122.3, 122.2, 121.3, 121.1, 120.9, 120.1, 119.8, 119.7, 119.3, 117.7, 117.5, 116.5, 109.80, 109.75, 109.7, 99.0, 98.9, 73.1, 66.2, 63.6, 62.3, 62.2, 62.0, 56.94, 56.87, 56.8, 56.51, 56.48, 56.4, 50.7, 46.16, 42.4, 40.6, 40.1, 36.9, 26.1, 25.8, 25.7, 18.3, 18.2, 18.0, −4.0, −4.1, −4.5, −4.6, −5.1 (2); IR (film) 3397, 3076, 2953, 2934, 2903, 2856, 1722, 1675, 1648, 1629, 1586, 1552, 1459 cm^{-1}; HRMS (ES) calcd for $C_{29}H_{36}O_8SiNa$ (MNa^+) 563.2077, found 563.2060.

6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-4-(2-hydroxy-phenyl)-2-oxo-butyryl]-2,5,8-trimethoxy-[1,4]naphthaquinone (16). Isolated as a byproduct (<49%) from the above experiment: a yellow film; R_f = 0.58 (66% EtOAc/hexanes); the material exists as a 1:1:1 mixture of inseparable tautomers, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 0.33H), 7.69 (s, 0.33H), 7.54 (s, 0.33H), 7.39 (d, J = 7.6 Hz, 0.67H), 7.32 (s, 0.33H), 7.25 (dt, J = 1.6, 8.0 Hz, 0.33H), 7.19 (dd, J = 1.5, 7.5 Hz, 0.33H), 7.18 (dt, J = 1.7, 8.4 Hz, 0.33H), 7.14 (dt, J = 1.3, 7.7 Hz, 0.33H), 7.08 (s, 0.33H), 7.07 (dd, J = 1.6, 7.6 Hz, 0.33H), 7.00 (dt, J = 1.1, 7.4 Hz, 0.33H), 6.98 (dt, J = 1.0, 7.4 Hz, 0.33H), 6.89 (dd, J = 0.9, 8.1 Hz, 0.33H), 6.86 (d, J = 8.2 Hz, 0.33H), 6.83 (dt, J = 1.1, 7.4 Hz, 0.33H), 6.71 (dd, J = 0.9, 8.1 Hz, 0.33H), 6.05 (s, 0.33H), 6.043 (s, 0.33H), 6.038 (s, 0.33H), 5.43 (dd, J = 5.3, 7.3 Hz, 0.33H), 5.34 (d, J = 1.6 Hz, 0.33H), 5.14 (dd, J = 5.4, 10.4 Hz, 0.33H), 5.04 (dd, J = 3.1, 3.1 Hz, 0.33H), 3.99 (s, 2H), 3.91 (s, 1H), 3.87 (s, 1H), 3.858 (s, 1H), 3.855 (s, 2H), 3.851 (s, 1H), 3.58 (dd, J = 7.4, 17.8 Hz, 0.33H), 3.55 (s, 1H), 3.21 (dd, J = 5.2, 17.8 Hz, 0.33H), 2.58 (dd, J = 2.9, 14.4 Hz, 0.33H), 2.43 (dd, J = 3.4, 13.7 Hz, 0.33H), 2.40 (dd, J = 5.5, 12.9 Hz, 0.33H), 2.08 (ddd, J = 1.6, 10.6, 12.6 Hz, 0.33H), 0.96 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.26 (s, 1H), 0.22 (s, 1H), 0.18 (s, 1H), 0.17 (s, 1H), 0.16 (s, 1H), 0.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 197.7, 195.6, 193.4, 184.0, 183.8, 183.6, 178.9, 178.6, 178.5, 160.0 (2), 159.9, 156.62, 156.57 (2), 156.0, 155.8, 153.3, 151.2, 150.8, 149.9, 141.5, 141.1, 136.3, 130.6, 129.9, 129.5, 128.9, 127.2, 127.1, 127.0, 126.8, 125.81, 125.78, 125.7, 124.3, 122.4, 122.1, 121.9, 121.8, 121.4, 120.1, 118.8, 118.4, 118.2, 118.0, 117.6, 116.7, 116.2, 110.0, 109.94, 109.87, 98.6, 98.4, 72.0, 65.7, 64.3, 63.9, 63.4, 63.1, 57.2, 57.01, 56.97, 56.7, 56.6, 56.5, 45.9, 36.9, 34.5, 26.0, 25.8 (2), 18.3, 18.2, 18.1, −4.15, −4.17, −4.5, −4.7, −5.0, −5.1; IR (film) 3374, 3080, 2953, 2934, 2856, 1776, 1725, 1679, 1652, 1629, 1586, 1463 cm^{-1}; HRMS (ES) calcd for $C_{29}H_{34}O_9SiNa$ (MNa^+) 577.1870, found 577.1883.

6-Bromo-3-hydroxy-2-methoxy-4-morpholin-4-ylmethyl-benzaldehyde (24morph). To a solution of 37% aqueous formaldehyde (0.323 mL, 4.32 mmol) and morpholine (0.377 mL, 4.32 mmol) in EtOH (2 mL) was added **24**[37] [500 mg (77% pure), 2.16 mmol] in one portion at rt. After heating at reflux for 15 h, the reaction mixture was concentrated and chromatographed (83% hexanes/EtOAc) to afford **24morph** (282 mg, 51%) as a semisolid: R_f = 0.30 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.06 (s, 1H), 3.97 (s, 3H), 3.90 (s, 4H), 3.80 (s, 2H), 2.61 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 150.8, 150.4, 128.5, 127.9, 127.6, 110.8, 66.3, 61.7, 60.9, 50.7; IR (neat) 3374, 2853, 1698 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{16}BrNO_4$ (M^+) 329.0263, found 329.0247.

Acetic Acid 2-Acetoxy-5-bromo-4-formyl-3-methoxy-benzyl Ester (25). To Ac_2O (25 mL, 260 mmol) was added **24morph** (1.00 g, 3.03 mmol) in one portion at rt. After heating at reflux for 48 h, the reaction mixture was concentrated. Chromatography (90% hexanes/EtOAc) afforded **25** (1.03 g, 99%) as a semisolid: R_f = 0.50 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.44 (s, 1H), 4.97 (s, 2H), 3.80 (s, 3H), 2.30 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 169.9, 167.7, 154.2, 142.3, 136.0, 129.2, 128.3, 121.0, 63.1, 60.0, 20.4, 20.0; IR (neat) 2945, 1776, 1745, 1702 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{14}BrO_6$ (MH^+) 344.9974, found 344.9985.

6-Bromo-3-hydroxy-4-hydroxymethyl-2-methoxy-benzaldehyde (26). To a solution of **25** (1.0 g, 2.9 mmol) in THF was added 1 N NaOH (17.4 mL, 17.4 mmol). After stirring 30 min at rt, the reaction mixture was neutralized with 1 N HCl (21 mL, pH ~5) and extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford **26** (713 mg, 94%) as a semisolid: R_f = 0.40 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.40 (s, 1H), 6.42 (s, 1H), 4.80 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 149.0, 148.0, 134.2, 128.0, 126.0, 115.0, 63.2, 61.0; IR (neat) 3316, 2953, 1679 cm^{-1}; HRMS (CI) calcd for $C_9H_8BrO_4$ (MH^-) 258.9606, found 258.9604.

3-Benzyloxy-6-bromo-4-hydroxymethyl-2-methoxy-benzaldehyde (27). To a solution of **26** (700 mg, 2.70 mmol) in dry DMF (35 mL) was added K_2CO_3 (1.12 g, 8.09 mmol). After stirring 15 min at rt, BnBr (0.962 mL, 8.09 mmol) was added under N_2. After stirring 17 h at rt, the reaction mixture was neutralized with 1 N HCl (35 mL), diluted with water (35 mL), and extracted four times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (83% hexanes/EtOAc) afforded **27** (755 mg, 80%) as a semisolid: R_f = 0.60 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.46 (s, 1H), 7.34−7.37 (m, 5H), 5.05 (s, 2H), 4.55 (s, 2H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 155.2, 148.7, 142.5, 136.3, 128.5, 128.4, 128.3, 128.2, 127.6, 118.4, 75.1, 62.2, 59.6; IR (neat) 3439, 2941, 1698 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{15}BrO_4$ (M^+) 350.0154, found 350.0142.

(3-Benzyloxy-6-bromo-4-hydroxymethyl-2-methoxy-phenyl)-methanol (27red). To a solution of **27** (735 mg, 2.09 mmol) in MeOH (22 mL) was added $NaBH_4$ (277 mg, 7.32 mmol). After stirring 12 h at rt, the resulting suspension was neutralized with 1 N HCl (35 mL, pH ~5), diluted with water (35 mL), and extracted five times with CH_2Cl_2. The combined organic layers were dried over

Na_2SO_4, filtered, and concentrated. Chromatography (83% hexanes/EtOAc) afforded **27red** (547 mg, 74%) as a viscous solid: R_f = 0.50 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.40 (m, 5H), 7.34 (s, 1H), 5.03 (s, 2H), 4.85 (s, 2H), 4.50 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 149.0, 137.1, 136.9, 134.3, 128.9, 128.8 (2C), 127.9, 119.0, 75.4, 62.0, 60.9, 60.6; IR (neat) 3331, 2968 cm^{-1}; HRMS (ES) calcd for $C_{16}H_{17}BrO_4Na$ (MNa^+) 375.0208, found 375.0223.

3-Benzyloxy-6-bromo-4-hydroxymethyl-2-methoxy-phenyl)-methanol (28). To a solution of **27red** (537 mg, 1.52 mmol) in CH_2Cl_2 (40 mL) were added pyridine (3 mL, 36.5 mmol) and Ac_2O (1.8 mL, 18 mmol). After stirring 5 d at rt, the reaction mixture was concentrated and chromatographed (83% hexanes/EtOAc) to afford **28** (520 mg, 78%) as a liquid: R_f = 0.70 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.41 (m, 6H), 5.27 (s, 2H), 5.04 (s, 2H), 5.02 (s, 2H), 3.89 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.1, 153.5, 149.2, 136.5, 132.9, 129.9, 128.3 (2C), 128.2, 128.1, 119.0, 74.9, 61.5, 60.9, 60.4, 20.6, 20.5; IR (neat) 3034, 2945, 1741 cm^{-1}; HRMS (ES) calcd for $C_{20}H_{21}BrO_6Na$ (MNa^+) 459.0420, found 459.0441.

Acetic Acid 4-Acetoxymethyl-5-allyl-2-benzyloxy-3-methoxy-benzyl Ester (29). In a sealed, flame-dried tube Pd(PPh_3)$_4$ (0.1 g), **28** (0.69 g, 1.58 mmol), toluene (6 mL), and allyltributyltin (0.63 mL, 2.03 mmol) were combined. The solution was stirred in an oil bath at 115−120 °C for 18 h. The reaction mixture was chromatographed (25% EtOAc/hexanes, SiO_2) giving **29** (0.39 g, 62%) as a liquid: R_f = 0.30 (83% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.46 (m, 5H), 6.99 (s, 1H), 5.92−5.97 (m, 1H), 5.23 (s, 2H), 5.09 (s, 2H), 5.00−5.07 (m, 4H), 3.90 (s, 3H), 3.42−3.44 (m, 2H), 2.06 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.3, 152.7, 148.4, 137.1, 136.6, 136.1, 131.1, 128.5, 128.3, 128.1, 127.9, 125.9, 115.9, 74.9, 61.2, 61.1, 57.9, 36.6, 20.7, 20.6; IR (neat) 2961, 1741 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{26}O_6Na$ (MNa^+) 421.1627, found 421.1622.

Acetic Acid 6-(2,3-Dihydroxy-propyl)-4-ethyl-2,3-dimethyl-benzyl Ester (30). To a solution of **29** (0.39 g, 0.98 mmol) in acetone (17 mL) and water (6 mL) were added NMO (0.128 g, 1.09 mmol) and a small crystal of OsO_4 (~10 mg). The solution was stirred at rt for 12 h. The reaction mixture was diluted with water (40 mL), and the aqueous layer was extracted with CH_2Cl_2 (4 × 40 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated. The resultant material was chromatographed (EtOAc, SiO_2), giving **30** (0.353 g, 83%) as a liquid: R_f = 0.40 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.43 (m, 5H), 7.04 (s, 1H), 5.25 (s, 2H), 5.06 (s, 2H), 5.01 (s, 2H), 3.84−3.89 (m, 1H), 3.86 (s, 3H), 3.65−3.66 (m, 1H), 3.62−3.63 (m, 1H), 3.30 (br, 2H), 2.79−2.83 (m, 2H), 2.04 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.7, 152.7, 148.5, 137.0, 134.7, 131.0, 129.0, 128.3, 128.0, 127.9, 126.7, 74.9, 72.7, 65.7, 61.3, 61.2, 58.2, 35.9, 20.8, 20.7; IR (neat) 3439, 2964, 1737 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{28}O_8Na$ (MNa^+) 455.1682, found 455.1666.

Acetic Acid 4-Acetoxymethyl-2-benzyloxy-5-[3-(*tert*-butyldiphenylsilanyloxy)-2-hydroxypropyl]-3-methoxy-benzyl Ester (31). To a solution of **30** (50 mg, 0.116 mmol) in dry DMF (0.5 mL) were added imidazole (40 mg, 0.58 mmol) and TBDPSCl (0.1 mL, 0.4 mmol). After stirring 2.5 h at rt, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (10 mL) and saturated $NaHCO_3$ (10 mL). The combined aqueous layers were extracted five times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography (90% hexanes/EtOAc) afforded **31** (52 mg, 68%) as a liquid: R_f = 0.15 (83% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.68 (m, 4H), 7.38−7.45 (m, 11H), 7.02 (s, 1H), 5.20−5.26 (m, 2H), 5.07 (s, 2H), 5.05 (s, 2H), 3.88−3.93 (m, 1H), 3.88 (s, 3H), 3.71 (dd, 1H, J = 4.0 Hz, J = 10.0 Hz), 3.63 (dd, 1H, J = 6.7 Hz, J = 10.0 Hz) 2.79−2.81 (m, 2H), 2.02 (coincidental s, 6H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (2C), 153.0, 148.9, 137.4, 135.7, 135.2, 133.2, 131.3, 130.0, 129.8, 128.7, 128.4, 128.3, 128.0, 126.9, 75.3, 72.9, 67.7, 61.5, 61.6, 58.5, 36.0, 27.0, 26.7, 21.1, 19.4; IR (neat) 3462, 2934, 2860, 1741, 1722 cm^{-1}; HRMS (ES) calcd for $C_{39}H_{46}O_8SiNa$ (MNa^+) 693.2860, found 693.2832.

Acetic Acid 4-Acetoxymethyl-2-benzyloxy-5-[3-(*tert*-butyldiphenylsilanyloxy)-2-oxopropyl]-3-methoxy-benzyl Ester (32). To a solution of **31** (32 mg, 0.048 mmol) in CH_2Cl_2 (15 mL) was added DMP[38] (122 mg, 0.29 mmol). After stirring 12 h at rt, the reaction mixture was filtered through a short pad of SiO_2 with CH_2Cl_2, concentrated, and chromatographed (83% hexanes/EtOAc) to afford **32** (25 mg, 78%) as a liquid: R_f = 0.40 (83% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.68 (m, 4H), 7.36−7.46 (m, 11H), 6.86 (s, 1H), 5.09 (s, 2H), 5.05 (s, 2H), 5.04 (s, 2H), 4.31 (s, 2H), 3.94 (s, 2H), 3.90 (s, 3H) 2.01 (s, 3H), 1.98 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 170.9, 170.8, 153.0, 149.5, 137.4, 135.7, 132.7, 131.4, 130.6, 130.3, 129.8, 128.7, 128.4, 128.3, 128.1, 127.7, 75.3, 69.8, 61.6, 61.5, 58.6, 43.1, 27.0, 21.2, 21.0, 19.4; IR (neat) 2934, 2856, 1741 cm^{-1}; HRMS (ES) calcd for $C_{39}H_{44}O_8SiNa$ (MNa^+) 691.2703, found 691.2691.

7-Benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-6-hydroxymethyl-8-methoxy-isochroman-3-ol (22). To a solution of **32** (25 mg, 0.37 mmol) in HPLC grade MeOH (12 mL) was added dry K_2CO_3 (48 mg, 0.35 mmol). After 4 h at 0 °C, the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL) and water (8 mL). The mixture was concentrated, and the resultant solution was extracted five times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Chromatography (83% hexanes/EtOAc) afforded **22** (20 mg, 91%) as a liquid: R_f = 0.70 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.76 (m, 4H), 7.39−7.45 (m, 11H), 6.80 (s, 1H), 5.05−5.06 (m, 2H), 4.90 (d, 1H, J = 15.5 Hz), 4.97 (d, 1H, J = 15.5 Hz), 4.49−4.55 (m, 2H), 3.93 (s, 3H), 3.88 (d, 1H, J = 11.4 Hz), 3.67 (d, 1H, J = 11.4 Hz), 3.63 (s, 1H), 2.67−2.75 (m, 2H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 147.4, 137.4, 135.9, 135.8, 133.8, 133.2, 132.9, 130.1 (2C), 128.8, 128.7, 128.5, 128.1, 128.0, 127.9, 127.6, 124.4, 94.9, 75.3, 69.5, 61.5, 60.4, 58.9, 33.9, 27.0, 19.5; IR (neat) 3412, 2930, 2856, 1455, 1428 cm^{-1}; HRMS (ES) calcd for $C_{35}H_{40}O_6SiNa$ (MNa^+) 607.2492, found 607.2485.

[7-Benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-3,8-dimethoxy-isochroman-6-yl]-methanol (33). To a solution of **22** (46 mg, 0.079 mmol) in MeOH (15 mL) was added PPTS (67 mg, 0.24 mmol). After stirring 42 h at rt, the reaction mixture was directly adsorbed onto SiO_2 and chromatographed (90% hexanes/EtOAc) to afford **33** (27 mg, 57%) as a liquid: R_f = 0.70 (60% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.72 (m, 4H), 7.38−7.44 (m, 11H), 6.86 (s, 1H), 5.06 (d, 1H, J = 11.0 Hz), 5.01 (d, 1H, J = 11.0 Hz), 4.85 (d, 1H, J = 15.4 Hz), 4.65 (d, 1H, J = 15.4 Hz), 4.51−4.59 (m, 2H), 3.90 (d, 1H, J = 11.0 Hz), 3.93 (s, 3H), 3.61 (d, 1H, J = 11.0 Hz), 3.25 (s, 3H), 2.92−3.02 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.2, 137.4, 135.8 (2C), 133.9, 133.5 (2C), 129.9 (2C), 128.8 (2C), 128.6, 128.5, 128.2, 127.9, 127.8, 124.3, 98.8, 75.4, 65.1, 61.6, 60.4, 59.0, 49.2, 34.6, 27.0, 19.6; IR (neat) 3451, 2934, 2860, 1455, 1428 cm^{-1}; HRMS (ES) calcd for $C_{36}H_{42}O_6SiNa$ (MNa^+) 621.2648, found 621.2652.

7-Benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-3,8-dimethoxy-isochroman-6-carbaldehyde (34). To a solution of **33** (27 mg, 0.045 mmol) in CH_2Cl_2 (25 mL) was added DMP[38] (33 mg, 0.078 mmol). After stirring 1 h at rt, the reaction mixture was directly adsorbed onto SiO_2 and chromatographed (90% hexanes/EtOAc) to afford **34** (22 mg, 80%) as an oil: R_f = 0.50 (60% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.26−7.71 (m, 16H), 5.08−5.14 (m, 2H), 4.65 (d, 1H, J = 20.0 Hz), 4.88 (d, 1H, J = 20.0 Hz) 3.92 (s, 3H), 3.89 (d, 1H, J = 10.0 Hz), 3.60 (d, 1H, J = 10.0 Hz), 3.25 (s,

3H), 2.99 (s, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 152.1, 148.7, 138.2, 137.1, 136.4, 135.8 (2C), 135.7, 135.6, 133.4, 133.3, 130.0, 129.4, 128.9 (2C), 128.8, 127.9, 123.4, 98.7, 76.8, 65.0, 60.7, 59.1, 49.2, 34.6, 27.0, 19.6; IR (neat) 3080, 1671 cm^{-1}; HRMS (ES) calcd for $C_{36}H_{40}O_6SiNa$ (MNa^+) 619.2492, found 619.2487.

(7-Benzyloxy-3,8-dimethoxy-6-vinyl-isochroman-3-yl-methoxy)-*tert*-butyldiphenylsilane (21). To a solution of **34** (22 mg, 0.036 mmol) in dry THF (2 mL) was added a freshly prepared solution of the Wittig ylid (115 μL, 0.11 mmol) in THF. After stirring 10 min at rt, the reaction mixture was quenched with water (1 mL) and extracted with CH_2Cl_2. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated. Chromatography (90% hexanes/EtOAc) afforded **21** (20 mg, 98%) as a liquid: R_f = 0.50 (83% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.73 (m, 4H), 7.33−7.48 (m, 11H), 7.06 (s, 1H), 6.99 (dd, 1H, J = 17.5 Hz, J = 11.0 Hz), 5.72 (d, 1H, J = 17.5 Hz), 5.24 (d, 1H, J = 11.0 Hz), 4.89−4.95 (m, 2H), 4.84 (d, 1H, J = 15.0 Hz), 4.65 (d, 1H, J = 15.0 Hz), 3.87 (s, 3H), 3.90 (d, 1H, J = 10.0 Hz), 3.61 (d, 1H, J = 10.0 Hz), 3.25 (s, 3H), 2.94−3.04 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.2, 137.6, 135.9, 135.8, 134.0, 133.8, 133.5, 131.4, 131.3, 130.0, 129.9, 128.6, 128.4, 128.2, 128.0, 127.9, 127.5, 121.4, 114.9, 98.8, 75.5, 65.1, 60.7, 59.1, 49.2, 34.7, 27.1, 19.6; IR (neat) 2930, 1455, 1428 cm^{-1}; HRMS (ES) calcd for $C_{37}H_{42}O_5SiNa$ (MNa^+) 617.2699, found 617.2701.

3-(2-Benzyloxy-benzyl)-5-[7-benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-3,8-dimethoxy-isochroman-6-yl]-4,5-dihydroisoxazole (36). To a solution of **21** (20 mg, 0.034 mmol) in benzene (2.5 mL) were added **35** (19.3 mg, 0.075 mmol), phenyl isocyanate (0.055 mL, 0.51 mmol), and Et_3N (0.020 mL, 0.14 mmol). After stirring 18 h at rt, the reaction mixture was filtered and concentrated. Chromatography (90% hexanes/EtOAc) afforded **36** (25 mg, 89%, *dr* = 1.5:1) as a liquid: R_f = 0.35 (75% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.83 (m, 4H), 7.32−7.43 (m, 15H), 7.10−7.19 (m, 2H), 6.80−6.92 (m, 4H), 5.59−5.67 (m, 1H), 5.03 (minor), 5.02 (major) (s, 2H), 4.88−4.97 (m, 2H), 4.76−4.82 (m, 1H), 4.56−4.61 (m, 1H), 3.84−3.87 (m, 1H), 3.79 (major), 3.78 (minor) (s, 3H), 3.63−3.76 (m, 2H), 3.55−3.58 (m, 1H), 3.22 (minor), 3.19 (major) (s, 3H), 3.09−3.19 (m, 1H), 2.86−2.96 (m, 2H), 2.64−2.70 (m, 1H), 1.12 (minor), 1.10 (major) (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer) δ 158.0, 156.6, 148.4, 146.5, 137.6, 137.1, 135.7, 135.9, 134.3, 133.5, 133.4, 130.8, 129.9, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.5, 127.4, 124.9, 122.2, 122.0, 121.3, 112.1, 98.7, 75.2, 75.1, 70.2, 65.3, 60.4, 58.9, 49.2, 44.6, 34.6, 28.3, 27.1, 19.6; IR (neat) 2934, 1737 cm^{-1}; HRMS (ES) calcd for $C_{52}H_{55}NO_7SiNa$ (MNa^+) 856.3646, found 856.3652.

3-(*tert*-Butyldiphenylsilanyloxymethyl)-6-[1-hydroxy-2-(2-hydroxy-2,3-dihydrobenzofuran-2-yl)-ethyl]-3,8-dimethoxy-isochroman-7-ol (37). To a solution of **36** (15 mg, 0.018 mmol) in MeOH (3 mL), THF (3 mL), and H_2O (1.2 mL) were added boric acid (12 mg, 0.201 mmol) and Raney Ni (a 50% suspension in water, 7 drops, ~0.4 mL). After stirring 3.75 h at rt, the reaction mixture was filtered through a short pad of silica, diluted with H_2O (10 mL), and extracted five times with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in EtOAc (15 mL), and 10% Pd/C (25 mg) was added. After stirring 18 h at rt under a hydrogen atmosphere, the reaction mixture was filtered through a short pad of Celite, concentrated, and chromatographed (50% hexanes/EtOAc) to afford **37** as a mixture of diastereomers (4 mg, 34%) as a liquid: R_f = 0.45 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.75 (m, 4H), 7.37−7.43 (m, 6H), 7.82−7.25 (m, 5H), 4.78−4.88 (m, 1H), 4.62−4.64 (m, 1H), 3.75−3.89 (m, 5H), 3.40−3.63 (m, 2H), 3.21−3.24 (m, 3H), 3.14−2.92 (m, 3H), 2.04−2.44 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 135.8 (2C), 135.4, 133.4, 132.9, 129.9 (2C), 129.4 (2C), 128.8 (2C), 127.9, 126.9, 125.8, 125.2, 124.4, 122.8, 121.9, 120.8, 118.2, 100.0, 98.7, 65.1, 60.6, 49.2, 43.8, 32.4, 27.0, 26.5, 23.6, 19.6; IR (neat) 3447, 2926, 1737 cm^{-1}; HRMS (ES) calcd for $C_{38}H_{44}O_8SiNa$ (MNa^+) 679.2703, found 679.2707.

Spiroketal (38). To a solution of **37** (0.002 g, 0.003 mmol) dissolved in CH_2Cl_2 (1 mL) was added *p*-toluenesulfonic acid (0.2 mg, 0.001 mmol). The mixture was stirred at rt for 1 h and concentrated. The residue was dissolved in 50% EtOAc/hexanes, eluted through a short pad of SiO_2 (50% EtOAc/hexanes), and concentrated. LRMS (ES) 661 (MNa^+).

[7-Benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-8-methoxy-1*H*-isochromen-6-yl]-methanol (39). To a solution of **22** (260 mg, 0.44 mmol) in H_2SO_4/dry acetone (25 mL, 0.179 N) was added activated 4 Å molecular sieves (~100 mg). After stirring 84 h at rt, the reaction mixture was diluted with water (25 mL). After concentration, the aqueous portion was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography (90% hexanes/EtOAc) afforded **39** (150 mg, 60%) as a liquid: R_f = 0.30 (83% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76−7.77 (m, 4H), 7.36−7.48 (m, 11H), 6.77 (s, 1H), 5.98 (s, 1H), 5.20 (s, 2H), 5.12 (s, 2H), 4.57 (s, 2H), 4.21 (s, 2H), 3.90 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 148.2, 148.0, 137.3, 135.7, 134.8, 133.4, 129.9, 128.7, 128.6, 128.5, 128.3, 127.9, 121.3, 118.9, 100.3, 75.5, 63.9, 62.9, 61.3, 61.0, 27.0, 19.4; IR (neat) 3428, 2930, 2856, 1455, 1428 cm^{-1}; HRMS (ES) calcd for $C_{35}H_{38}O_5SiNa$ (MNa^+) 589.2386, found 589.2402.

7-Benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-8-methoxy-1*H*-isochromene-6-carbaldehyde (40). To a solution of **39** (167 mg, 0.30 mmol) in CH_2Cl_2 (60 mL) was added DMP[38] (318 mg, 0.75 mmol). After stirring 50 min at rt, the reaction mixture was filtered through a short pad of Celite and washed with CH_2Cl_2. Concentration afforded **40** (141 mg, 85%) as a liquid: R_f = 0.70 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.73−7.74 (m, 4H), 7.40−7.46 (m, 11H), 7.20 (s, 1H), 6.00 (s, 1H), 5.21 (s, 2H), 5.16 (s, 2H), 4.23 (s, 2H), 3.93 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 157.0, 153.3, 148.6, 136.1, 135.7, 134.9, 133.3, 130.3, 130.0, 129.7, 128.8 (2C), 128.7 (2C), 128.6, 127.9 (2C), 127.8, 117.0, 99.6, 76.9, 63.9, 62.8, 61.2, 26.9, 19.4; IR (neat) 2930, 2860, 1687 cm^{-1}; HRMS (ES) calcd for $C_{35}H_{36}O_5SiNa$ (MNa^+) 587.2230, found 587.2211.

(7-Benzyloxy-8-methoxy-6-vinyl-1*H*-isochromen-3-yl-methoxy)-*tert*-butyldiphenylsilane (41). To a solution of **40** (140 mg, 0.25 mmol) in dry THF (30 mL) was added freshly prepared Wittig ylid (0.557 mL, 0.625 mmol). After stirring 10 min at rt, the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2. The combined organic portions were dried over Na_2SO_4, filtered, and concentrated. Chromatography (66% hexanes/EtOAc) afforded **41** (110 mg, 79%) as a liquid: R_f = 0.70 (83% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.80 (m, 4H), 7.37−7.52 (m, 11H), 7.04 (dd, 1H, J = 17.5 Hz, J = 11.0 Hz), 7.09 (s, 1H), 6.02 (s, 1H), 5.78 (d, 1H, J = 17.5 Hz), 5.30 (d, 1H, J = 11.0 Hz), 5.21 (s, 2H), 5.00 (s, 2H), 4.28 (s, 2H), 3.92 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 148.7, 148.1, 137.5, 135.7, 134.0, 133.8, 133.4, 132.0, 131.3, 129.9, 128.8, 128.6 (2C), 128.4, 128.2, 128.1, 127.9, 121.3, 115.8, 115.1, 100.2, 75.6, 63.9, 63.0, 61.2, 27.0, 19.5; IR (neat) 2934, 1451, 1428 cm^{-1}; HRMS (ES) calcd for $C_{36}H_{38}O_4SiNa$ (MNa^+) 585.2437, found 585.2441.

3-(2-Benzyloxy-benzyl)-5-[7-benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-8-methoxy-1*H*-isochromen-6-yl]-4,5-dihydroisoxazole (42). To a solution of **41** (108 mg, 0.20 mmol) in benzene (20 mL) were added **35** (129 mg, 0.50 mmol), phenyl isocyanate (0.217 mL, 2 mmol), and Et_3N (0.050 mL, 0.36 mmol). After stirring 36 h at rt, the reaction mixture was filtered and concentrated. Chromatography (94% hexanes/EtOAc) afforded **42** (108 mg, 70%) as a liquid: R_f = 0.30 (80% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.74−7.76 (m, 4H), 7.34−7.45 (m, 16H), 7.18−7.26 (m, 2H), 6.94−6.96 (m, 2H), 6.77 (s, 1H), 5.92 (s, 1H), 5.64 (dd, 1H, J = 8.0 Hz, 11.0 Hz), 5.12−5.20 (m, 2H), 5.08 (s, 2H), 4.97−5.02 (m, 2H) 4.23 (s, 2H), 3.82 (s, 3H), 3.73−3.79 (m, 2H), 3.10 (dd, 1H, J = 11.0 Hz, 17.5 Hz), 2.68 (dd, 1H, J = 8.0 Hz, 17.4 Hz) 1.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 156.6, 156.1, 148.2, 147.3, 137.4, 137.0, 135.7, 135.4, 133.4 (2C), 129.9, 129.2, 128.7, 128.6, 128.5, 128.4 (2C), 128.3, 128.0, 127.9, 127.3, 124.8, 121.3, 121.2, 116.5, 112.1, 100.4, 77.0, 75.3, 70.2, 63.8, 62.9, 61.0, 44.7, 27.0, 19.4; IR (neat) 2934, 1737, 1660, 1602, 1494, 1451 cm^{-1}; HRMS (ES) calcd for $C_{51}H_{51}NO_6SiNa$ (MNa^+) 824.3383, found 824.3413.

4-[7-Benzyloxy-3-(*tert*-butyldiphenylsilanyloxymethyl)-8-methoxy-1*H*-isochromen-6-yl]-1-(2-benzyloxy-phenyl)-4-hydroxybutan-2-one (43). To a solution of **42** (15 mg, 0.02 mmol) in MeOH (4 mL), THF (4 mL), and H_2O (1 mL) were added boric acid (12 mg, 0.22 mmol) and Raney Ni (2 drops, ∼0.1 mL). After stirring for 2 h at rt, the reaction mixture was filtered through a short pad of Celite, diluted with H_2O (2 mL) and brine solution (5 mL), and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated. Chromatography (90% hexanes/EtOAc) afforded **43** (11 mg, 73%) as a liquid: R_f = 0.25 (80% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.72 (m, 4H), 7.32−7.43 (m, 16H), 7.22−7.31 (m, 1H), 7.08−7.09 (m, 1H), 6.90−6.92 (m, 2H), 6.79 (s, 1H), 5.95 (s, 1H), 5.31 (dd, 1H, J = 4.0 Hz, 8.0 Hz), 5.10 (d, 1H, J = 13.3 Hz), 5.16 (d, 1H, J = 13.3 Hz), 5.01 (s, 2H), 4.92−5.01 (m, 2H), 4.20 (s, 2H), 3.81 (s, 3H), 3.61−3.69 (m, 2H), 3.28 (br s, 1H), 2.67−2.75 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 156.6, 156.1, 148.1, 146.8, 137.4, 136.9, 136.6, 135.7, 133.6, 133.4, 131.5, 129.9, 128.8 (2C), 128.7, 128.4, 128.3, 128.1, 127.9, 127.5, 125.6, 121.2, 120.9, 116.8, 112.0, 100.4, 75.3, 70.3, 65.0, 63.9, 62.9, 61.0, 49.5, 45.5, 27.0, 19.5; IR (neat) 3501, 2956, 1710 cm^{-1}; HRMS (ES) calcd for $C_{51}H_{52}O_7SiNa$ (MNa^+) 827.3380, found 827.3358.

Spiroketal 47. To a solution of **42** (60 mg, 0.075 mmol) in EtOAc (15 mL) under an atomosphere of hydrogen was added 10% Pd/C (30 mg) in four portions over 30 h (10 mg, 10 mg, 5 mg, 5 mg). After stirring an additional 6 h at rt, TLC analysis indicated complete cleavage of the benzyl groups. The reaction mixture was filtered through short pad of silica, concentrated, and chromatographed (83% hexanes/EtOAc) to afford **46** as a mixture of the hemiketal and keto alcohol (13 mg) as a liquid: R_f = 0.40 (50% hexanes/EtOAc). To a solution of **46** (13 mg, 0.02 mmol) in dry CH_2Cl_2 (4 mL) was added $TsOH·H_2O$ (1 mg, 0.004 mmol). After stirring for 20 min at rt, the reaction mixture was concentrated and chromatographed [99% hexanes/EtOAc eluted one diastereomer (1 mg) as a liquid, R_f = 0.70 (50% hexanes/EtOAc); 83% hexanes/EtOAc eluted the remaining diastereomers (4 mg) as a liquid, R_f = 0.60 (50% hexanes/EtOAc)] to afford **47** (5 mg) with an overall 34% yield. For the pure diastereomer: R_f = 0.70 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.70 (m, 4H), 7.37−7.44 (m, 6H), 7.14−6.74 (m, 5H), 4.90−4.99 (m, 1H), 4.70−4.80 (m, 1H), 4.65−4.75 (m, 1H), 3.80−3.90 (m, 1H), 3.72−3.75 (m, 2H), 3.55−3.59 (m, 1H), 3.55 (s, 3H), 3.37−3.55 (m, 2H), 2.60−2.67 (m, 3H), 2.55−2.58 (m, 1H), 1.08 (s, 9H); IR (neat) 3397, 2930, 2856, 1463, 1428 cm^{-1}; HRMS (ES) calcd for $C_{37}H_{40}O_6SiNa$ (MNa^+) 631.2492, found 631.2479. For the mixture of three diastereomers: R_f = 0.60 (50% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.71 (m, 4H), 7.38−7.42 (m, 6H), 6.59−7.07 (m, 5H), 5.19−5.54 (m, 1H), C*H*OH 5.07−5.09, 4.99−5.02, 4.94−4.99 in a 1:1:2 ratio (m, 1H), ArC*H*HO 4.84−4.92, 4.73−4.77, 4.67−4.72 in a 1:1:2 ratio (m, 1H), ArCH*H*O 4.62−4.66, 4.58−4.63, 4.44−4.54 in a 1:2:1 ratio (m 1H), 3.62−4.01 (m, 4H), *Me*O 3.55, 3.56, 3.60 in a 1:2:1 ratio (s, 3H), 3.32−3.52 (m, 2H), 2.76−3.30 (m, 1H), 2.24−2.72 (m, 3H), 1.08 (s, 9H).

■ ASSOCIATED CONTENT

Supporting Information. General experimental information, characterization data including ^{1}H and ^{13}C NMR spectra, and X-ray crystal structure data for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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