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Total Synthesis of the Aglycone of IB-00208.

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Abstract— A total synthesis of the aglycone of IB-00208 was accomplished in 22 steps using a newly developed approach towards polycyclic 1,4-dioxygenated xanthenes from benzocyclobutenones. The generality of this entry to xanthenes was initially established on several model systems before it was successfully applied to the construction of the hexacyclic core of the natural product. A new and potentially general approach towards angularly-fused benzocyclobutenones using ring-closing metathesis (RCM) was also developed.

Keywords. cyclobutenediones, natural products, polycyclic xanthenes, Moore rearrangement, total synthesis.

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1. Introduction

The polycyclic xanthone IB-00208 (**1**) (Figure 1) was isolated by Romero and coworkers in 2003 from the culture broth of *Actinomadura* sp.¹ This novel compound exhibits potent cytotoxic activity (MIC = 1 nM) against several tumor cell lines, including P388D1, A-549, HT-29 and SK-MEL-28. It also displayed strong antibiotic activity against several Gram-positive bacteria. The hexacyclic core of IB-00208 contains a 1,4-dioxygenated xanthone subunit and is structurally related to other naturally-occurring polycyclic xanthenes such as citreamicin α (**2**),² kibdelone A (**3**),³ and cervinomycin A₂ (**4**),⁴ all of which have been reported to exhibit significant biological activities (Figure 1). The stereochemistry of the sugar moiety in IB-00208 (**1**) was established by analysis of spin-spin coupling constants and NOESY experiments, but the stereochemistry of the methyl group at C(3) of **1** is unknown.

Owing to the complex polycyclic structures and potent biological activities of **1–4**, there has been considerable interest in the total synthesis of these and other polycyclic xanthenes.^{5–8} However, to date neither IB-00208 nor citreamicin α have succumbed to total synthesis. A key structural subunit embedded in many of these natural

Figure 1. Xanthone-Containing Natural Product **1–4**

products is a 1,4-dioxygenated xanthone, which itself presents some significant challenges to synthesis.⁹ In the context of our interest in these and other polycyclic xanthone natural products, we developed a concise and general route to 1,4-dioxygenated xanthenes that features a novel extension of the Moore cyclization,^{10,11} and we recently reported the application of this approach to xanthenes to the first total synthesis of the aglycone of IB-00208 (**1**).¹² Herein, we report a detailed account of these efforts.

2. Background for Synthetic Planning

When considering potential approaches to construct the xanthone moiety of IB-00208 (**1**), we were inspired by the conversion of cyclobutenones to quinones as reported by

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Moore and coworkers (Scheme 1).¹⁰ For example, **5** undergoes a rearrangement upon heating to give quinone **9** by a sequence of reactions that was proposed to be initiated by a 4π -electrocyclic ring opening reaction to provide ketene intermediate **6**, which underwent radical cyclization to diradical **7** followed by intermolecular hydrogen abstraction to provide **9**.¹³ The carbon-centered, aryl radical of **7** can also participate in homolytic aromatic substitution reactions, which our group exploited in a concise total synthesis of cribrastatin **6**.¹⁴

Scheme 1.

In another finding relevant to our own research plan, Fuganti and coworkers reported that 3-en-5-ynoic acids **10** were converted into dibenzofurans **12** when heated under reflux in acetic anhydride in the presence of sodium acetate (Scheme 2).^{15,16} The newly formed furan and benzene rings were suggested to have been formed in a single annulation step via the ketene intermediate **11**.

Scheme 2.

3. The First Generation Approach

3.1. Retrosynthetic Analysis

In our initial consideration of possible approaches towards IB-00208 (**1**), we envisioned a key step that combines both of these two precedents for the construction of the xanthone core of the natural product (Scheme 3).

Specifically, heating of the key intermediate cyclobutenone **15** was expected to produce the acetylenic vinyl ketene **14** in accord with the findings of Moore (*cf.* Scheme 1). Cyclization of the proximal phenol in **14** via an ionic pathway as proposed by Fuganti (*cf.* Scheme 2) would then deliver xanthone **13**. Elaboration of **13** to the natural product would require oxidation of the hydroquinone ring, construction of the A-ring, and regioselective glycosylation.

Compound **15** was envisaged to be accessed by the union of acetylide **17** and fused-cyclobutenone **16** by a 1,2-addition. When we initiated this project, angularly-fused, polycyclic cyclobutenedione derivatives such as **16** were unknown, but we reasoned that **16** might be readily accessible from coupling of arylbromide **18** and the known vinyl squarate **19**,¹⁷ followed by ring closing metathesis (RCM) to form the benzene ring.¹⁸ The synthesis of acetylene **17** would then entail the straightforward addition of an acetylide anion to aldehyde **20**, followed by removal of the MOM protecting group and formation of a cyclic silyl bis-ether.

Scheme 3.

3.2. Initial Model Studies

The synthesis of acetylide **17** commenced with the addition of an alkynyl Grignard reagent to the known aldehyde **20**^{19,20} to produce **21** exclusively (Scheme 4). We welcomed the unexpected, yet fortuitous, loss of the MOM protecting group, because it enabled the direct formation of the requisite cyclic silyl ether that protected both the phenol and secondary alcohol of **21**.²¹ This silyl protecting

group was selected because of its robustness to various reaction conditions and its orthogonality to other protecting groups that were envisioned in route to IB-00208 (**1**).

Scheme 4.

With alkyne **17** in hand, we wanted to validate the proposed reaction sequence for forming the xanthone subunit of IB-00208 (**1**) using a model system. Toward this end, the known benzocyclobutenedione **22** was selected as a substrate because it possessed an aryl group fused to a cyclobutenone, was symmetrical, and was readily accessible (Scheme 5).²² Deprotonation of alkyne **17** using *n*-BuLi followed by addition of the resultant anion to **22** provided the 1,2-addition product, which was treated with HF·pyridine to remove the cyclic silyl group to furnish **23** in 48% yield over two steps. Unfortunately, attempts to oxidize the secondary alcohol in **23** were unsuccessful, perhaps owing to the instability of the ynone product. When the cyclobutenol **23** was heated, a simple Moore rearrangement occurred to give **24**.^{10,11} The putative acetylenic vinyl ketene intermediate did not undergo the desired cyclization as expected from the work of Fuganti¹⁵ under any of the conditions examined.

Notwithstanding our disappointment of the failed cyclization, we reasoned that the ketone **25** might undergo cyclization to give the desired tetracyclic xanthone **26**. In the event, addition of IBX to the reaction mixture produced after heating **23** afforded a mixture of the ketone **25** and spirocycle **26**. When the crude reaction mixture was stirred with silica gel, complete conversion to spirocycle **26** ensued in 68% overall yield from **23**. The regiochemical outcome of the cyclization to form the spirocyclic ring system in **26** rather than the desired 1,4-dioxygenated xanthone ring in **27** was consistent with previous observations from our laboratory in which we found that the substitution pattern on the F-ring of **25** governs the regioselectivity of cyclization.¹¹ Microwave heating of **25** resulted in rearrangement of the spirocycle to the thermodynamically favored xanthone, and an aqueous base work-up resulted in oxidation of the hydroquinone intermediate and isolation of quinone **27** in quantitative yield. Although our initially proposed reaction sequence for forming xanthones directly from cyclobutenones was unsuccessful, we devised an alternative approach that

allowed us to effectively convert cyclobutenedione **22** into xanthone **27** in only five steps.

Scheme 5.

Having successfully validated our approach to prepare tetracyclic 1,4-dioxygenated xanthones in a model system, we turned our attention towards accessing the angularly-fused cyclobutenone **16** and transforming it into IB-00208 (**1**) by the plan adumbrated in Scheme 3.

3.3. Synthesis of Angularly-Fused Benzocyclobutenones.

Based on our retrosynthetic approach in Scheme 3, the syntheses of IB-00208 (**1**) and other polycyclic natural products such as **2–4** required the development of a workable plan to prepare angularly-fused benzocyclobutenones. Toward this end, synthesis of a model system began with conversion of commercially available 2,5-dimethoxybenzaldehyde (**28**) to an acetal, which would serve as an *ortho*-directing group for selective lithiation with *n*-BuLi. (Scheme 6). Quenching of the intermediate aryllithium reagent with 1,2-dibromo-1,1,2,2-tetrachloroethane, followed by deprotection of the acetal provided **29** in 62% yield over three steps. Peterson olefination of the aldehyde moiety in **29** afforded styrene **30**. Metal-halogen exchange of the arylbromide followed by coupling of the resulting aryllithium with vinyl squarate **19** following a procedure reported by Moore gave diene **31** in 66% yield.¹⁷ In a novel extension of ring closing metathesis (RCM) to form an aromatic ring,¹⁸ heating of **31** with 5 mol% of Grubbs II catalyst in toluene gave benzocyclobutenone **32** in 90% yield.

Scheme 6.

Having established a viable new route to angularly-fused benzocyclobutenones, we turned our attention to preparing the requisite cyclobutenone **16** (Scheme 7). Commercially available hydroquinone **33** was regioselectively brominated,²³ and the hydroquinone was protected as its *bis*-MOM ether giving **34** in 92% overall yield. Wittig olefination of the aldehyde moiety in **34** afforded bromide **18**.²⁴ Although initial attempts to couple of **18** with squarate **19** using *n*-BuLi to promote lithium-halogen exchange were plagued by extensive protodelithiation, this problem was easily solved by utilizing *t*-BuLi giving **35** in 57% overall yield from **34**. When diene **35** was heated under reflux in the presence of Grubbs II catalyst, the angular cyclobutenone **16** was isolated in 75% yield.

Scheme 7.

3.4. Synthesis of Pentacyclic Core of IB-00208.

In preliminary experiments we discovered that the acetylide anion of **17** did not add to the angular cyclobutenone **32** under a variety of conditions. Attributing this lack of reactivity to increased steric effects of **32** relative to **22**, we were required to adopt an alternate approach using a smaller acetylide anion nucleophile (Scheme 8). To this end, **16** was treated with bromomagnesium acetylide to provide alcohol **36**. The dianion of **36** added smoothly to the aldehyde **37**, which was prepared via silylation²⁰ of the corresponding known phenol,¹⁹ to furnish an intermediate adduct that was converted into **38** in 78% yield from **36** by removal of the dimethoxy ketal using *p*-toluenesulfonic acid.

Scheme 8.

Heating **38** eventuated in the expected Moore rearrangement, and the intermediate secondary alcohol of the resulting product was oxidized using IBX to give the ketone **39** in 41% overall yield (Scheme 9). Treatment of ketone **39** with TBAF in an attempt to affect its cyclization to the pentacycle **41** in analogy with work reported by Theodorakis and coworkers produced only complex mixtures (not shown).²⁵ However, removal of the TBS group using HF·pyridine gave exclusively the spirocycle **40** via spontaneous cyclization of the intermediate phenoxide, in a mode that is consistent with results observed in our model study (*cf.* Scheme 5) and earlier work.¹¹ Gratifyingly, heating **40** in nitrobenzene led to the rearrangement of the spirocycle to furnish **41** in 58% yield. This critical sequence of reactions established the underlying viability of our novel approach to the pentacyclic core of IB-00208.

Scheme 9.

The structure of **41** was confirmed by X-ray crystallography (Figure 2). The two oxygen atoms O(5) and O(6) (crystal structure numbering) at the angular fusion are in very close proximity (2.55 Å) to each other, which forces the carbonyl group C8–O5 to bend out of plane significantly giving rise to a helix-like structure with the angle between the C(11)–O(6) and C(8)–O(5) bonds being 42.9°.

Figure 2. X-Ray Crystal Structure of **41**

3.5. Attempts to Complete Synthesis of IB-00208 (**1**).

Having successfully accomplished the synthesis of the pentacycle **41**, the stage was set to complete the assembly of the core of IB-00208 (**1**) by annelating the A-ring of the natural product. Numerous efforts toward this end were met with unanticipated challenges, only a few of which will be discussed here. For example, all strategies for introducing substituents on the B-ring that would enable A-ring formation required removal of the MOM protecting groups. However, endeavours (*e.g.*, TFA, H₂O) to effect either selective mono- or di-deprotection of the MOM ethers only afforded complex mixtures with at best trace amounts of the mono-deprotected material being observed (Scheme 10).

Scheme 10.

In view of the difficulties encountered with deprotecting **41**, we queried whether the spirocycle **40** might be more accommodating. Accordingly, **40** was readily transformed into **43** under acidic conditions (TFA/H₂O, 9:1) to provide exclusively the mono-deprotected phenol **43** in quantitative yield (Scheme 11). However, all attempts to brominate (*e.g.*, NBS; Br₂; CuBr₂) or formylate [*e.g.*, (CHO)_n, SnCl₄; POCl₃, DMF]**43** were unavailing.

Scheme 11.

At this stage, it became apparent that neither **40** nor **41** would likely serve as an intermediate in a synthesis of IB-00208 (**1**). Not only were these compounds uncooperative in our exploratory experiments, but any plans for forming the A-ring on either **40** or **41** would require a disproportionately large number of steps. A new, more concise plan was needed.

4. The Second Generation Approach

4.1. Revised Retrosynthetic Analysis

The lessons of our previous efforts suggested that a better approach to IB-00208 (**1**) would involve having the A-ring present from the outset. After considering several possibilities, we decided upon incorporating the A-ring as a dihydropyran ring. Such a plan would necessarily lead to an advanced intermediate such as **45** in which the requisite lactone A-ring in **1** would be accessible via a late-stage benzylic oxidation at C(1) (Scheme 12). Compound **45** would be formed from **46** via a sequence involving a Moore rearrangement, cyclizations, and an oxidation in close analogy with the preparation of **41** from **38**. The synthesis of **46** required an acetylide stitching sequence that joins aldehyde **37** and benzocyclobutenone **47** in a

process similar to that employed to assemble **38** from **16** and **37**. The angularly-fused benzocyclobutenone **47** would be accessed by coupling the aryl anion generated from bromide **48** with squarate **19** followed by RCM.

Scheme 12.

4.2. Synthesis of Hexacyclic Core of IB-00208 (**1**).

The first task that needed to be addressed in this second generation approach to IB-00208 (**1**) was the synthesis of **48**. Because the stereochemistry at C(3) of the natural product was unknown, we sought a route that might be easily adjusted to prepare either enantiomer of **48**. Accordingly, commercially available 2-bromo-1,4-dimethoxybenzene (**49**) was treated with *n*-BuLi to induce a lithium-halogen exchange, and the resulting aryllithium reagent was allowed to react with propylene oxide to furnish the racemic secondary alcohol **50** (Scheme 13).²⁶ Because either antipode of optically pure propylene oxide is commercially available, this route may be readily adapted to access either enantiomer of **50** as needed once the absolute stereochemistry at C(3) of IB-00208 (**1**) is known. Bromination of **50** by NBS in the presence of a catalytic amount of ammonium nitrate (NH_4NO_3),²⁷ followed by formation of the MOM-ether gave **51** in 98% yield over two steps.

The key conversion of **51** to **52** was first effected by a TMSOTf-induced oxa-Pictet-Spengler cyclization²⁸ to generate the dihydropyran ring followed by oxidation of the aromatic ring using ceric ammonium nitrate [$(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$] (CAN) and reduction of the intermediate quinone giving **52** in 43% yield (sequence not shown). This approach, however, required chromatographic purifications after each step because of unavoidable side reactions. For example, when **51** was

treated with TMSOTf, some of the MOM ether was lost to generate the secondary alcohol derivative of **51**. The oxidation using CAN²⁷ also led to overoxidation giving a product containing a hydroxyl group at C(1). These problems were easily addressed by resequencing the oxidation/reduction and cyclization steps (Scheme 13). Namely, oxidation of **51** using CAN proceeded smoothly without any overoxidation, and TMSOTf-induced cyclization occurred to give **52** in 89% overall yield from **51** that was contaminated with only small amounts (ca 5%) of the deprotected alcohol. A Duff reaction of **52** with hexamethylenetetramine (HMTA)²⁹ gave aldehyde **53** in 65% yield. Following protection of the two phenolic hydroxy groups in **53** as their MOM ethers, a Wittig olefination provided key arylbromide **48** in 73% yield from **53**.

Scheme 13.

The next stage of the synthesis required annelation of a benzocyclobutenone ring on **48** to give **47** (Scheme 14). Toward this end, coupling of the aryllithium reagent generated from **48** with vinyl squarate **19** gave diene **54** in 64% yield. For this reaction, we found that use of Et_2O as the solvent rather than THF gave reproducibly better yields. Cyclization of **54** via RCM using Grubbs II catalyst delivered the angularly-fused benzocyclobutenone **47** in 81% yield.

Scheme 14.

The acetylide stitching sequence that would join **47** and aldehyde **37** was now at hand. Although the addition of

bromomagnesium acetylide to **47** proceeded smoothly to give **55** in 88% yield (Scheme 15), the subsequent coupling of **55** with **37** proved to be somewhat problematic. Reaction of the dianion of **55**, which was generated *in situ* using EtMgBr as the base, with **37** gave the desired product in up to 81% yield, but the reaction was somewhat capricious because reproducibly eliminating all traces of moisture from **55** was difficult. We discovered, however, that deprotonation of **55** using an excess of the strong, non-nucleophilic base bromomagnesium 2,2,6,6-tetramethylpiperidide (TMPMgBr), followed by reaction with **37** reproducibly gave **56** in 80% yield. Deprotection of the dimethoxy ketal moiety of **56** under acid conditions gave **46** in 79% yield. Heating **46** in DMSO at 100 °C induced a Moore rearrangement to furnish **57**, which was then transformed into **58** via oxidation of the intermediate alcohol and fluoride-induced removal of the TBS protecting group, which proceeded with concomitant cyclization. It is perhaps noteworthy that deprotection of the TBS group using HF·pyridine only proceeded in about 10–29% yield. When **58** was heated at increasingly higher temperatures from 150 to 215 °C (see experimental section), rearrangement to **45** proceeded in 67% yield.

Scheme 15.

4.3. Endgame Chemistry to Complete the Synthesis of the Aglycone of IB-00208.

In order to complete the synthesis of IB-00208 (**1**) from hexacycle **45**, a benzylic oxidation at C(1) was needed to produce the lactone moiety present in the A-ring of **1**. We had found in a much simpler model substrate (not shown) that this oxidation could be successfully performed using a variety of reagents, including RuCl₃·H₂O and NaIO₄,³⁰ RuO₂ and NaIO₄,³¹ and CrO₃ and 3,5-dimethylpyrazole.³² To our dismay, however, when these and other conditions were applied to **45**, only complex reaction mixtures were obtained (Scheme 16). Similar attempts to effect oxidation at C(1) of spirocycle **58** were also unavailing (Scheme 17).

Scheme 16.

Scheme 17.

We eventually discovered that oxidation at C(1) could be promoted using DDQ in the presence of MeOH for the earlier-stage intermediate **57** (Scheme 18).³³ Three equivalents of DDQ in the presence of BaCO₃ provided **61** in 85% yield.³⁴ In an exploratory sequence of experiments, hydrolysis of the mixed acetal at C(1) of **61** using a catalytic amount of *p*-toluenesulfonic acid gave hemiacetal **62** in 83% yield. Unfortunately, all attempts to oxidize both alcohol groups in **62** using IBX or other oxidants were uniformly unsuccessful and provided only complex mixtures.

Scheme 18.

The failed attempts to convert **62** into **63** dictated the design of a slightly modified approach. We thus discovered that oxidation of the secondary alcohol function in **61** with IBX, proceeded readily to give **64** in 70% yield (Scheme 19). Fluoride-induced removal of the TBS group was accompanied by spontaneous spirocyclization to generate **65** in 87% yield. To our dismay, repeated efforts to rearrange spirocycle **65** to the fused hexacyclic intermediate **66** proved futile.

Scheme 19.

At this stage the options for making adjustments to the sequence were limited. Hopeful that introducing the A-ring lactone prior to performing the thermal rearrangement might prove successful, the acetal moiety at C(1) of **65** was hydrolyzed, and the resulting hemiacetal was oxidized with pyridinium dichromate (PDC) in the presence of 3 Å molecular sieves to give **67** in 81% overall yield from **65** (Scheme 20).³⁵ Gratifyingly, heating spirocycle **67** at 180 °C in a microwave reactor delivered a mixture of hydroquinone **68** and quinone **69**, both of which lacked the phenolic MOM protecting group at C(17). Although the oxidation of **68** to **69** was slow when the reaction mixture was simply stirred open to air, continued heating of the reaction mixture in the presence of oxygen resulted in

complete conversion to **69**, which was isolated in 79% yield from spirocycle **67**.

Efforts to remove the C(5) phenolic MOM protecting group from **69** under acidic conditions only gave complex mixtures. However, reaction of **69** with freshly distilled TMSBr³⁶ furnished a mixture (~2:1) of compounds for which LC-HRMS and ¹H NMR spectral data were consistent with those expected for **70a**, the aglycone of IB-00208 (**1**), and its tautomer **70b**. Formation of **70a** and **70b** in approximately equal amounts is perhaps not unexpected because the redox potentials of the B- and D-rings might be predicted to be similar. Unfortunately, all efforts to separate and purify **70a** and **70b** were unsuccessful, in part due to their facile interconversion and lability toward decomposition pathways. We were thus neither able to characterize them independently nor to explore glycosylation experiments that would provide IB-00208 (**1**).

Scheme 20.

5. Summary

In summary, the first total synthesis of the racemic aglycone of IB-00208 (**1**) was accomplished in a total of 22 steps from commercially available starting materials. The hexacyclic aglycone **70a** was isolated as a mixture of hydroquinone-quinone tautomers, which were both prone toward decomposition and could not be separated or elaborated further. Accordingly, application of our approach to IB-00208 (**1**) itself will require some adjustments to the protecting group strategy that was implemented in the present synthesis of its aglycone.

Several aspects of the synthesis are notable. Facile preparation of polycyclic benzocyclobutenones **16**, **32**, and **47** is a novel and potentially general extension of the RCM reaction. The scope of this approach toward angularly-fused benzocyclobutenones is currently under investigation in our laboratories and will be reported in due course. Although the cascade reaction that was originally conceived to generate polycyclic xanthenes in a one-pot sequence was unsuccessful, a stepwise variant of this process was successfully implemented. Exploitation of the Moore rearrangement to elaborate benzocyclobutenones into highly-functionalized, polycyclic xanthenes is significant, and application of this general approach toward the synthesis of other complex xanthone natural products is currently in progress. Results of those investigations will be reported in due course.

6. Experimental

6.1 General

Solvents and reagents were reagent grade and used without purification unless otherwise specified. Tetrahydrofuran (THF) and diethyl ether (Et₂O) was passed through two columns of neutral alumina. Methanol (MeOH), acetonitrile (CH₃CN), and dimethyl formamide (DMF) were passed through two columns of molecular sieves and stored under argon. Dichloromethane (CH₂Cl₂) and triethylamine (Et₃N) were distilled from calcium hydride and stored under nitrogen. Toluene (PhMe) was passed through a column of Q5 reactant and stored under argon. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon or nitrogen in glassware that had been oven dried. Reaction temperatures refer to bath temperatures. Melting points are uncorrected. Infrared (IR) spectra were recorded neat on sodium chloride plates and are reported in wave numbers (cm⁻¹). ¹H and ¹³C NMR spectra were obtained as solutions in CDCl₃ unless otherwise noted, and chemical shifts are reported in parts per million (ppm) in reference to CDCl₃ (7.24 ppm and 77.0 ppm, respectively). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; app, apparent; br, broad; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons.

6.2 Experimental Procedures.

3,6-Dimethoxy-2-methoxymethoxybenzaldehyde (20). A solution of *n*-BuLi (39.2 mL, 1.6 M, 62.72 mmol) in hexanes was added to a solution of 1,4-dimethoxy-2-methoxymethoxybenzene (10.884 g, 59.73 mmol) in THF (100 mL) at -10 °C. After 30 min, DMF (6.94 mL, 89.60 mmol) was added. The cold bath was removed, and stirring was continued for 4 h at room temperature. Saturated aqueous NH₄Cl (40 mL) and Et₂O (200 mL) were added, and the layers were separated. The organic phase was washed with H₂O (3 × 100 mL) and dried (Na₂SO₄). The

solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 7.760 g (57%) of **20** as a yellow oil. Spectral data were consistent with those reported in the literature.¹⁹

2-(1-Hydroxyprop-2-ynyl)-3,6-dimethoxyphenol (21). A solution of **20** (740 mg, 2.78 mmol) in THF (2.8 mL) was added dropwise to a solution ethynylmagnesium bromide (41.7 mL, 0.5 M, 20.85 mmol) in THF at 0 °C. After stirring at 0 °C for 10 min, the cold bath was removed, and the mixture was stirred for 16 h at room temperature. Saturated aqueous NH₄Cl (3 mL) was added, and the solution was transferred to a separatory funnel containing H₂O (50 mL). The mixture was extracted with Et₂O (3 × 30 mL), and the combined organic phases were dried (Na₂SO₄). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 482 mg (83%) of **21** as a pale yellow solid: mp 104-105 °C; ¹H NMR (500 MHz, CDCl₃) δ 6.73 (d, *J* = 8.9 Hz, 1 H), 6.38 (d, *J* = 8.9 Hz, 1 H), 6.10 (app s, 1 H), 5.87 (dd, *J* = 10.9, 2.3 Hz, 1H), 3.98 (app d, *J* = 11.0 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 2.46 (d, *J* = 2.4 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 151.5, 143.6, 141.4, 115.5, 110.4, 101.9, 84.2, 71.7, 56.8, 56.5, 56.1; IR (neat) 3486, 3282, 2942, 2838, 1601, 1494, 1247 cm⁻¹; mass spectrum (CI) *m/z* 209.0816 [C₁₁H₁₃O₄ (M+1) requires 209.0814], 209, 191 (base), 181.

2,2-Di-*tert*-butyl-4-ethynyl-5,8-dimethoxy-4H-benzo[1,3,2]dioxasiline (17). 2,6-Lutidine (0.19 mL, 1.64 mmol) and *tert*-Bu₂Si(OTf)₂ (0.24 mL, 0.75 mmol) were added dropwise to a solution of **21** (142 mg, 0.68 mmol) in CH₂Cl₂ (7 mL) at 0 °C. After 30 min at 0 °C, NH₄Cl (6 mL) was added, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic phases were dried (Na₂SO₄), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 189 mg (79%) of **17** as a white solid: mp 125-127 °C; ¹H NMR (500 MHz, CDCl₃) δ 6.76 (d, *J* = 8.9 Hz, 1 H), 6.37 (d, *J* = 8.9 Hz, 1 H), 5.99 (d, *J* = 2.3 Hz, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 2.43 (d, *J* = 2.3 Hz, 1 H), 1.18 (s, 9 H), 0.92 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 150.3, 144.5, 144.0, 116.2, 113.5, 102.3, 84.1, 71.8, 60.3, 57.5, 55.9, 27.02, 26.99, 21.7, 20.1; IR (neat) 3284, 2936, 2860, 1596, 1492, 1258 cm⁻¹; mass spectrum (CI) *m/z* 349.1832 [C₁₉H₂₉O₄Si (M+1) requires 349.1835], 349 (base).

8-((2,2-di-*tert*-Butyl-5,8-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-8-hydroxybicyclo[4.2.0]octa-1(6),2,4-trien-7-one. A solution of *n*-BuLi (0.045 mL, 2.7 M, 0.12 mmol) in hexanes was added dropwise to a solution of **17** (40 mg, 0.16 mmol) in THF (3 mL) at -78 °C. After 15 min at -78 °C, dione **22** (15 mg, 0.16 mmol) was added, and stirring was continued for 1 h at -78 °C. NH₄Cl (3 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (MgSO₄), and the solvent was removed under reduced pressure. The residue

was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 27 mg (48%) of 8-((2,2-di-tert-butyl-5,8-dimethoxy-4*H*-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-8-hydroxybicyclo[4.2.0]octa-1(6),2,4-trien-7-one as a yellow oil; ^1H NMR (500 MHz, CDCl_3 , mixture of two diastereomers) δ 7.67–7.68 (m, 0.6 H), 7.66–7.63 (m, 0.4 H), 7.62–7.57 (comp, 1 H), 7.56–7.51 (comp, 1 H), 7.50–7.45 (comp, 1 H), 6.78–6.73 (comp, 1 H), 6.38–6.32 (comp, 1 H), 6.04 (s, 0.6 H), 6.02 (s, 0.4 H), 3.79 (s, 1.2 H), 3.77 (s, 1.8 H), 3.74 (s, 1.2 H), 3.73 (s, 1.8 H), 3.20–3.07 (comp, 1 H), 1.10–1.03 (comp, 9 H), 0.93–0.82 (comp, 9 H); ^{13}C NMR (125 MHz, CDCl_3 , mixture of two diastereomers) δ 186.6, 186.4, 157.88, 157.85, 150.4, 150.3, 148.03, 147.98, 144.5, 144.4, 144.1, 144.0, 136.2, 131.74, 131.73, 122.8, 122.7, 122.5, 122.4, 115.8, 115.6, 113.51, 113.46, 102.45, 102.42, 91.3, 86.5, 79.21, 79.19, 60.5, 60.4, 57.5, 56.0, 27.0, 26.9, 21.69, 21.67, 20.1, 20.0; IR (neat) 3414, 2934, 2860, 1778, 1595, 1492 cm^{-1} ; mass spectrum (CI, ESI) m/z 481.2050 [$\text{C}_{27}\text{H}_{33}\text{O}_6\text{Si}$ (M+1) requires 481.2046], 481 (base).

8-Hydroxy-8-(3-hydroxy-3-(2-hydroxy-3,6-dimethoxyphenyl)prop-1-yn-1-yl)bicyclo[4.2.0]octa-1(6),2,4-trien-7-one (23). HF·pyridine (6.3 μL , 70% HF, 0.23 mmol) was added using a polypropylene syringe to a solution of 8-((2,2-di-tert-butyl-5,8-dimethoxy-4*H*-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-8-hydroxybicyclo[4.2.0]octa-1(6),2,4-trien-7-one (36 mg, 0.07 mmol) and pyridine (15.1 μL , 0.19 mmol) in THF (1.5 mL) at room temperature. After 10 min at room temperature, the reaction was diluted with Et_2O (5 mL). The mixture was washed with sat. aq. NH_4Cl (3 $\times$ 5 mL) and dried (MgSO_4), and the solvent was removed under reduced pressure to 1 mL. The crude mixture was purified by column chromatography eluting with hexanes/EtOAc (1:2) to give 31 mg (100%) of **23** as a clear oil; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (app d, J = 7.6 Hz, 1 H), 7.62 (app t, J = 7.6 Hz, 1 H), 7.55 (app t, J = 8.4 Hz, 1 H), 7.52–7.47 (comp, 1 H), 6.71 (d, J = 8.8 Hz, 1 H), 6.35 (d, J = 8.8 Hz, 1 H), 6.10 (s, 1 H), 5.90 (br s, 1 H), 3.91 (br s, 1 H), 3.82 (s, 3 H), 3.79–3.73 (comp, 3 H), 3.34 (br s, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.3, 158.4, 151.8, 148.2, 144.0, 141.7, 136.6, 132.0, 123.0, 122.8, 115.4, 110.7, 102.2, 91.3, 86.7, 79.5, 57.1, 56.8, 56.4; IR (neat) 3448, 2922, 1712, 1513, 1263, 1093 cm^{-1} ; mass spectrum (CI) m/z 340.0946 [$\text{C}_{19}\text{H}_{16}\text{O}_6$ (M+1) requires 340.0947], 321 (base), 340.

4,7-Dimethoxy-1*H*,3*H*-spiro[benzofuran-2,2'-naphthalene]-1',3,4'(3'*H*)-trione (26). A solution of **23** (12 mg, 0.03 mmol) in THF (1.8 mL) was heated at 120 $^\circ\text{C}$ for 30 min in a microwave oven. The reaction was cooled to room temperature, and IBX (15 mg, 0.05 mmol) was added. The reaction was stirred at 60 $^\circ\text{C}$ for 4 h and then cooled to room temperature, whereupon hexanes/EtOAc (3:1, 5 mL) was added. The mixture was filtered through Celite and added to CH_2Cl_2 (2 mL). Silica gel (135 mg) was added, and the reaction was stirred at room temperature for 1.5 h. The solution was filtered through Celite and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with

hexanes/EtOAc (2:1) to give 8 mg (68%) of **26** as a yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 8.19 (app d, J = 7.8 Hz, 1 H), 8.06 (app d, J = 7.8 Hz, 1 H), 7.81 (dt, J = 7.6, 1.2 Hz, 1 H), 7.73 (dt, J = 7.6, 1.2 Hz, 1 H), 7.15 (d, J = 8.8 Hz, 1 H), 6.40 (d, J = 8.8 Hz, 1 H), 3.95 (s, 3 H), 3.82 (s, 3 H), 3.54 (d, J = 16.4 Hz, 1 H), 3.30 (d, J = 16.4 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 192.1, 190.4, 186.8, 162.2, 152.2, 139.8, 136.7, 135.2, 134.2, 133.0, 128.2, 126.7, 122.8, 108.9, 103.6, 92.5, 57.1, 56.1, 45.1; IR (neat) 2926, 1698, 1596, 1514, 1271 cm^{-1} ; mass spectrum (CI) m/z 339.0865 [$\text{C}_{19}\text{H}_{15}\text{O}_6$ (M+1) requires 339.0869], 339 (base).

1,4-Dimethoxy-6*H*-benzo[b]xanthene-6,11,12-trione (27). Spirocycle **26** (1 mg) was added to toluene (3 mL), and the mixture was heated at 250 $^\circ\text{C}$ for 2 $\times$ 3 h. The solvent was removed and the residue was dissolved in CH_2Cl_2 (10 mL). The organic layer was shaken with 1 M KOH (10 mL), neutralized with 1 M HCl, and extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 1 mg (100%) of **27** as a red solid; ^1H NMR (400 MHz, CDCl_3) δ 8.19 (app d, J = 7.2 Hz, 1 H), 8.14 (app d, J = 7.2 Hz, 1 H), 7.79 (dt, J = 7.6, 1.0 Hz, 1 H), 7.73 (dt, J = 7.6, 1.0 Hz, 1 H), 7.16 (d, J = 9.2 Hz, 1 H), 6.78 (d, J = 9.2 Hz, 1 H), 3.95 (s, 3 H), 3.88 (s, 3 H); IR (neat) 2923, 2852, 2360, 1738, 1692, 1489, 1288 cm^{-1} ; mass spectrum (CI) m/z 337.0710 [$\text{C}_{19}\text{H}_{13}\text{O}_6$ (M+1) requires 337.0712], 337 (base).

2-(2',5'-Dimethoxyphenyl)-1,3-dioxane. A solution of 2,5-dimethoxybenzaldehyde (5.00 g, 30.0 mmol), *p*-TsOH (0.570 g, 3.00 mmol), and 1,3-propane diol (11.0 mL, 150 mmol) were heated under reflux in benzene (60 mL) in a round-bottom flask equipped with a Dean-Stark trap and condenser for 24 h. The mixture was cooled to ambient temperature, Et_2O (50 mL) was added, and the mixture was washed with water (3 $\times$ 30 mL) and brine (1 $\times$ 30 mL). The organic layer was dried (MgSO_4), filtered, and concentrated to provide an oil. The residue was purified by column chromatography eluting with EtOAc/Hexanes (1:6.7) to provide 6.30 g (94%) of the title compound as a clear colorless oil. Spectral data were in accord with that reported in the literature.³⁷

2-(2'-Bromo-3',6'-dimethoxyphenyl)-1,3-dioxane. A solution of 2-(2',5'-dimethoxyphenyl)-1,3-dioxane (6.30 g, 28.0 mmol) dissolved in hexanes (140 mL) was cooled to -25 $^\circ\text{C}$, whereupon benzene (46 mL) was added. A solution of *n*-BuLi (17.0 mL of a 2.5 M solution in hexanes, 42.0 mmol) was then added dropwise. The mixture was stirred for 18 h at -25 $^\circ\text{C}$. (Note: Care must be taken to keep the internal temperature above -30 $^\circ\text{C}$ otherwise the mixture freezes. In addition, the use of an overhead stirrer is recommended as the mixture becomes increasingly viscous as the reaction proceeds.) A solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (17.3g, 53.0 mmol) in THF (50 mL) was then added dropwise. The cooling bath was removed, and the mixture stirred for 0.5 h at room temperature. The solvent was removed *in vacuo* to give a solid, which was purified by column chromatography

eluting with EtOAc/hexanes (1:5 to 2:5 gradient) to provide 5.50 g (66%) of the title compound as a pale yellow solid. Spectral data were in accord with that reported in the literature.³⁷

2-Bromo-3,6-dimethoxybenzaldehyde (29).

Concentrated HCl (92.0 mL) was added to a solution of 2-(2'-bromo-3',6'-dimethoxyphenyl)-1,3-dioxane (5.50 g, 18.0 mmol) in THF (92 mL), and the mixture was stirred at ambient temperature for 20 min. The mixture was extracted with Et₂O (3x100 mL) and the combined organic layers were washed with brine (1x100 mL), dried (MgSO₄), filtered, and concentrated to provide 4.90 g (100%) of **29** as a yellow solid, which was used without further purification. Spectral data were in accord with that reported in the literature.³⁷

2-Bromo-1,4-dimethoxy-3-vinylbenzene (30).

TMSCH₂Cl (0.88 mL, 6.25 mmol) added to a mixture of freshly ground Magnesium turnings (0.61 g, 25 mmol) in THF (50 mL). The mixture was stirred for 15 min then the remaining TMSCH₂Cl (2.6 mL, 18.75 mmol) was added and the mixture was stirred rapidly for 12 h. The freshly prepared TMSCH₂MgCl was transferred via cannula to a solution of 2-bromo-3,6-dimethoxybenzaldehyde (4.4 g, 18 mmol) in THF (40 mL) over 0.5 h. The solution was stirred for another 0.5 h whereupon 30% H₂SO₄ (45 mL) was added. The solution was rapidly stirred for 1 h. The mixture was diluted with Et₂O (100 mL) and the layers separated. The organic layer was washed with sat. NaHCO₃ (1x100 mL), H₂O (1x100 mL), and brine (1x100 mL), dried (MgSO₄), filtered and concentrated to give 4.2 g (97%) of **30** as an off-white solid.

3-(3',6'-Dimethoxy-2'-vinylphenyl)-4,4-dimethoxy-2-vinylcyclobut-2-enone (31). A solution of 2.6 M solution of *n*-BuLi in hexanes (1.0 mL, 2.7 mmol) was added dropwise to a solution of **30** (660 mg, 2.7 mmol) in THF (3 mL) at -78 °C and the solution was stirred for 0.5 h. A solution of **19** (500 mg, 2.7 mmol) in THF (0.5 mL) was then added and the mixture was stirred and allowed to warm to room temperature over 0.5 h. Saturated NaHCO₃ (2 mL) was added and the mixture was extracted with Et₂O (3x1mL). The combined organic layers were washed with brine (1x3 mL), dried (MgSO₄), filtered, and concentrated. The crude residue was purified by column chromatography eluting with EtOAc/Hexanes (1:50 to 1:13) gradient to provide 570 mg (66%) of **31** as a yellow solid: ¹H NMR (500 MHz, CDCl₃) δ 6.88 (d, 1 H, *J* = 9.0 Hz), 6.78 (d, 1 H, *J* = 9.0 Hz), 6.64 (dd, 1 H, *J* = 18.0, 12.0 Hz), 6.09 (dd, 1 H, *J* = 18.0, 2.0 Hz), 6.02 (dd, 1 H, *J* = 18.0 Hz, 10.5 Hz), 5.92 (dd, 1 H, *J* = 18.0, 2.0 Hz), 5.51 (dd, 1 H, *J* = 10.5, 2.0 Hz), 5.42 (dd, 1 H, *J* = 12.0, 2.0 Hz), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.45 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 191.7, 172.1, 152.6, 152.4, 149.8, 131.1, 125.8, 125.5, 124.0, 121.1, 117.5, 112.7, 110.4, 56.3, 56.0, 52.8; IR (neat) 2835, 1764, 1578, 1474, 1435, 1256 cm⁻¹; HRMS (CI) calcd 317.1389 for C₁₈H₂₁O₅ (M⁺); found 317.1387.

1,1,5,8-Tetramethoxy-1H-cyclobuta-2-one[3,4a]naphthalene (32). A mixture of Grubb's II

catalyst (19.5 mg, 0.023 mmol) and **31** (37.0 mg, 0.12 mmol) in CH₂Cl₂ (2.4 mL) was heated to 40 °C for 2 h. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography eluting with EtOAc/Hexanes (1:10 to 1:5 gradient) to provide 31.0 mg (90%) of **32** as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.41 (d, 1 H, *J* = 8.5 Hz), 7.50 (d, 1 H, *J* = 8.5 Hz), 6.99 (d, 1 H, *J* = 9.0 Hz), 6.93 (d, 1 H, *J* = 9.0 Hz), 4.00 (s, 3 H), 3.97 (s, 3 H), 3.54 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 192.9, 160.2, 150.2, 149.6, 146.9, 129.0, 127.6, 121.5, 118.1, 116.7, 108.9, 107.1, 56.1, 56.0, 53.6; IR (neat) 1759, 1617, 1579, 1462, 1265 cm⁻¹; HRMS (CI) calcd 289.1076 for C₁₆H₁₇O₅ (M+H)⁺; found 289.1074.

2-Bromo-3,6-bis(methoxymethoxy)benzaldehyde (34).

MOMCl (9.2 mL, 121.23 mmol) and *i*-Pr₂Net (17.6 mL, 100.94 mmol) were added dropwise to a solution of 2-bromo-3,6-dihydroxybenzaldehyde (8.72 g, 40.38 mmol) in CH₂Cl₂ (80 mL) at room temperature. After 17 h at room temperature, H₂O (100 mL) was added, and the mixture was extracted with Et₂O (3 × 100 mL). The combined organic phases were dried (MgSO₄), and the solvent was removed under reduced pressure to give 12.32 g (100%) of **34** as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 10.37 (s, 1 H, C7-H), 7.26 (d, *J* = 9.2 Hz, 1 H, C5-H or C6-H), 7.12 (d, *J* = 9.2 Hz, 1 H, C5-H or C6-H), 5.18 (s, 4 H, C8-H & C10-H), 3.50 (s, 3 H, C9-H or C11-H), 3.47 (s, 3 H, C9-H or C11-H); ¹³C NMR (100 MHz, CDCl₃) δ 190.5, 153.8, 149.2, 126.0, 121.6, 116.0, 115.2, 95.9, 95.7, 56.5; IR (neat) 2963, 2913, 1700, 1556, 1469, 1394, 1263, 1150 cm⁻¹; mass spectrum (CI) *m/z* 305.0031 [C₁₁H₁₃O₅Br (M+1) requires 305.0025], 305 (base).

2-Bromo-1,4-bis(methoxymethoxy)-3-vinylbenzene (18).

Ph₃PCH₃Br (28.97 g, 81.36 mmol) and NaH (4.77 g, 119.33 mmol, 60% dispersion in mineral oil) were added to solution of **26** (16.55 g, 54.24 mmol) in THF (540 mL). After 18 h at room temperature, H₂O (200 mL) and brine (50 mL) were added, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried (Na₂SO₄), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/EtOAc (2:1) to give 16.44 g (100%) of **18** as a pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 8.8 Hz, 1 H), 6.98 (d, *J* = 8.8 Hz, 1 H), 6.78 (dd, *J* = 17.7, 11.9 Hz, 1 H), 5.86 (dd, *J* = 17.7, 2.2 Hz, 1 H), 5.59 (dd, *J* = 11.9, 2.2 Hz, 1 H), 5.16 (s, 2 H), 5.11 (s, 2 H), 3.51 (s, 3 H), 3.46 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 150.7, 149.0, 132.1, 129.2, 121.6, 115.8, 115.4, 115.0, 95.8, 95.4, 56.3, 56.2; IR (neat) 2955, 2901, 2826, 1470, 1251, 1154, 1008 cm⁻¹; mass spectrum (CI) *m/z* 302.0150 [C₁₂H₁₄O₄Br (M+1) requires 302.0154], 302, 273, 271 (base).

3-(3,6-Bis(methoxymethoxy)-2-vinylphenyl)-4,4-dimethoxy-2-vinylcyclobut-2-enone (35). A solution of *t*-BuLi (9.1 mL, 14.55 mmol, 1.6 M) in heptane was added quickly to a solution of freshly dried (azeotropic distillation, 2 × 2 mL PhH) **18** (2.052 g, 6.77 mmol) in THF (30 mL) at -78 °C. After 30 sec at -78 °C, a solution

of **19** (1.500 g, 8.26 mmol) in THF (5 mL) at -78°C was added quickly via syringe. After 10 min at -78°C , the reaction was stirred for 20 min at 0°C . Upon cooling to -78°C , TFAA (2.82 mL, 20.31 mmol) was added dropwise, and the reaction was stirred for 20 min at -78°C and 5 min at room temperature. Upon addition of saturated aqueous NaHCO_3 (15 mL), the reaction was allowed to warm to room temperature. H_2O (20 mL) was added, and the mixture was extracted with Et_2O (3×50 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ EtOAc (4:1) to give 1.46 g (57%) of **35** as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 7.10 (d, $J = 9.2$ Hz, 1 H), 7.00 (d, $J = 9.2$ Hz, 1 H), 6.63 (dd, $J = 17.6$, 11.7 Hz, 1 H), 6.21–6.00 (comp, 2 H), 5.88 (dd, $J = 17.7$, 2.1 Hz, 1 H), 5.52 (dd, $J = 10.0$, 2.9 Hz, 1 H), 5.42 (dd, $J = 11.7$, 2.1 Hz), 5.14 (s, 2 H), 5.07 (s, 2 H), 3.47 (s, 3 H), 3.44 (app s, 6 H), 3.42 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.4, 171.6, 152.5, 150.5, 148.2, 131.0, 126.6, 125.7, 123.9, 121.8, 121.2, 117.3, 117.1, 114.5, 95.21, 95.18, 56.2, 56.0, 52.7; IR (neat) 2946, 2904, 2835, 1766, 149, 1251, 1016 cm^{-1} ; mass spectrum (ESI) m/z 399.1415 [$\text{C}_{20}\text{H}_{24}\text{O}_7$ (M+23) requires 399.1414], 399 (base).

1,1-Dimethoxy-5,8-

bis(methoxymethoxy)cyclobuta[*a*]naphthalen-2(1*H*)-

one (16). Grubbs second generation catalyst (16 mg, 0.12 mmol) was added to a degassed (Ar , 15 min) solution of diene **35** (145 mg, 0.39 mmol) in toluene (15 mL). The solution was then heated for 5 h at 110°C , whereupon the reaction was cooled to room temperature. The reaction mixture was concentrated to ca. 1 mL and purified by flash column chromatography eluting with hexanes/ EtOAc (4:1) to give 100 mg (75%) of **16** as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 8.8$ Hz, 1 H), 7.49 (d, $J = 8.8$ Hz, 1 H), 7.28 (d, $J = 8.6$ Hz, 1 H), 7.18 (d, $J = 8.6$ Hz, 1 H), 5.33 (s, 2 H), 5.31 (s, 2 H), 3.54 (s, 3 H), 3.50 (app s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.3, 160.5, 148.4, 147.6, 147.0, 129.4, 127.6, 121.9, 118.4, 116.6, 113.6, 111.6, 95.3, 94.8, 56.22, 56.18, 53.6; IR (neat) 2946, 2906, 2833, 1762, 1458, 1257, 1055 cm^{-1} ; mass spectrum (ESI) m/z 371.1102 [$\text{C}_{18}\text{H}_{20}\text{O}_7$ (M+23) requires 371.1101], 719, 371 (base).

2-(*tert*-Butyldimethylsilyloxy)-3,6-

dimethoxybenzaldehyde (37). NaH (60% dispersion in mineral oil, 322 mg, 8.05 mmol) was added to a solution of 2-hydroxy-3,6-dimethoxybenzaldehyde¹⁹ (1.12 g, 6.19 mmol) in DMF (22 mL) at 0°C . The mixture was then stirred for 30 min at room temperature and then cooled to 0°C , whereupon TBSCl (1.40 g, 9.29 mmol) was added. The reaction was stirred for 5 min at 0°C and 2 h at room temperature, whereupon H_2O (50 mL) was added. The mixture was extracted with Et_2O (3×50 mL), and the combined organic layers were washed with H_2O (2 $\times$ 50 mL), brine (1 $\times$ 50 mL), dried (MgSO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ EtOAc (3:1) to provide 1.55 g (85%) of aldehyde **37** as a yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 10.49 (app d, $J = 0.6$ Hz, 1 H),

6.96 (d, $J = 9.0$ Hz, 1 H), 6.45 (d, $J = 8.9$ Hz, 1 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 0.96 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 190.0, 154.6, 149.1, 144.6, 118.1, 117.4, 103.1, 56.1, 55.7, 25.8, 18.19, -4.1; IR 2933, 2857, 2770, 1693, 1597, 1449, 1283 cm^{-1} ; mass spectrum (CI) m/z 297.1522 [$\text{C}_{15}\text{H}_{25}\text{O}_4\text{Si}$ (M+1) requires 297.1522].

2-Ethynyl-1,1-dimethoxy-5,8-bis(methoxymethoxy)-1,2-

dihydrocyclobuta[*a*]naphthalen-2-ol (36)

A solution of **16** (97 mg, 0.28 mmol) in THF (3.4 mL) was added to a solution of ethynylmagnesium bromide (3.4 mL, 0.5 M, 1.68 mmol) in THF at 0°C . After 5 min at 0°C and 2 h at room temperature, saturated aqueous NH_4Cl (5 mL) was added. The reaction was diluted with Et_2O (50 mL), and the mixture was washed with H_2O (3×10 mL). The organic phase was dried (MgSO_4) and the solvent was removed under reduced pressure to give 80 mg (77%) of **36** as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.37 (d, $J = 8.4$ Hz, 1 H), 7.55 (d, $J = 8.4$ Hz, 1 H), 7.08 (d, $J = 8.4$ Hz, 1 H), 7.04 (d, $J = 8.4$ Hz, 1 H), 5.35–5.21 (comp, 4 H), 3.82 (br s, 1 H), 3.66 (s, 3 H), 3.64 (s, 3 H), 3.55 (s, 3 H), 3.50 (s, 3 H), 2.68 (s, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.5, 146.5, 145.7, 137.4, 127.7, 126.4, 112.9, 118.9, 111.0, 109.4, 107.5, 95.6, 95.2, 81.6, 77.4, 75.6, 56.2, 56.1, 53.0, 52.3; IR (neat) 3439, 3285, 2943, 2839, 1595, 1458, 1258, 1153, 1078, 1009 cm^{-1} ; mass spectrum (ESI) m/z 397.1258 [$\text{C}_{20}\text{H}_{22}\text{O}_7$ (M+23) requires 397.1258], 397 (base).

2-(3-(2-(*tert*-Butyldimethylsilyloxy)-3,6-dimethoxyphenyl)-3-hydroxyprop-1-ynyl)-1,1-dimethoxy-5,8-bis(methoxymethoxy)-1,2-

dihydrocyclobuta[*a*]naphthalen-2-ol

A solution of EtMgBr (0.55 mL, 3 M, 1.64 mmol) in THF was added dropwise to a solution of freshly dried (azeotropic distillation, 2×2 mL PhH) **36** (204 mg, 0.545 mmol) in THF (5.4 mL) at 0°C . After 2 h at room temperature, the reaction was cooled to 0°C , and a solution of freshly dried (azeotropic distillation, 2×2 mL PhH) aldehyde **37** (323 mg, 1.09 mmol) in THF (1 mL) was added dropwise. After 30 min at 0°C and 10 min at room temperature, saturated aqueous NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (3×30 mL), and the organic phase was dried (MgSO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes/ EtOAc (1:1) to give 42 mg (21%) of recovered **36** and 288 mg (79%) of 2-(3-(2-(*tert*-butyldimethylsilyloxy)-3,6-dimethoxyphenyl)-3-hydroxyprop-1-ynyl)-1,1-dimethoxy-5,8-bis(methoxymethoxy)-1,2-dihydrocyclobuta[*a*]naphthalen-2-ol as a yellow oil; ^1H NMR (400 MHz, CDCl_3 , mixture of diastereomers) δ 8.33 (d, $J = 8.4$ Hz, 0.4 H), 8.32 (d, $J = 8.4$ Hz, 0.6 H), 7.49 (d, $J = 8.4$ Hz, 0.4 H), 7.48 (d, $J = 8.4$ Hz, 0.6 H), 7.06 (d, $J = 8.6$ Hz, 0.4 H), 7.05 (d, $J = 8.6$ Hz, 0.6 H), 7.02 (d, $J = 8.6$ Hz, 0.4 H), 7.01 (d, $J = 8.6$ Hz, 0.6 H), 6.64 (d, $J = 8.6$ Hz, 0.4 H), 6.63 (d, $J = 8.6$ Hz, 0.6 H), 6.39 (app d, $J = 8.6$ Hz, 1 H), 5.86 (br s, 0.4 H), 5.83 (br s, 0.6 H), 5.47–5.45 (comp, 4 H), 3.73 (s, 1.8 H), 3.69 (s, 1.2 H), 3.68 (s, 1.2 H), 3.67 (s, 1.8 H), 3.59 (app s, 3 H), 3.53 (s, 1.2 H), 3.52 (s, 1.8 H), 3.50 (s, 1.2 H), 3.49 (s, 1.8 H), 3.48 (s, 1.2 H),

3.47 (s, 1.8 H), 0.91 (s, 3.6 H), 0.89 (s, 5.4 H), 0.12 (s, 1.2 H), 0.11 (s, 1.2 H), 0.10 (s, 1.8 H), 0.04 (s, 1.8 H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of diastereomers) δ 152.4, 148.7, 146.6, 146.3, 144.9, 142.1, 137.4, 127.6, 126.1, 123.1, 121.5, 121.4, 119.2, 111.2, 110.5, 109.3, 107.8, 103.8, 103.6, 95.7, 95.3, 88.3, 88.2, 81.1, 77.6, 57.7, 56.2, 56.1, 55.3, 53.0, 52.1, 26.0, 18.7, -4.2, -4.3; IR (neat) 3515, 2940, 2856, 1490, 1257, 1076 cm^{-1} ; mass spectrum (ESI) m/z 693.2700 [$\text{C}_{35}\text{H}_{46}\text{O}_{11}\text{Si}$ (M+23) requires 693.2702], 693 (base).

2-(3-(2-(*tert*-Butyldimethylsilyloxy)-3,6-dimethoxyphenyl)-3-hydroxyprop-1-ynyl)-2-hydroxy-5,8-bis(methoxymethoxy)cyclobuta[*a*]naphthalen-1(2*H*)-one (38). *p*-TsOH (2.6 mg, 0.04 mmol) was added to a solution of 2-(3-(2-(*tert*-butyldimethylsilyloxy)-3,6-dimethoxyphenyl)-3-hydroxyprop-1-ynyl)-1,1-dimethoxy-5,8-bis(methoxymethoxy)-1,2-dihydrocyclobuta[*a*]naphthalen-2-ol (91 mg, 0.14 mmol) in acetone (2 mL) at room temperature. After 10 min at room temperature, the reaction was diluted with Et_2O (50 mL). The mixture was washed with H_2O (2×10 mL) and brine (10 mL). The organic phase was dried (MgSO_4), and the solvent was removed under reduced pressure to give 84 mg (99%) of **38** as an orange oil; ^1H NMR (400 MHz, CDCl_3 , mixture of diastereomers) δ 8.52 (d, $J = 8.5$ Hz, 0.4 H), 8.51 (d, $J = 8.5$ Hz, 0.6 H), 7.71 (app d, $J = 8.5$ Hz, 1 H), 7.19 (d, $J = 8.6$ Hz, 0.4 H), 7.28 (d, $J = 8.6$ Hz, 0.6 H), 7.15 (d, $J = 8.6$ Hz, 0.4 H), 7.14 (d, $J = 8.6$ Hz, 0.6 H), 6.67 (d, $J = 8.9$ Hz, 0.4 H), 6.66 (d, $J = 8.9$ Hz, 0.6 H), 6.42 (app d, $J = 8.9$ Hz, 1 H), 5.87 (app s, 1 H), 5.31 (app s, 4 H), 4.07 (app br s, 1 H), 3.79 (s, 1.8 H), 3.77 (s, 1.2 H), 3.69 (s, 1.2 H), 3.68 (s, 1.8 H), 3.54 (s, 1.2 H), 3.53 (s, 1.8 H), 3.50 (app s, 3 H), 0.94 (s, 3.6 H), 0.92 (s, 5.4 H), 0.15 (s, 1.2 H), 0.14 (s, 1.2 H), 0.13 (s, 1.8 H), 0.09 (s, 1.8 H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of diastereomers) δ 183.3, 159.8, 152.3, 148.4, 147.3, 144.9, 143.0, 142.2, 132.2, 127.7, 120.8, 120.7, 118.6, 113.9, 111.3, 110.8, 103.9, 95.4, 95.3, 91.3, 85.7, 79.6, 57.5, 56.3, 55.3, 26.0, 18.8, -4.09, -4.14; IR (neat) 3375, 2930, 2855, 1774, 1491, 1256, 1078 cm^{-1} ; mass spectrum (ESI) m/z 647.2288 [$\text{C}_{33}\text{H}_{40}\text{O}_{10}\text{Si}$ (M+23) requires 647.2283], 647 (base).

3-((2-(*tert*-Butyldimethylsilyloxy)-3,6-dimethoxyphenyl)(hydroxymethyl)-5,8-bis(methoxymethoxy)phenanthrene-1,4-dione. A solution of benzocyclobutenone **38** (45 mg, 0.07 mmol) in DMSO (3 mL) was heated to 100 $^\circ\text{C}$ for 20 min and 120 $^\circ\text{C}$ for 10 min. Upon cooling to room temperature, H_2O (10 mL) was added, and the mixture was extracted with Et_2O (3×10 mL). The combined organic phases were washed with H_2O (3×10 mL) and brine (10 mL) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes/ EtOAc (1:2) to give 19 mg (42%) of 3-((2-(*tert*-butyldimethylsilyloxy)-3,6-dimethoxyphenyl)(hydroxymethyl)-5,8-bis(methoxymethoxy)phenanthrene-1,4-dione as a burnt orange oil: ^1H NMR (400 MHz, CDCl_3) δ 8.42 (d, $J = 8.8$ Hz, 1 H), 8.05 (d, $J = 8.8$ Hz, 1 H), 7.24 (d, $J = 8.6$ Hz, 1 H), 7.13 (d, $J = 8.6$ Hz, 1 H), 6.78 (d, $J = 2.3$ Hz, 1 H),

6.75 (d, $J = 8.8$ Hz, 1 H), 6.46 (d, $J = 10.0$, 2.3 Hz, 1 H), 6.41 (d, $J = 8.8$ Hz, 1 H), 5.31 (d, $J = 10.0$ Hz, 1 H), 5.30 (d, $J = 8.4$ Hz, 1 H), 5.29 (d, $J = 8.4$ Hz, 1 H), 4.77 (d, $J = 6.8$ Hz, 1 H), 4.59 (d, $J = 6.8$ Hz, 1 H), 3.77 (s, 3 H), 3.62 (s, 3 H), 3.49 (s, 3 H), 3.33 (s, 3 H), 1.00 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 187.4, 185.2, 157.1, 152.3, 149.9, 147.8, 145.1, 143.8, 135.1, 132.5, 129.6, 128.1, 126.5, 122.2, 121.1, 120.3, 113.5, 112.1, 110.6, 102.9, 96.0, 95.3, 64.6, 56.2, 55.8, 55.7, 55.1, 26.0, 18.9, -3.8, -4.2; IR (neat) 3425, 2956, 2931, 2856, 1659, 1489, 1454, 1255 cm^{-1} ; mass spectrum (ESI) m/z 647.2285 [$\text{C}_{33}\text{H}_{40}\text{O}_{10}\text{Si}$ (M+23) requires 647.2283], 647 (base).

3-(2-(*tert*-Butyldimethylsilyloxy)-3,6-dimethoxybenzoyl)-5,8-bis(methoxymethoxy)phenanthrene-1,4-dione (39). IBX (81 mg, 0.29 mmol) was added to a solution of 3-((2-(*tert*-butyldimethylsilyloxy)-3,6-dimethoxyphenyl)(hydroxymethyl)-5,8-bis(methoxymethoxy)phenanthrene-1,4-dione (60 mg, 0.10 mmol) in DMSO (2.5 mL) at room temperature. After 18 h at room temperature, saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and saturated aqueous NaHCO_3 (5 mL) were added, and the reaction was stirred for 10 min at room temperature. Brine (10 mL) was added, and the mixture was extracted with Et_2O (3×15 mL). The combined organic phases were washed with saturated aqueous NaHCO_3 (10 mL) and H_2O (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give 58 mg (97%) of **39** as a red oil; ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, $J = 8.7$ Hz, 1 H), 8.07 (d, $J = 8.7$ Hz, 1 H), 7.35 (d, $J = 8.9$ Hz, 1 H), 7.19 (d, $J = 8.9$ Hz, 1 H), 7.11 (s, 1 H), 6.89 (d, $J = 8.9$ Hz, 1 H), 6.43 (d, $J = 8.9$ Hz, 1 H), 5.32 (s, 2 H), 4.74 (s, 2 H), 3.78 (s, 3 H), 3.51 (s, 3 H), 3.51 (s, 3 H), 3.36 (s, 3 H), 0.85 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.7, 185.8, 185.4, 151.9, 150.1, 148.6, 148.0, 145.4, 144.6, 133.8, 132.6, 132.0, 130.0, 127.1, 122.1, 121.7, 121.1, 114.5, 113.8, 112.5, 102.4, 96.2, 95.3, 56.3, 55.8, 55.7, 25.7, 18.6, -4.4; IR (neat) 2932, 2856, 1662, 1592, 1483, 1254, 1102, cm^{-1} ; mass spectrum (ESI) m/z 623.2306 [$\text{C}_{33}\text{H}_{39}\text{O}_9\text{Si}$ (M+1) requires 623.2307], 645 (base).

4,7-Dimethoxy-5',8'-bis(methoxymethoxy)-1'*H*,3*H*-spiro[benzofuran-2,3'-phenanthrene]-1',3,4'(2'*H*)-trione (40). Pyridine (5 μL , 0.06 mmol) and HF $\cdot$ pyridine (2 drops, 70% wt, 0.07 mmol) were added to a solution of **39** (14 mg, 0.02 mmol) in THF (1 mL) in a plastic tube at room temperature. After 1 day at room temperature, additional HF $\cdot$ pyridine (2 drops) was added, and the reaction was stirred at room temperature. After 1 day, the reaction was diluted with Et_2O (30 mL), and the mixture was washed with brine (10 mL), saturated aqueous CuSO_4 (2×10 mL), and H_2O (10 mL). The organic phase was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ EtOAc (2:3) to give 10 mg (91%) of **40** as an orange oil; ^1H NMR (400 MHz, CDCl_3) δ 8.46 (d, $J = 8.7$ Hz, 1 H), 8.04 (d, $J = 8.7$ Hz, 1 H), 7.18 (d, $J = 8.6$ Hz, 1 H), 7.15 (d, $J = 8.9$ Hz, 1 H), 7.07 (d, $J = 8.6$ Hz, 1 H), 6.41 (d, $J = 8.9$ Hz, 1 H), 5.30 (s, 2 H), 4.85 (d, $J = 6.8$ Hz, 1 H), 4.76 (d, $J = 6.8$

Hz, 1 H), 3.93 (s, 3 H), 3.81 (s, 3 H), 3.58 (d, $J = 17.8$ Hz, 1 H), 3.51 (d, $J = 17.8$ Hz, 1 H), 3.49 (s, 3 H), 3.14 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.4, 190.4, 189.2, 161.3, 151.7, 148.5, 147.5, 139.9, 135.6, 135.3, 129.8, 127.2, 122.2, 122.1, 121.3, 112.7, 111.7, 109.7, 103.2, 95.3, 95.1, 93.5, 57.0, 56.2, 56.02, 55.97, 46.1; IR (neat) 2936, 2841, 1710, 1691, 1515, 1273, 1077 cm^{-1} ; mass spectrum (ESI) m/z 509.1451 [$\text{C}_{27}\text{H}_{24}\text{O}_{10}$ (M+1) requires 509.1442], 531, 509 (base).

9,12-Dimethoxy-1,4-bis(methoxymethoxy)-1*H*-naphtho[1,2-*b*]xanthene-7,13,14-trione (41). A solution of spirocycle **40** (10 mg, 0.01 mmol) in PhNO_2 was heated at 215 °C for 1.5 h. The reaction was cooled to room temperature, and the majority of the solvent was removed by distillation under high vacuum at 54–56 °C. The residual mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2×10 mL), 1 M KOH (2×10 mL). The aqueous KOH layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/EtOAc (1:3) to give 6 mg (58%) of **41** as a red solid: mp 192–194 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.47 (d, $J = 8.8$ Hz, 1 H), 8.12 (d, $J = 8.8$ Hz, 1 H), 7.37 (d, $J = 8.5$ Hz, 1 H), 7.25 (d, $J = 8.5$ Hz, 1 H), 7.21 (d, $J = 9.0$ Hz, 1 H), 6.82 (d, $J = 9.0$ Hz, 1 H), 5.33 (s, 2 H), 5.32 (s, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 3.60 (s, 3 H), 3.52 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 182.2, 178.8, 173.5, 153.3, 152.5, 150.2, 147.8, 147.0, 143.1, 136.4, 130.5, 129.9, 127.1, 122.5, 122.3, 120.6, 117.3, 117.1, 114.0, 113.6, 107.1, 96.7, 95.4, 57.1, 56.8, 56.4, 56.3; IR (neat) 2925, 2854, 1693, 1586, 1489, 1287, 1072 cm^{-1} ; mass spectrum (ESI) m/z 507.1290 [$\text{C}_{27}\text{H}_{22}\text{O}_{10}$ (M+1) requires 507.1286], 529, 507 (base).

5'-Hydroxy-4,7-dimethoxy-8'-(methoxymethoxy)-1'*H*,3*H*-spiro[benzofuran-2,3'-phenanthrene]-1',3,4'(2'*H*)-trione (43). A solution of H_2O (0.1 mL) in TFA (0.9 mL) was added dropwise to a solution of spirocycle **40** (32 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 30 min at 0 °C, saturated aqueous NaHCO_3 (20 mL) was slowly added (CO_2 evolved), and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with H_2O (2×10 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 30 mg (100%) of **43** as a dark red oil; ^1H NMR (400 MHz, CDCl_3) δ 8.83 (d, $J = 8.9$ Hz, 1 H), 8.82 (s, 1 H), 8.24 (d, $J = 8.9$ Hz, 1 H), 7.29 (d, $J = 8.9$ Hz, 1 H), 7.17 (d, $J = 8.9$ Hz, 1 H), 7.14 (d, $J = 8.9$ Hz, 1 H), 6.41 (d, $J = 8.9$ Hz, 1 H), 5.31 (s, 2 H), 3.96 (s, 3 H), 3.80 (s, 3 H), 3.63 (d, $J = 16.6$ Hz, 1 H), 3.51 (s, 3 H), 3.44 (d, $J = 16.6$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.9, 191.0, 190.1, 161.6, 152.1, 148.9, 147.2, 140.0, 139.7, 132.6, 130.5, 129.7, 123.0, 121.6, 121.1, 118.5, 114.2, 108.7, 103.8, 95.5, 93.2, 57.1, 56.3, 56.1, 45.2; IR (neat) 3416, 2953, 1705, 1596, 1515, 1271, 1077 cm^{-1} ; mass spectrum (ESI) m/z 487.1000 [$\text{C}_{25}\text{H}_{20}\text{O}_9$ (M+23) requires 487.1000], 951 (base), 465.

1-(4-Bromo-2,5-dimethoxyphenyl)propan-2-ol. A mixture of *N*-bromosuccinimide (28.12 g, 158.1 mmol) and ammonium nitrate (1.21 g, 15.05 mmol) was added to a stirred solution of **50** (29.54 g, 150.5 mmol) in CH_3CN (75 mL). Stirring was continued for 30 min at room temperature, whereupon H_2O (50 mL) was added, and the mixture was extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (2×50 mL) and dried (MgSO_4). The solvent was removed under reduced pressure to give 43.56 g (100%) of crude 1-(4-bromo-2,5-dimethoxyphenyl)propan-2-ol as a light brown solid that was used without further purification. Spectral data were consistent with those reported in the literature for enantiomerically pure (*S*)-alcohol.²⁸

2,5-Dimethoxy-4-(2-(methoxymethoxy)propyl)bromobenzene (51) MOMCl (5.74 mL, 6.08 g, 75.53 mmol) and *i*-Pr₂NEt (17.54 mL, 13.01 g, 100.7 mmol) were added dropwise to a stirred solution of 1-(4-bromo-2,5-dimethoxyphenyl)propan-2-ol (13.85 g, 50.35 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The solution was then stirred for 20 h at room temperature, and Et_2O (200 mL) was added. The layers were separated, and the organic phase was washed with 1 M HCl (50 mL), saturated NaHCO_3 (50 mL), and brine (50 mL) and then dried (MgSO_4). The solvent was removed under reduced pressure to give 15.69 g (98%) of **51** as a pale yellow oil that was used in the next step without further purification; ^1H NMR (400 MHz, CDCl_3) δ 7.00 (s, 1 H), 6.75 (s, 1 H), 4.59 (d, $J = 6.8$ Hz, 1 H), 4.48 (d, $J = 6.8$ Hz, 1 H), 3.98–3.89 (m, 1 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 3.18 (s, 3 H), 2.76 (ABX, $J_{\text{AB}} = 13.6$ Hz, $J_{\text{AX}} = 7.2$ Hz, $J_{\text{BX}} = 5.6$ Hz, $\Delta\nu(\text{AB}) = 30.2$ Hz, 1 H, C9-H), 2.60 (ABX, $J_{\text{AB}} = 13.6$ Hz, $J_{\text{AX}} = 7.2$ Hz, $J_{\text{BX}} = 5.6$ Hz, $\Delta\nu(\text{AB}) = 30.2$ Hz, 1 H), 1.15 (d, $J = 6.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.9, 149.5, 127.4, 115.6, 115.5, 108.8, 94.7, 72.2, 56.7, 55.9, 54.8, 38.0, 20.2; IR 2932, 1495, 1464, 1387, 1214, 1035 cm^{-1} ; mass spectrum (ESI) m/z 341.0349 [$\text{C}_{13}\text{H}_{19}\text{BrO}_4$ (M+Na)⁺ requires 341.0359].

2-Bromo-5-(2-(methoxymethoxy)propyl)benzene-1,4-diol. A solution of CAN (54.36 g, 99.20 mmol) in H_2O (42 mL) was added to a solution of **51** (10.55 g, 17.14 mmol) in CH_3CN (165 mL) at 0 °C, and the mixture was stirred for 25 min at room temperature. H_2O (50 mL) and brine (50 mL) were added, and the mixture was extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine (10×50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give 9.53 g (100%) of a substituted benzoquinone as yellow-orange oil, which was dissolved immediately in THF (150 mL) and a stirred solution of $\text{Na}_2\text{S}_2\text{O}_4$ (28.79 g, 165.37 mmol) in H_2O (50 mL) was added. After stirring for 10 min at room temperature, saturated NaHCO_3 (50 mL) was added, and the mixture was extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine (2×50 mL) and dried (MgSO_4). The solvent was removed under reduced pressure to give 9.09 g (94%) of 2-bromo-5-(2-(methoxymethoxy)propyl)benzene-1,4-diol as a yellow solid that was used without further purification; mp 88–90

°C; ^1H NMR (500 MHz) δ 6.82 (t, J = 1.1 Hz, 1 H), 4.58 (d, J = 7.0 Hz, 1 H), 4.50 (d, J = 7.0 Hz, 1 H), 3.92–3.81 (m, 1 H), 3.23 (s, 3 H), 2.62–2.50 (comp, 2 H), 1.17 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (126 MHz) δ 184.7, 179.4, 146.4, 138.1, 137.1, 133.7, 95.0, 71.5, 55.4, 36.4, 20.6; IR 3316, 2933, 1667, 1591, 1237 cm^{-1} ; mass spectrum (ESI) m/z 290.0146 [$\text{C}_{11}\text{H}_{15}\text{BrO}_4$ (M) requires 290.0154].

7-Bromo-3-methylisochroman-5,8-diol (52). TMSOTf (73 μL , 0.04 mmol) was added dropwise to a stirred solution of 2-bromo-5-(2-(methoxymethoxy)propyl)benzene-1,4-diol (118 mg, 0.41 mmol), which had been dried by azeotropic distillation under reduced pressure from benzene, in CH_3CN (2 mL) at 0 °C. The solution was then stirred for 18 h at room temperature, whereupon saturated NaHCO_3 (10 mL) was added, and the mixture was extracted with Et_2O (3×30 mL). The combined organic phases were dried (MgSO_4), and the solvent was removed under reduced pressure to give 100 mg (95%) of **52** as a pale yellow solid that was used without further purification; mp 61–63 °C; ^1H NMR (500 MHz) δ 6.79 (s, 1 H), 5.10 (s, 1 H), 4.93 (d, J = 16.0 Hz, 1 H), 4.62 (ddd, J = 16.0, 2.4, 1.5 Hz, 1 H), 4.51 (s, 1 H), 3.75–3.67 (m, 1 H), 2.64 (ddd, J = 16.6, 3.2, 1.5 Hz, 1 H), 2.35 (dddd, J = 16.6, 10.7, 1.6, 1.1 Hz, 1 H), 1.36 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (126 MHz) δ 146.8, 142.0, 123.7, 122.0, 115.1, 106.0, 69.9, 64.7, 29.9, 21.5; IR 3307, 2974, 1458, 1259 cm^{-1} ; mass spectrum (ESI) m/z 257.9883 [$\text{C}_{10}\text{H}_{11}\text{BrO}_3$ (M) requires 257.9892].

7-Bromo-5,8-dihydroxy-3-methylisochroman-6-carbaldehyde (53). HMTA (1.45 g, 10.37 mmol) was added to a solution of **52** (2.55 g, 9.88 mmol) in TFA (40 mL) in a sealed tube and heated at 100 °C for 16 h. H_2O (150 mL) was added, and the mixture was stirred at 60 °C for 4 h. The mixture was then extracted with EtOAc (5×100 mL), and the combined organic phases were washed with brine (8×100 mL) and dried (MgSO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes/ EtOAc (2:1) to give 1.85 g (65%) of **53** as a yellow solid; mp 141–143 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.99 (s, 1 H), 10.17 (s, 1 H), 5.36 (br s, 1 H), 4.95 (d, J = 17.5 Hz, 1 H), 4.64 (d, J = 17.5 Hz, 1 H), 3.78–3.65 (m, 1 H), 2.77 (ddd, J = 17.4, 3.6, 1.6 Hz, 1 H), 2.35 (app dd, J = 17.4, 10.8 Hz, 1 H), 1.37 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.5, 156.1, 141.2, 133.7, 124.6, 113.0, 108.1, 69.9, 64.9, 29.1, 21.4; IR 3362, 2974, 1638, 1423, 1300, 1204 cm^{-1} ; mass spectrum (ESI) m/z 284.9764 [$\text{C}_{11}\text{H}_{10}\text{O}_4\text{Br}$ (M-1) requires 284.9768].

7-Bromo-5,8-bis(methoxymethoxy)-3-methylisochroman-6-carbaldehyde. MOMCl (3.71 g, 3.52 mL, 46.39 mmol) and *i*-Pr₂NEt (4.99 g, 6.73 mL, 38.66 mmol) were added dropwise to a solution of **53** (4.44 g, 15.46 mmol) in CH_2Cl_2 (50 mL) at room temperature, and the mixture was stirred for 18 h at room temperature. H_2O (100 mL) was added, and the mixture was extracted with Et_2O (3×100 mL). The combined organic phases were dried (MgSO_4), and the solvent was removed under reduced pressure to give 5.06 g (87%) of 7-bromo-5,8-

bis(methoxymethoxy)-3-methylisochroman-6-carbaldehyde as a yellow solid; mp 47–49 °C; ^1H NMR (400 MHz, CDCl_3) δ 10.27 (s, 1 H), 5.08 (d, J = 16.8 Hz, 1 H), 5.06 (d, J = 6.2 Hz, 1 H), 5.04 (d, J = 6.2 Hz, 1 H), 5.00 (s, 2 H), 4.76 (d, J = 16.8 Hz, 1 H), 3.73–3.61 (m, 1 H), 3.59 (s, 3 H), 3.55 (s, 3 H), 2.88 (ddd, J = 16.8, 3.0, 1.1 Hz, 1 H), 2.44 (app dd, J = 16.8, 10.6 Hz, 1 H), 1.36 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.7, 153.9, 148.3, 137.2, 130.0, 126.6, 117.1, 101.9, 100.4, 70.1, 65.2, 57.73, 57.70, 30.7, 21.4; IR 2934, 1698, 1360, 1159 cm^{-1} ; mass spectrum (ESI) m/z 397.0256 [$\text{C}_{15}\text{H}_{19}\text{O}_6\text{Br}$ (M+23) requires 397.0257].

7-Bromo-5,8-bis(methoxymethoxy)-3-methyl-6-vinylisochroman (48). $\text{Ph}_3\text{PCH}_3\text{Br}$ (7.19 g, 20.19 mmol) and NaH (1.08 g, 26.92 mmol, 60% dispersion in mineral oil) were added to a solution of 7-bromo-5,8-bis(methoxymethoxy)-3-methylisochroman-6-carbaldehyde (5.05 g, 13.46 mmol) in THF (70 mL), and the mixture was stirred for 18 h at room temperature. Brine (100 mL) was slowly added, and the mixture was extracted with EtOAc (3×50 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ EtOAc (2:1) to give 4.24 g (84%) of **48** as a white solid; mp 40–42 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.68 (dd, J = 17.8, 11.6 Hz, 1 H), 5.75 (dd, J = 17.8, 2.0 Hz, 1 H), 5.56 (dd, J = 11.6, 2.0 Hz, 1 H), 5.05 (d, J = 16.0 Hz, 1 H), 5.03 (d, J = 6.0 Hz, 1 H), 5.01 (d, J = 6.0 Hz, 1 H), 4.87 (d, J = 5.8 Hz, 1 H), 4.85 (d, J = 5.8 Hz, 1 H), 4.74 (d, J = 16.0 Hz, 1 H), 3.74–3.60 (m, 1 H), 2.86 (ddd, J = 16.9, 2.8, 1.2 Hz, 1 H), 2.44 (app dd, J = 17.2, 10.4 Hz, 1 H), 1.35 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.4, 147.6, 132.5, 130.6, 129.9, 128.6, 121.4, 116.2, 100.0, 99.2, 70.2, 65.0, 57.6, 57.5, 31.0, 21.5; IR 2935, 1360, 1159, 965, 927 cm^{-1} ; mass spectrum (ESI) m/z 395.0465 [$\text{C}_{16}\text{H}_{21}\text{O}_5\text{Br}$ (M+23) requires 395.0465].

3-(5,8-Bis(methoxymethoxy)-3-methyl-6-vinylisochroman-7-yl)-4,4-dimethoxy-2-vinylcyclobut-2-enone (54). *tert*-BuLi (2.98 mL, 5.06 mmol, 1.7 M in pentane) was added dropwise to a stirred solution of **48** (900 mg, 2.41 mmol), which had been dried by azeotropic distillation of benzene under reduced pressure, in Et_2O (14 mL) at -78 °C, and stirring was continued for 5 min at -78 °C. The mixture was then warmed to 0 °C, and a solution of freshly dried (with NaH) **19** (532.7 mg, 2.89 mmol) in Et_2O (6 mL) was added dropwise. Stirring was continued for 30 min at 0 °C, whereupon the reaction was cooled to -78 °C, and TFAA (1.26 g, 0.84 mL, 6.02 mmol) was added dropwise. The solution was stirred for 20 min at -78 °C, the cold bath was removed, saturated aqueous NaHCO_3 (40 mL) was added, and the reaction was allowed to warm to room temperature. H_2O (20 mL) was added, and the mixture was extracted with Et_2O (3×40 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ EtOAc (4:1→3:1) to give 689.1 mg (64%) of **54** as a yellow oil;

^1H NMR (400 MHz, CDCl_3) δ 6.55 (dd, $J = 17.6, 11.6$ Hz, 1 H), 6.11–5.94 (comp, 2 H), 5.67 (dd, $J = 17.6, 2.0$ Hz, 1 H), 5.50 (dd, $J = 10.4, 2.8$ Hz, 1 H), 5.37 (dd, $J = 11.6, 2.0$ Hz, 1 H), 5.00 (d, $J = 15.8$ Hz, 1 H), 4.85 (d, $J = 6.2$ Hz, 1 H), 4.83 (d, $J = 6.2$ Hz, 1 H), 4.76 (d, $J = 6.4$ Hz, 1 H), 4.74 (d, $J = 6.4$ Hz, 1 H), 4.66 (d, $J = 15.8$ Hz, 1 H), 3.70–3.59 (m, 1 H), 3.48 (s, 3 H), 3.41 (s, 3 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 2.89 (dd, $J = 17.2, 2.0$ Hz, 1 H), 2.47 (dd, $J = 17.2, 10.4$ Hz, 1 H), 1.31 (d, $J = 6.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.5, 170.7, 152.3, 149.9, 146.8, 131.2, 131.0, 129.6, 128.4, 126.1, 123.9, 122.7, 121.2, 116.6, 100.3, 99.1, 70.1, 64.7, 57.4, 57.2, 52.5, 52.4, 31.2, 21.5; IR 2945, 1767, 1159, 974 cm^{-1} ; mass spectrum (ESI) m/z 469.1838 [$\text{C}_{24}\text{H}_{30}\text{O}_8$ ($\text{M}+\text{Na}$) $^+$ requires 169.1833].

1,1-Dimethoxy-5,10-bis(methoxymethoxy)-7-methyl-6,7-dihydro-1H-cyclobuta[3,4]benzo[1,2-g]isochromen-2(9H)-one (47). Grubbs second generation catalyst (56.0 mg, 0.066 mmol) was added to a degassed (freeze-pump-thaw, two cycles) solution of diene **54** (491 mg, 1.10 mmol) in toluene (11 mL), and the resulting solution was degassed one more time (freeze-pump-thaw). The solution was then heated under reflux for 5 h 30 min, whereupon the reaction was cooled to room temperature. The reaction mixture was concentrated to ca. 2 mL, and the residue was purified by flash column chromatography eluting with hexanes/EtOAc (4:1) to give 373.5 mg (81%) of **47** as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, $J = 8.6$ Hz, 1 H), 7.39 (d, $J = 8.6$ Hz, 1 H), 5.31 (d, $J = 16.0$ Hz, 1 H), 5.17 (d, $J = 7.2$ Hz, 1 H), 5.053 (d, $J = 7.2$ Hz, 1 H), 5.051 (d, $J = 5.6$ Hz, 1 H), 5.01 (d, $J = 5.6$ Hz, 1 H), 4.92 (d, $J = 16.0$ Hz, 1 H), 3.78–3.66 (m, 1 H), 3.58 (s, 3 H), 3.57 (s, 3 H), 3.49 (s, 3 H), 3.43 (s, 3 H), 3.07 (dd, $J = 17.2, 2.8$ Hz, 1 H), 2.64 (dd, $J = 17.2, 11.2$ Hz, 1 H), 1.34 (d, $J = 6.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.2, 159.7, 148.9, 146.8, 146.3, 130.7, 130.4, 130.2, 128.0, 122.7, 118.1, 116.1, 102.0, 100.1, 70.1, 65.2, 57.6, 57.2, 53.56, 53.47, 31.7, 21.5; IR 2945, 1766, 1258, 1157, 960 cm^{-1} ; mass spectrum (ESI) m/z 441.1521 [$\text{C}_{22}\text{H}_{26}\text{O}_8$ ($\text{M}+\text{Na}$) $^+$ requires 441.1520].

2-Ethynyl-1,1-dimethoxy-5,10-bis(methoxymethoxy)-7-methyl-2,6,7,9-tetrahydro-1H-cyclobuta[3,4]benzo[1,2-g]isochromen-2-ol (55). A solution of ethynylmagnesium bromide (28 mL, 0.5 M in THF, 14.05 mmol) was added to a stirred solution of **47** (1.68 g, 4.02 mmol) in THF (10 mL). Stirring was continued for 2 h at room temperature, and saturated NH_4Cl (5 mL) and H_2O (45 mL) were added. The mixture was extracted with Et_2O (3×100 mL), and the combined organic phases were washed with H_2O (2×50 mL), and dried (MgSO_4). The solvent was removed under reduced pressure to give 1.57 g (88%) of **55** as a pale yellow oil; ^1H NMR (400 MHz, CDCl_3 , mixture of diastereomers) δ 8.14 (d, $J = 8.7$ Hz, 0.7 H), 8.13 (d, $J = 8.7$ Hz, 0.3 H), 7.47 (d, $J = 8.7$ Hz, 0.3 H), 7.46 (d, $J = 8.7$ Hz, 0.7 H), 5.36 (d, $J = 16.0$ Hz, 0.7 H), 5.25 (d, $J = 16.0$ Hz, 0.3 H), 5.19 (d, $J = 6.8$ Hz, 0.3 H), 5.15 (d, $J = 6.8$ Hz, 0.7 H), 5.07 (d, $J = 5.6$ Hz, 0.7 H), 5.06 (d, $J = 5.6$ Hz, 0.3 H), 5.03 (d, $J = 5.6$ Hz, 0.3 H), 5.02 (d, $J = 5.6$ Hz, 0.7 H), 4.00 (d, $J = 6.8$ Hz, 0.7 H), 4.91 (d, $J = 6.8$ Hz, 0.3 H), 4.90 (app d, $J = 16.0$ Hz, 1 H), 3.84 (br s, 0.3 H), 3.83–3.66

(comp, 1 H), 3.71 (br s, 0.7 H), 3.627 (s, 0.9 H), 3.626 (s, 0.9 H), 3.62 (s, 2.1 H), 3.59 (s, 2.1 H), 3.56 (app s, 3 H), 3.55 (s, 0.9 H), 3.548 (s, 2.1 H), 3.13–3.03 (comp, 1 H), 2.71 (s, 0.7 H), 2.68 (s, 0.3 H), 2.65 (app dd, $J = 16.8, 10.8$ Hz, 1 H), 1.41–1.35 (comp, 3 H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of diastereomers) δ 148.6, 148.5, 145.3, 144.6, 144.5, 137.0, 136.8, 129.0, 128.91, 128.85, 128.8, 126.8, 126.7, 125.9, 125.7, 123.81, 123.77, 118.5, 107.7, 107.2, 102.00, 101.96, 100.1, 100.0, 81.6, 81.5, 77.6, 77.2, 75.8, 75.5, 70.6, 70.2, 65.6, 65.2, 57.75, 57.69, 57.34, 57.29, 52.8, 52.3, 52.2, 51.6, 31.52, 31.46, 21.8, 21.6; IR 3402, 3294, 2943, 2249, 1594, 1445, 1337, 1158, 1086 cm^{-1} ; mass spectrum (ESI) m/z 467.1677 [$\text{C}_{24}\text{H}_{28}\text{O}_8$ ($\text{M}+\text{Na}$) $^+$ requires 467.1676].

2-(3-(2-((tert-Butyldimethylsilyl)oxy)-3,6-dimethoxyphenyl)-3-hydroxyprop-1-yn-1-yl)-1,1-dimethoxy-5,10-bis(methoxymethoxy)-7-methyl-2,6,7,9-tetrahydro-1H-cyclobuta[3,4]benzo[1,2-g]isochromen-2-ol (56). *Method A.* A solution of EtMgBr (3.53 mL, 3 M in THF 10.60 mmol) was added dropwise to a stirred solution of **55** (1.57 g, 3.53 mmol), which had been dried by azeotropic distillation of benzene under reduced pressure, in THF (15 mL) at 0 $^\circ\text{C}$, and the solution was stirred for 2 h at room temperature. A solution of aldehyde **37** (2.09 g, 7.07 mmol), which had been dried by azeotropic distillation of benzene under reduced pressure, in THF (3 mL) was then added, and stirring was continued for 30 min at room temperature. Saturated NH_4Cl (5 mL) and H_2O (50 mL) were added, and the mixture was extracted with Et_2O (3×30 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure and the residue purified by flash column chromatography eluting with hexanes/EtOAc (2:1 $\rightarrow$ 1:1) to give 209 mg (13%) of recovered **55** and 2.11 g (81%) of **56** as a yellow oil; ^1H NMR (400 MHz, CDCl_3 , mixture of diastereomers) δ 8.14–8.06 (comp, 1 H), 7.44–7.38 (comp, 1 H), 6.66–6.61 (comp, 1 H), 6.42–6.35 (comp, 1 H), 5.90–5.82 (comp, 1 H), 5.40–5.21 (comp, 1 H), 5.20–5.13 (comp, 1 H), 4.95–4.82 (comp, 2 H), 4.09–3.95 (comp, 1 H), 3.83–3.71 (comp, 1 H), 3.75–3.68 (comp, 3 H), 3.68–3.65 (comp, 3 H), 3.63–3.61 (comp, 3 H), 3.56–3.50 (comp, 6 H), 3.47–3.40 (comp, 3 H), 3.14–3.03 (comp, 1 H), 2.70–2.59 (comp, 3 H), 1.39–1.35 (comp, 3 H), 0.93–0.87 (comp, 9 H), 0.12–0.02 (comp, 6 H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of diastereomers) δ 152.3, 148.5, 145.8, 144.9, 144.6, 144.5, 142.0, 136.7, 136.6, 128.8, 128.6, 128.5, 126.4, 126.3, 125.5, 125.4, 123.8, 123.7, 121.4, 118.8, 110.4, 107.8, 107.4, 103.73, 103.67, 102.0, 99.99, 99.95, 88.3, 88.2, 88.0, 87.8, 81.0, 80.9, 77.6, 77.3, 70.6, 70.1, 65.6, 65.1, 57.7, 57.6, 57.3, 57.2, 56.0, 55.2, 52.7, 52.4, 51.7, 51.2, 31.5, 31.4, 25.9, 21.8, 21.6, 18.6, -4.3, -4.4; IR 3528, 3429, 2940, 1595, 1491, 1257, 1078 cm^{-1} ; mass spectrum (ESI) m/z 763.3121 [$\text{C}_{39}\text{H}_{52}\text{O}_{12}\text{Si}$ ($\text{M}+\text{Na}$) $^+$ requires 763.3120].

Method B. A solution of EtMgBr (2.77 mL, 0.9 M in THF, 2.49 mmol) was added to a solution of tetramethylpiperidine (0.45 mL, 2.64 mmol) in THF (2.23 mL) at room temperature. The resulting mixture was stirred under reflux for 6.5 h and cooled to room

temperature. A portion of this solution (2.8 mL) was added to the solution of **55** (123 mg, 0.275 mmol), which had been dried by azeotropic distillation of benzene under reduced pressure, and aldehyde **37** (179 mg, 0.605 mmol) in THF (2.8 mL). The solution was stirred for 6.5 h at room temperature, and saturated NH_4Cl (5 mL) and H_2O (10 mL) were added. The mixture was extracted with Et_2O (3×15 mL), and the combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes/ EtOAc (2:1 $\rightarrow$ 1:1) to give 163 mg (80%) of **56** as a yellow oil.

2-(3-(2-((*tert*-Butyldimethylsilyloxy)-3,6-dimethoxyphenyl)-3-hydroxyprop-1-yn-1-yl)-2-hydroxy-5,10-bis(methoxymethoxy)-7-methyl-2,6,7,9-tetrahydro-1*H*-cyclobuta[3,4]benzo[1,2-*g*]isochromen-1-one (46). *p*-TsOH (54 mg, 0.29 mmol) was added to a solution of **56** (2.11 g, 2.85 mmol) in acetone (50 mL). After 15 min at room temperature, the reaction was diluted with Et_2O (100 mL), and the mixture was washed with brine (3×50 mL). The organic phase was dried (MgSO_4), and the solvent was removed under reduced pressure to give 1.95 g (98%) of **46** as an orange foam; ^1H NMR (400 MHz, CDCl_3 , complex mixture of diastereomers) δ 8.37–8.24 (comp, 1 H), 7.68–7.60 (comp, 1 H), 6.66–6.59 (comp, 1 H), 6.38 (app d, $J = 9.2$ Hz, 1 H), 5.84 (app br s, 1 H), 5.32–4.73 (comp, 6 H), 4.48–4.25 (br 2, 1 H), 4.15–3.88 (br s, 1 H), 3.84–3.69 (comp, 1 H), 3.78–3.72 (comp, 1 H), 3.69–3.59 (comp, 6 H), 3.59–3.48 (comp, 3 H), 3.03 (app t, $J = 17.8$ Hz, 1 H), 2.73–2.56 (comp, 1 H), 1.38 (app d, $J = 6.0$ Hz, 3 H), 0.93–0.88 (comp, 9 H), 0.18–0.05 (comp, 6 H); ^{13}C NMR (100 MHz, CDCl_3 , mixture of diastereomers) δ 184.2, 183.8, 161.0, 160.4, 152.2, 148.5, 148.3, 145.7, 145.5, 144.8, 142.1, 141.7, 141.6, 133.2, 133.0, 131.1, 130.7, 129.1, 129.0, 127.8, 127.6, 120.8, 120.7, 120.6, 118.3, 118.2, 110.7, 103.9, 101.6, 101.4, 100.2, 91.4, 91.2, 85.7, 85.5, 79.2, 70.5, 70.1, 65.2, 65.1, 57.9, 57.8, 57.5, 57.4, 56.3, 55.2, 31.5, 31.3, 25.9, 21.5, 21.4, 18.7, -4.16, -4.19; IR (neat) 3532, 3347, 2934, 1767, 1491, 1256, 1158 cm^{-1} ; mass spectrum (ESI) m/z 717.2699 [$\text{C}_{37}\text{H}_{46}\text{O}_{11}\text{Si}$ ($\text{M}+23$) requires 717.2702].

2-((2-((*tert*-Butyldimethylsilyloxy)-3,6-dimethoxyphenyl)(hydroxy)methyl)-7,12-bis(methoxymethoxy)-9-methyl-8,9-dihydro-1*H*-naphtho[2,1-*g*]isochromene-1,4(1*H*)-dione (57). A solution of benzocyclobutenone **46** (124 mg, 0.178 mmol) in DMSO (36 mL) was heated at 80 $^\circ\text{C}$ for 5 min and then 100 $^\circ\text{C}$ for 25 min in dark. After cooling to room temperature, EtOAc (40 mL) was added, and the mixture was washed with brine (3×30 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexanes/ EtOAc (1:1) to give 123.6 mg (67%) of **57** as a red amorphous solid; ^1H NMR (500 MHz, CDCl_3 , mixture of diastereomers) δ 8.30 (d, $J = 8.7$ Hz, 0.5 H), 8.29 (d, $J = 8.7$, 0.5 H), 7.99 (d, $J = 8.7$ Hz, 1 H), 6.76 (d, $J = 9.0$ Hz, 0.5 H), 6.755 (d, $J = 9.0$ Hz, 0.5 H), 6.57 (dd, $J = 10.0$, 1.8 Hz, 0.5 H), 6.55 (dd, $J =$

10.0, 1.8 Hz, 0.5 H), 6.48–6.43 (comp, 1.5 H), 6.36 (d, $J = 1.8$ Hz, 0.5 H), 5.36 (d, $J = 16.1$ Hz, 0.5 H), 5.27 (d, $J = 16.3$ Hz, 0.5 H), 5.09–5.03 (comp, 2 H), 4.92–4.83 (comp, 1.5 H), 4.72 (d, $J = 6.7$ Hz, 0.5 H), 4.49 (d, $J = 6.8$ Hz, 0.5 H), 4.31 (d, $J = 6.7$ Hz, 0.5 H), 4.11 (d, $J = 10.2$ Hz, 0.5 H), 3.98 (d, $J = 10.3$ Hz, 0.5 H), 3.78–3.68 (comp, 7 H), 3.62 (s, 3 H), 3.35 (s, 1.5 H), 3.31 (s, 1.5 H), 3.14–3.06 (m, 1 H), 2.70–2.62 (m, 1 H), 1.39 (d, $J = 6.0$ Hz, 1.5 H), 1.38 (d, $J = 6.1$ Hz, 1.5 H), 0.94 (s, 4.5 H), 0.92 (s, 4.5 H), 0.203 (s, 1.5 H), 0.196 (s, 1.5 H), 0.19 (s, 1.5 H), 0.15 (s, 1.5 H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.3, 186.2, 185.1, 185.1, 155.0, 154.7, 152.4, 152.3, 147.64, 147.57, 147.4, 147.3, 145.1, 145.0, 143.8, 143.7, 134.06, 134.05, 132.4, 132.3, 131.07, 131.05, 130.3, 130.2, 129.3, 129.1, 129.0, 127.8, 127.7, 121.4, 121.3, 120.8, 118.9, 118.5, 111.0, 110.9, 103.03, 102.95, 100.34, 100.32, 99.4, 99.2, 70.2, 70.1, 65.67, 65.65, 65.1, 65.0, 57.8, 57.7, 57.5, 57.4, 55.72, 55.71, 55.1, 31.53, 31.49, 26.03, 25.97, 21.62, 21.58, 18.9, 18.8, -3.75, -3.77, -4.0. IR 3504, 2934, 2857, 1660, 1627, 1594, 1489, 1467, 1443, 1388, 1359, 1338, 1303, 1256, 1227, 1158, 1127, 1105, 1056, 1029, 1001. Mass spectrum (ESI) m/z 717.2713 [$\text{C}_{37}\text{H}_{46}\text{O}_{11}\text{NaSi}$ ($\text{M}+\text{Na}$) $^+$ requires 747.2702].

2-(2-(*tert*-Butyldimethylsilyloxy)-3,6-dimethoxybenzoyl)-7,12-bis(methoxymethoxy)-9-methyl-8,9-dihydro-1*H*-naphtho[2,1-*g*]isochromene-1,4(1*H*)-dione. IBX (172 mg, 0.61 mmol) was added to a solution of **57** (142 mg, 0.20 mmol) in DMSO (10 mL). After 21 h at room temperature, saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and saturated aqueous NaHCO_3 (5 mL) were added, and the reaction was stirred for 10 min at room temperature. Brine (50 mL) was added, and the mixture was extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (2×50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give 142 mg (100%) of 2-(2-(*tert*-butyldimethylsilyloxy)-3,6-dimethoxybenzoyl)-7,12-bis(methoxymethoxy)-9-methyl-8,9-dihydro-1*H*-naphtho[2,1-*g*]isochromene-1,4(1*H*)-dione as a red oil; ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, $J = 8.8$ Hz, 1 H), 7.98 (d, $J = 8.8$ Hz, 1 H), 6.91 (s, 1 H), 6.86 (d, $J = 9.2$ Hz, 1 H), 6.46 (d, $J = 9.2$ Hz), 5.33 (d, $J = 16.4$ Hz, 1 H), 5.09 (d, $J = 5.8$ Hz, 1 H), 5.05 (d, $J = 5.8$ Hz, 1 H), 4.90 (d, $J = 16.4$ Hz, 1 H), 4.86 (d, $J = 6.8$ Hz, 1 H), 4.83 (d, $J = 6.8$ Hz, 1 H), 3.77 (s, 3 H), 3.66 (s, 3 H), 3.64 (s, 3 H), 3.45 (s, 3 H), 3.11 (dd, $J = 17.3$, 2.4 Hz, 1 H), 2.68 (dd, $J = 17.3$, 11.0 Hz, 1 H), 1.40 (d, $J = 6.0$ Hz, 3 H), 0.80 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.0, 186.0, 184.2, 151.6, 147.8, 147.7, 146.2, 144.7, 143.5, 135.0, 133.9, 132.1, 131.4, 130.6, 129.8, 128.0, 121.6, 120.7, 120.6, 113.4, 103.4, 100.4, 99.9, 70.2, 65.8, 57.8, 57.6, 56.2, 55.3, 31.6, 25.7, 21.7, 18.6, -4.0, -4.1; IR (neat) 2934, 1697, 1663, 1599, 1486, 1256, 1099 cm^{-1} ; mass spectrum (ESI) m/z 715.2557 [$\text{C}_{39}\text{H}_{39}\text{O}_{11}\text{Si}$ ($\text{M}+1$) requires 715.2545], 747, 715 (base).

4,7-Dimethoxy-7',12'-bis(methoxymethoxy)-9'-methyl-8',9'-dihydro-3*H*-spiro[benzofuran-2,2'-naphtho[2,1-*g*]isochromene]-1',3,4'(3'*H*,11'*H*)-trione (58). $\text{Et}_3\text{N} \cdot \text{HF}$ (51 μL , 0.31 mmol) was added to a solution of 2-(2-(*tert*-

butyldimethylsilyloxy)-3,6-dimethoxybenzoyl)-7,12-bis(methoxymethoxy)-9-methyl-8,9-dihydro-1*H*-naphtho[2,1-*g*]isochromene-1,4(11*H*)-dione (51 mg, 0.07 mmol) in CH₃CN at room temperature. The reaction was stirred for 20 min, then diluted with EtOAc (15 mL). The mixture was washed with brine (3 x 10 mL). The organic layers were separated, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1: 2 to 1:1) to give 36 mg (86%) of **58** as an amorphous yellow solid; ¹H NMR (400 MHz, CDCl₃, 1:1 mixture of diastereomers) δ 8.34 (d, *J* = 8.8 Hz, 0.5 H), 8.33 (d, *J* = 9.2 Hz, 0.5 H), 8.06 (d, *J* = 8.8 Hz, 0.5 H), 8.05 (d, *J* = 9.2 Hz, 0.5 H), 7.14 (d, *J* = 8.9 Hz, 0.5 H), 7.13 (d, *J* = 8.9 Hz, 0.5 H), 6.41 (app d, *J* = 8.9 Hz, 1 H), 5.25 (d, *J* = 16.4 Hz, 0.5 H), 5.16 (d, *J* = 16.4 Hz, 0.5 H), 5.12 (d, *J* = 5.6 Hz, 0.5 H), 5.08 (d, *J* = 6.0 Hz, 0.5 H), 5.06 (d, *J* = 6.0 Hz, 0.5 H), 5.05 (d, *J* = 5.6 Hz, 0.5 H), 4.87 (d, *J* = 16.4 Hz, 0.5 H), 4.76 (d, *J* = 16.4 Hz, 0.5 H), 4.50 (d, *J* = 6.0 Hz, 0.5 H), 4.46 (d, *J* = 6.0 Hz, 0.5 H), 4.42 (d, *J* = 6.4 Hz, 0.5 H), 4.41 (d, *J* = 6.4 Hz, 0.5 H), 3.93 (s, 1.5 H), 3.91 (s, 1.5 H), 3.83 (app s, 3 H), 3.78-3.69 (m, 1 H), 3.64 (s, 1.5 H), 3.63 (s, 1.5 H), 3.57 (d, *J* = 17.6 Hz, 0.5 H), 3.55 (d, *J* = 17.6 Hz, 0.5 H), 3.50 (d, *J* = 17.6 Hz, 0.5 H), 3.48 (d, *J* = 17.6 Hz, 0.5 H), 3.15 (dd, *J* = 17.2, 2.8 Hz, 0.5 H), 3.12 (s, 1.5 H), 3.08 (s, 1.5 H), 3.07 (dd, *J* = 17.2, 10.8 Hz, 0.5 H), 2.71 (dd, *J* = 17.2, 10.8 Hz, 0.5 H), 1.38 (d, *J* = 6.0 Hz, 1.5 H), 1.37 (d, *J* = 6.0 Hz, 1.5 H); ¹³C NMR (100 MHz, CDCl₃, mixture of diastereomers) δ 191.6, 191.3, 190.5, 190.4, 187.7, 187.1, 161.4, 161.2, 151.8, 148.0, 147.8, 147.2, 147.0, 140.0, 139.9, 136.4, 136.1, 134.3, 134.0, 131.1, 130.4, 130.3, 129.9, 129.8, 128.4, 128.2, 122.6, 122.5, 122.3, 121.5, 109.9, 109.7, 103.5, 103.4, 100.4, 100.0, 93.5, 93.3, 70.3, 70.1, 65.5, 57.8, 57.3, 57.1, 57.02, 56.98, 56.1, 46.8, 46.7, 31.6, 31.5, 21.7, 21.6; IR (neat) 2934, 1704, 1598, 1515, 1272 cm⁻¹; mass spectrum (ESI) *m/z* 601.1680 [C₃₁H₃₀O₁₁ (M+23) requires 601.1680].

10,13-Dimethoxy-5,16-bis(methoxymethoxy)-3-methyl-3,4-dihydropyrano[4',3':6,7]naphtho[1,2-*b*]xanthene-8,14,15(1*H*)-trione (45). A solution of spirocycle **58** (10 mg, 0.02 mmol) in PhNO₂ (2.5 mL) was heated for 15 min at 150 °C, 30 min at 200 °C, and 45 min at 215 °C. The reaction was cooled to room temperature, and the majority of the solvent was removed by distillation under high vacuum at 54–56 °C. The residual mixture was dissolved in CH₂Cl₂ (15 mL), and the solution was extracted with 1 M KOH (2 x 10 mL). The combined aqueous phases were extracted with CH₂Cl₂ (3 x 10 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes/EtOAc (1:3→0:1) to give 6.6 mg (67%) of **45** as a red oil; ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, *J* = 8.8 Hz, 1 H), 8.10 (d, *J* = 8.8 Hz, 1 H), 7.22 (d, *J* = 9.2 Hz, 1 H), 6.82 (d, *J* = 9.2 Hz, 1 H), 5.36 (d, *J* = 16.4 Hz, 1 H), 5.11 (d, *J* = 6.0 Hz, 1 H), 5.06 (d, *J* = 6.0 Hz, 1 H), 5.05 (d, *J* = 6.8 Hz, 1 H), 4.97 (d, *J* = 6.8 Hz, 1 H), 4.93 (d, *J* = 16.4 Hz, 1 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.84-3.69 (m, 1 H), 3.65 (s, 3 H), 3.48 (s, 3 H), 3.13 (dd, *J* = 16.8, 2.8 Hz, 1 H), 2.69 (dd, *J* = 16.8, 11.2 Hz, 1 H), 1.42

(d, *J* = 6.0 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 181.7, 178.7, 173.3, 153.2, 152.4, 148.0, 147.8, 146.6, 143.1, 135.4, 131.8, 130.1, 129.9, 128.0, 122.4, 121.5, 120.4, 117.4, 117.1, 107.4, 104.8, 100.5, 99.9, 70.1, 65.7, 57.9, 57.8, 57.1, 56.8, 31.7, 21.7; IR (neat) 2928, 1691, 1648, 1630, 1585, 1489, 1273, 1158, 1099 cm⁻¹; mass spectrum (ESI) *m/z* 577.1704 [C₃₁H₂₉O₁₁ (M+1) requires 577.1704].

2-((2-((*tert*-Butyldimethylsilyl)oxy)-3,6-dimethoxyphenyl)(hydroxymethyl)-11-methoxy-7,12-bis(methoxymethoxy)-9-methyl-8,9-dihydro-1*H*-naphtho[2,1-*g*]isochromene-1,4(11*H*)-dione (61). A mixture of **57** (174 mg, 0.250 mmol), BaCO₃ (148.3 mg, 0.751 mmol), dry MeOH (30.4 μL, 0.751 mmol), and DDQ (170.5 mg, 0.751 mmol) in CH₂Cl₂ (5 mL) was stirred at room temperature for 18 h. Saturated NaHCO₃ (20 mL) was added, and the reaction mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/Hexane (1: 2) to give 154 mg (85%) of **61** as a red oil; ¹H NMR (600 MHz, CDCl₃, mixture of diastereomers) δ 8.25 (d, *J* = 8.8 Hz, 0.5 H), 8.22 (d, *J* = 8.8, 0.5 H), 8.00 (d, *J* = 8.8 Hz, 0.5 H), 7.997 (d, *J* = 8.7 Hz, 0.5 H), 6.77 (d, *J* = 9.0 Hz, 0.5 H), 6.76 (d, *J* = 9.0 Hz, 0.5 H), 6.59 (dd, *J* = 10.2, 1.8 Hz, 0.5 H), 6.58 (dd, *J* = 10.6, 2.0 Hz, 0.5 H), 6.464 (d, *J* = 9.0 Hz, 0.5 H), 6.462 (d, *J* = 9.0 Hz, 0.5 H), 6.31 (d, *J* = 1.8 Hz, 0.5 H), 6.28 (d, *J* = 1.9 Hz, 0.5 H), 5.95 (s, 0.5 H), 5.92 (s, 0.5 H), 5.08-5.03 (comp, 2.5 H), 4.91 (d, *J* = 5.9 Hz, 0.5 H), 4.76 (d, *J* = 6.3 Hz, 0.5 H), 4.73 (d, *J* = 5.9 Hz, 0.5 H), 4.38-4.32 (m, 1 H), 4.29 (d, *J* = 10.2 Hz, 0.5 H), 4.15 (d, *J* = 10.6 Hz, 0.5 H), 3.75 (s, 3 H), 3.73 (s, 1.5 H), 3.71 (s, 1.5 H), 3.63 (s, 1.5 H), 3.62 (s, 1.5 H), 3.56 (s, 1.5 H), 3.52 (s, 1.5 H), 3.28 (s, 1.5 H), 3.17-3.09 (comp, 2.5 H), 2.69-2.58 (m, 1 H), 1.411 (d, *J* = 6.2 Hz, 1.5 H), 1.408 (d, *J* = 6.2 Hz, 1.5 H), 0.924 (s, 4.5 H), 0.919 (s, 4.5 H), 0.22 (s, 1.5 H), 0.19 (s, 1.5 H), 0.154 (s, 1.5 H), 0.145 (s, 1.5 H). ¹³C NMR (150 MHz, CDCl₃) δ 186.8, 186.3, 185.13, 185.08, 155.1, 154.5, 152.5, 152.4, 150.2, 149.9, 147.3, 147.2, 145.05, 144.98, 143.69, 143.66, 136.4, 135.6, 132.0, 131.98, 131.82, 131.78, 129.5, 129.4, 129.1, 129.0, 128.3, 128.0, 127.2, 126.6, 123.5, 122.5, 121.49, 121.48, 119.0, 118.6, 111.0, 103.12, 103.05, 100.8, 100.38, 100.35, 100.2, 95.52, 95.47, 65.3, 65.2, 61.6, 61.4, 57.79, 57.76, 57.7, 57.4, 55.7, 55.6, 55.23, 55.17, 54.9, 54.8, 31.0, 30.9, 26.02, 25.99, 21.5, 21.4, 18.9, 18.8, -3.7, -3.94, -3.95, -3.98. IR 3519, 2933, 2857, 1661, 1600, 1489, 1466, 1443, 1361, 1337, 1303, 1256, 1228, 1159, 1104, 1052, 1003 cm⁻¹. Mass spectrum (ESI) *m/z* 747.2807 [C₃₈H₄₈O₁₂NaSi (M+Na)⁺ requires 747.2813].

2-(2-((*tert*-Butyldimethylsilyl)oxy)-3,6-dimethoxybenzoyl)-11-methoxy-7,12-bis(methoxymethoxy)-9-methyl-8,9-dihydro-1*H*-naphtho[2,1-*g*]isochromene-1,4(11*H*)-dione (64). A solution of **61** (58.0 mg, 0.080 mmol) and IBX (45.0 mg, 0.161 mmol) in DMSO (4.0 mL) was stirred at room temperature for 5 h. The reaction mixture was diluted with Et₂O (40 mL) and then washed with saturated NaHCO₃ (10 mL) and brine (3 x 20 mL). The organic layer was dried

(Na₂SO₄), filtered, and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/hexane (1: 2) to give 41 mg (70%) of **64** as a red oil; ¹H NMR (600 MHz, CDCl₃) δ 8.26 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 6.86–6.84 (comp, 2 H), 6.45 (d, *J* = 8.8 Hz, 1 H), 5.97 (s, 1 H), 5.08 (d, *J* = 5.9 Hz, 1 H), 5.06 (d, *J* = 5.9 Hz, 1 H), 5.05 (s, *J* = 5.9 Hz, 1 H), 4.83 (d, *J* = 5.9 Hz, 1 H), 4.38–4.32 (m, 1 H), 3.77 (s, 3 H), 3.64 (comp, 6 H), 3.54 (s, 3 H), 3.39 (s, 3 H), 3.15 (dd, *J* = 17.6, 3.5 Hz, 1 H), 2.62 (dd, *J* = 17.6, 11.7 Hz, 1 H), 1.41 (d, *J* = 6.5 Hz, 3 H), 0.82 (s, 9 H), 0.14 (s, 6 H). ¹³C NMR (150 MHz, CDCl₃) δ 191.0, 186.2, 183.8, 151.7, 150.6, 147.3, 145.4, 144.8, 143.6, 135.9, 135.7, 132.2, 131.7, 129.7, 128.4, 127.1, 123.3, 121.2, 120.6, 113.3, 103.3, 101.2, 100.4, 95.4, 61.4, 57.8, 57.6, 56.1, 55.4, 54.8, 31.0, 25.8, 21.5, 18.7, -3.96, -4.01. IR 2933, 2857, 1699, 1663, 1599, 1485, 1441, 1361, 1335, 1256, 1206, 1159, 1010, 1051, 1014 cm⁻¹. Mass spectrum (ESI) *m/z* 745.2654 [C₃₈H₄₆O₁₂NaSi (M+Na)⁺ requires 745.2651].

4,7,11'-Trimethoxy-7',12'-bis(methoxymethoxy)-9'-methyl-8',9'-dihydro-3H-spiro[benzofuran-2,2'-naphtho[2,1-g]isochromene]-1',3,4'(3'H,11'H)-trione (65). A solution of **64** (58.4 mg, 0.081 mmol) and Et₃N·3HF (45.6 mg, 46.0 μL, 0.283 mmol) in CH₃CN (4.0 mL) was stirred at room temperature for 20 min. EtOAc (40 mL) was added, and the solution was washed with brine (3 x 10 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/Hexane (1:1) to give 43 mg (87%) of **65** as a yellow oil; ¹H NMR (600 MHz, CDCl₃, mixture of diastereomers) δ 8.31 (d, *J* = 9.0 Hz, 0.52 H), 8.29 (d, *J* = 9.0 Hz, 0.48 H), 8.10 (d, *J* = 8.8 Hz, 0.52 H), 8.07 (d, *J* = 9.0 Hz, 0.48 H), 7.12 (d, *J* = 8.8 Hz, 0.48 H), 7.11 (d, *J* = 8.8 Hz, 0.52 H), 6.39 (d, *J* = 8.8 Hz, 0.52 H), 6.38 (d, *J* = 8.8 Hz, 0.48 H), 5.82 (s, 0.52 H), 5.79 (s, 0.48 H), 5.08–5.03 (comp, 2 H), 4.74–4.73 (comp, 1 H), 4.49 (d, *J* = 5.7, 0.48 H), 4.40 (d, *J* = 5.1 Hz, 0.52 H), 4.34–4.25 (m, 1 H), 3.93 (s, 1.6 H), 3.90 (s, 1.4 H), 3.82 (s, 1.4 H), 3.81 (s, 1.6 H), 3.622 (s, 1.4 H), 3.616 (s, 1.6 H), 3.55–3.40 (comp, 5 H), 3.14 (dd, *J* = 17.2, 3.4 Hz, 0.52 H), 3.09 (dd, *J* = 17.3, 3.7 Hz, 0.48 H), 3.01 (s, 1.4 H), 2.89 (s, 1.6 H), 2.66 (dd, *J* = 17.3, 11.2 Hz, 0.48 H), 2.56 (dd, *J* = 17.2, 11.4 Hz, 0.52 H), 1.38 (d, *J* = 6.3 Hz, 1.6 H), 1.37 (d, *J* = 6.3 Hz, 1.4 H). ¹³C NMR (150 MHz, CDCl₃) δ 191.39, 191.37, 190.6, 190.3, 187.55, 187.49, 161.5, 160.6, 152.0, 151.8, 149.4, 149.1, 147.44, 147.39, 140.0, 139.9, 136.6, 135.9, 135.4, 135.3, 132.13, 132.06, 129.7, 129.4, 128.8, 128.4, 127.8, 127.7, 123.4, 123.3, 122.31, 122.27, 122.2, 122.1, 110.3, 109.9, 103.4, 103.3, 101.5, 100.40, 100.38, 95.35, 95.27, 93.20, 93.18, 61.5, 61.3, 57.81, 57.78, 57.1, 57.0, 56.69, 56.67, 56.2, 56.1, 54.6, 54.5, 48.3, 46.8, 30.9, 30.8, 21.40, 21.37. IR 2933, 2831, 1708, 1600, 1515, 1441, 1359, 1340, 1273, 1208, 1162, 1127, 1045 cm⁻¹. Mass spectrum (ESI) *m/z* 631.1787 [C₃₂H₃₂O₁₂Na (M+Na)⁺ requires 631.1786].

11'-Hydroxy-4,7-dimethoxy-7',12'-bis(methoxymethoxy)-9'-methyl-8',9'-dihydro-3H-spiro[benzofuran-2,2'-naphtho[2,1-g]isochromene]-

1',3,4'(3'H,11'H)-trione. A solution of **65** (24.0 mg, 0.039 mmol) and *p*-TsOH (4.5 mg, 0.024 mmol) in a mixture of acetone (4.0 mL) and H₂O (0.8 mL) was stirred at room temperature for 8 h. Et₂O (40 mL) was added, and the solution was washed with H₂O (3 x 15 mL) and brine (15 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with EtOAc/Hexane (2:1) to give 2.0 mg (8%) of recovered **65** and 21.0 mg (90%) of 11'-hydroxy-4,7-dimethoxy-7',12'-bis(methoxymethoxy)-9'-methyl-8',9'-dihydro-3H-spiro[benzofuran-2,2'-naphtho[2,1-g]isochromene]-1',3,4'(3'H,11'H)-trione as an amorphous yellow solid; ¹H NMR (600 MHz, CDCl₃, mixture of diastereomers) δ 8.34 (d, *J* = 8.8 Hz, 0.52 H), 8.32 (d, *J* = 8.8 Hz, 0.48 H), 8.09 (d, *J* = 8.8 Hz, 0.52 H), 8.06 (d, *J* = 9.0 Hz, 0.48 H), 7.14 (d, *J* = 8.8 Hz, 0.52 H), 7.13 (d, *J* = 8.8 Hz, 0.48 H), 6.408 (d, *J* = 8.8 Hz, 0.52 H), 6.406 (d, *J* = 8.8 Hz, 0.48 H), 6.33 (d, *J* = 1.8 Hz, 0.52 H), 6.25 (s, 0.48 H), 5.09–5.04 (comp, 2 H), 4.67 (d, *J* = 6.2, 0.48 H), 4.57 (d, *J* = 5.6 Hz, 0.52 H), 4.52–4.43 (comp, 2 H), 4.17 (d, *J* = 1.8 Hz, 0.52 H), 3.92 (s, 1.6 H), 3.90 (s, 1.4 H), 3.823 (s, 1.4 H), 3.821 (s, 1.6 H), 3.63 (s, 1.4 H), 3.62 (s, 1.6 H), 3.58–3.47 (comp, 2 H), 3.17–3.05 (comp, 4 H), 2.63 (dd, *J* = 17.3, 11.4 Hz, 0.48 H), 2.55 (dd, *J* = 17.2, 11.4 Hz, 0.52 H), 1.37 (d, *J* = 6.2 Hz, 3 H). ¹³C NMR (150 MHz, CDCl₃) δ 191.6, 191.2, 190.4, 190.2, 187.5, 186.7, 161.23, 161.22, 151.84, 151.82, 149.1, 148.8, 147.83, 147.78, 140.0, 139.9, 136.7, 136.0, 134.9, 134.3, 132.1, 132.0, 130.8, 130.5, 129.6, 129.3, 128.5, 128.2, 122.9, 122.6, 122.4, 122.3, 122.2, 109.9, 109.8, 103.53, 103.49, 100.5, 100.45, 100.39, 100.1, 93.5, 93.2, 88.8, 88.3, 62.2, 62.0, 57.84, 57.81, 57.05, 57.00, 56.98, 56.95, 56.1, 47.2, 46.5, 31.1, 30.8, 21.44, 21.40. IR 3422, 2934, 1703, 1599, 1515, 1441, 1345, 1273, 1206, 1159, 1076, 1041 cm⁻¹. Mass spectrum (ESI) *m/z* 617.1636 [C₃₁H₃₀O₁₂Na (M+Na)⁺ requires 617.1630].

4,7-Dimethoxy-7',12'-bis(methoxymethoxy)-9'-methyl-8',9'-dihydro-3H-spiro[benzofuran-2,2'-naphtho[2,1-g]isochromene]-1',3,4',11'(3'H)-tetraone (67). A suspension of 11'-hydroxy-4,7-dimethoxy-7',12'-bis(methoxymethoxy)-9'-methyl-8',9'-dihydro-3H-spiro[benzofuran-2,2'-naphtho[2,1-g]isochromene]-1',3,4'(3'H,11'H)-trione (20.2 mg, 0.034 mmol), pyridinium dichromate (PDC) (38.3 mg, 0.102 mmol), and 3 Å molecular sieves (34 mg) in CH₂Cl₂ (3.4 mL) was stirred at room temperature for 3 h. The mixture was then filtered through a thin plug of silica gel, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (2: 1) to give 18.1 mg (90%) of **67** as an amorphous yellow solid; ¹H NMR (600 MHz, CDCl₃, mixture of diastereomers) δ 8.303 (d, *J* = 8.8 Hz, 0.46 H), 8.302 (d, *J* = 8.8 Hz, 0.54 H), 8.20 (d, *J* = 8.7 Hz, 0.54 H), 8.19 (d, *J* = 8.8 Hz, 0.46 H), 7.15 (d, *J* = 9.0 Hz, 0.54 H), 7.14 (d, *J* = 8.8 Hz, 0.46 H), 6.412 (d, *J* = 8.8 Hz, 0.54 H), 6.411 (d, *J* = 8.8 Hz, 0.46 H), 5.11–5.05 (comp, 2.46 H), 4.81 (d, *J* = 5.3, 0.54 H), 4.71 (d, *J* = 5.3 Hz, 0.54 H), 4.70 (d, *J* = 4.6 Hz, 0.46 H), 4.55–4.48 (m, 1 H), 3.94 (s, 1.6 H), 3.93 (s, 1.4 H), 3.824 (s, 1.6 H), 3.823 (s, 1.4 H), 3.61 (s, 1.4 H), 3.60 (s, 1.6 H), 3.56–3.46 (comp, 2 H), 3.38 (dd, *J*

= 16.4, 2.3 Hz, 0.54 H), 3.31 (dd, J = 16.4, 2.6 Hz, 0.46 H), 2.98 (s, 1.4 H), 2.97 (s, 1.6 H), 2.89 (dd, J = 16.4, 10.6 Hz, 0.46 H), 2.80 (dd, J = 16.4, 11.4 Hz, 0.54 H), 1.52 (d, J = 6.3 Hz, 1.6 H), 1.48 (d, J = 6.5 Hz, 1.4 H). ^{13}C NMR (150 MHz, CDCl_3) δ 191.3, 191.1, 190.03, 190.0, 188.7, 187.9, 162.6, 162.2, 161.4, 160.8, 153.5, 152.9, 152.0, 151.9, 145.5, 144.9, 140.1, 139.9, 137.4, 136.9, 136.45, 136.38, 134.9, 134.6, 131.1, 130.9, 127.2, 127.0, 125.3, 124.8, 124.7, 124.6, 122.7, 122.3, 117.4, 116.5, 110.1, 109.8, 103.50, 103.45, 100.8, 100.7, 100.5, 100.1, 93.3, 93.0, 74.4, 74.1, 58.0, 57.98, 57.4, 57.14, 57.08, 56.14, 56.07, 47.9, 47.3, 31.6, 31.5, 20.6, 20.5. IR 2926, 2853, 1711, 1600, 1515, 1444, 1352, 1274, 1210, 1189, 1159, 1134, 1077, 1044. Mass spectrum (ESI) m/z 615.1478 [$\text{C}_{31}\text{H}_{28}\text{O}_{12}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ requires 615.1473].

16-Hydroxy-10,13-dimethoxy-5-(methoxymethoxy)-3-methyl-3,4-dihydropyrano[4',3':6,7]naphtho[1,2-b]xanthene-1,8,14,15-tetraone (69). A solution of **67** (10.0 mg, 0.017 mmol) in CH_3CN (6 mL) was heated in a microwave oven (sealed tube) at 180 °C (300 watts) for 25 min. The reaction mixture was then stirred under O_2 at room temperature overnight and then again heated in a sealed tube at 180 °C in a microwave oven for 15 min. The solution was concentrated under reduced pressure to give a red-colored residue. The residue was precipitated from a mixture of CHCl_3 /Hexane (0.1 mL/0.9 mL) 5-times to give 7.3 mg (79%) of **69** as a red powder. ^1H NMR (600 MHz, CDCl_3): δ 12.62 (br s, 1H), 8.28 (d, J = 8.6 Hz, 1 H), 8.26 (d, J = 8.6 Hz, 1 H), 7.21 (d, J = 9.2 Hz, 1 H), 6.82 (d, J = 8.9 Hz, 1 H), 5.04 (d, J = 6.3 Hz, 1 H), 5.03 (d, J = 6.3 Hz, 1 H), 4.74-4.69 (m, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.62 (s, 3 H), 3.40 (dd, J = 16.4, 3.0 Hz, 1 H), 2.92 (dd, J = 16.4, 11.2 Hz, 1 H), 1.58 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (150 MHz, CDCl_3): δ 181.1, 178.3, 172.8, 170.1, 159.8, 153.5, 152.5, 146.5, 143.0, 141.4, 138.5, 136.7, 129.82, 129.78, 126.8, 124.8, 122.1, 119.9, 117.5, 117.1, 107.8, 104.6, 100.8, 75.6, 57.9, 57.0, 56.9, 30.3, 20.9. IR 1698, 1679, 1647, 1614, 1586, 1491, 1441, 1409, 1323, 1277, 1210, 1161, 1132, 1102, 1073, 1017 cm^{-1} . Mass spectrum (ESI) m/z 569.1050 [$\text{C}_{29}\text{H}_{22}\text{O}_{11}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ requires 569.1054].

5,16-Dihydroxy-10,13-dimethoxy-3-methyl-3,4-dihydropyrano[4',3':6,7]naphtho[1,2-b]xanthene-1,8,14,15-tetraone and 8,15-dihydroxy-10,13-dimethoxy-3-methyl-3,4-dihydropyrano[4',3':6,7]naphtho[1,2-b]xanthene-1,5,14,16-tetraone (70a,b). A mixture of **69** (4.0 mg, 0.0073 mmol) and freshly distilled TMSBr (9.7 μL , 11.2 mg, 0.073 mmol) in CH_2Cl_2 (1.2 mL) containing 4 Å molecular sieves (7.3 mg) was stirred at room temperature for 16 h, whereupon another portion of TMSBr (4.8 μL , 5.5 mg, 0.036 mmol) was added and stirring continued for another 5 h. CH_2Cl_2 (15 mL) was added, and the molecular sieves were removed by filtration. The filtrate was washed with H_2O (3 x 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a red-colored residue. The residue was then dissolved in CHCl_3 (0.25 mL) and precipitated with hexane (0.75 mL), and this process was repeated three-

times. A final reprecipitation from CHCl_3 (0.5 mL) and hexane (0.5 mL) gave 2.0 mg (54%) of an mixture (~2:1) of two isomeric compounds **70a,b** as an amorphous red solid. ^1H NMR (600 MHz, CD_3CN) δ 8.44 (d, J = 8.8 Hz, 0.67 H, major), 8.20 (d, J = 9.3 Hz, 0.33 H, minor), 8.17 (d, J = 8.8 Hz, 0.67 H, major), 8.12 (d, J = 9.3 Hz, 0.33 H, minor), 7.41 (d, J = 9.0 Hz, 0.33 H, minor), 7.38 (d, J = 9.1 Hz, 0.67 H, major), 6.96 (d, J = 9.1 Hz, 0.67 H, major), 6.87 (d, J = 9.1 Hz, 0.33 H, minor), 4.84-4.77 (comp, 1 H), 3.99 (s, 1 H, minor), 3.98 (s, 2 H, major), 3.93 (s, 1 H, minor), 3.89 (s, 2 H, major), 3.35-3.27 (comp, 1 H), 2.90-2.82 (comp, 1 H), 1.56 (d, J = 6.3 Hz, 1 H, minor), 1.55 (d, J = 6.3 Hz, 2 H, major). Mass spectrum: major isomer (ESI) m/z 525.0792 [$\text{C}_{27}\text{H}_{18}\text{O}_{10}\text{Na}^+$ ($\text{M}+\text{Na}$) $^+$ requires 525.0792]; (ESI neg) m/z 501.0804 [$\text{C}_{27}\text{H}_{17}\text{O}_{10}^-$ ($\text{M}-\text{H}$) $^-$ requires 501.0827]; Mass spectrum: minor isomer (ESI) m/z 525.0790 [$\text{C}_{27}\text{H}_{18}\text{O}_{10}\text{Na}^+$ ($\text{M}+\text{Na}$) $^+$ requires 525.0792]; (ESI neg) m/z 501.0812 [$\text{C}_{27}\text{H}_{17}\text{O}_{10}^-$ ($\text{M}-\text{H}$) $^-$ requires 501.0827].

Acknowledgments

We thank the National Institutes of Health (GM31077) and the Robert A. Welch Foundation (F-0652) for support. DK thanks the National Science Foundation for a graduate research fellowship, JY thanks the Cancer Prevention Research Institute of Texas for support as postdoctoral trainee, and DM thanks the NIH for a postdoctoral fellowship. We thank Dr. Richard Pederson (Materia, Inc.) for catalyst support, Mr. Shawn Blumberg (The University of Texas at Austin) for technical assistance, and Dr. Ian Riddington (The University of Texas at Austin) for helpful discussions of mass spec data. We would also like thank Vincent Lynch (The University of Texas at Austin) for obtaining X-ray data for compound **41**.

References

- (a) Malet-Cascon, L.; Romero, F.; Espliego-Vazquez, F.; Gravalos, D.; Fernandez-Puentes, J. L. *J. Antibiot.* **2003**, *56*, 219-225. (b) Rodriguez, J. C.; Puentes, J. L. F.; Baz, J. P.; Canedo, L. M. *J. Antibiot.* **2003**, *56*, 318-321.
- (a) Carter, G. T.; Nietzsche, J. A.; Williams, D. R.; Borders, D. B. *J. Antibiot.* **1990**, *43*, 504-512. (b) Hopp, D. C.; Milanowski, D. J.; Rhea, J.; Jacobsen, D.; Rabenstein, J.; Smith, C.; Romari, K.; Clarke, M.; Francis, L.; Irigoyen, M.; Luche, M.; Carr, G. J.; Mocek, U. *J. Nat. Prod.* **2008**, *71*, 2032-2035.
- (a) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Org. Lett.* **2006**, *8*, 5267-5270. (b) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Chem. Eur. J.* **2007**, *13*, 1610-1690.
- (a) Nakagawa, A.; Iwai, Y.; Shimizu, H.; Omura, S. *J. Antibiot.* **1986**, *39*, 1636-1638. (b) Omura, S.; Nakagawa, A.; Kushida, K.; Shimizu, H.; Lukacs, G. *J. Antibiot.* **1987**, *40*, 301-308. (c) Tanka, H.; Kawakita, K.; Suzuki, H.; Nakagawa, P. S.; Omura, S. *J. Antibiot.* **1989**, *42*, 431-439.

- 5 For syntheses of cervinomycins, see: (a) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522-4524. (b) Rao, A. V. R.; Yadav, J. S.; Reddy, K. K.; Upender, V. *Tetrahedron Lett.* **1991**, *32*, 5199-5202. (c) Mehta, G.; Shah, S. R.; Venkateswarlu, Y. *Tetrahedron* **1994**, *50*, 11729-11742.
- 6 For syntheses of the kibdelones, see: (a) Sloman, D. L.; Bacon, J. W.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 9952-9955. (b) Butler, J. R.; Wang, C.; Bian, J.; Ready, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 9956-9959.
- 7 For syntheses of other natural polycyclic xanthenes, see: Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 3452-3465.
- 8 For a review, see: Winter, D. K.; Sloman, D. L.; Porco Jr., J. A. *Nat. Prod. Rep.* **2013**, *30*, 382-391.
- 9 For leading references to prepare 1,4-dioxygenated xanthenes: (a) Ellis, R. C.; Whalley, W. B.; Ball, K. *Chem. Commun.* **1967**, 803-804. (b) Stout, G. H.; Balkenhol, W. J. *Tetrahedron* **1969**, *25*, 1947-1960. (c) Jain, A. C.; Khanna, V. K.; Seshadri, T. R. *Indian J. Chem.* **1970**, *8*, 667-669. (d) Simoneau, B.; Brassard, P. *J. Chem. Soc., Perkin Trans. I* **1984**, 1507-1510. (e) Bekaert, A.; Andrieux, J.; Plat, M. *Tetrahedron Lett.* **1992**, *33*, 2805-2806. (f) Elix, J. A.; Gaul, K. L.; Jiang, H. *Aust. J. Chem.* **1993**, *46*, 95-110. (g) Sun, L.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *118*, 12473-12474. (h) Hauser, F. M.; Dorsch, W. A. *Org. Lett.* **2003**, *5*, 3753-3754. (i) Masuo, R.; Ohmori, K.; Hintermann, L.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3462-3465.
- 10 (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392-3393. (b) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975-989.
- 11 (a) Nichols, A. L.; Zhang, P.; Martin, S. F. *Org. Lett.* **2011**, *13*, 4696-4699. (b) Nichols, A. L.; Zhang, P.; Martin, S. F. *Tetrahedron* **2012**, *68*, 7591-7597.
- 12 Yang, J.; Kneuppel, D.; Cheng, B.; Mans, D. Martin, S. F. *Org. Lett.* **2015**, *17*, 114-117.
- 13 For a related transformation, see: (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672-1674. (b) Danheiser, R. L.; Brisbois, R. G.; James, J.; Kowalczyk, Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093-3100.
- 14 (a) Kneuppel, D.; Martin, S. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 2569-2571. (b) Kneuppel, D.; Martin, S. F. *Tetrahedron* **2011**, *67*, 9765-9770.
- 15 Serra, S.; Fuganti, C. *Synlett* **2003**, *13*, 2005-2008.
- 16 For related work: (a) Serra, S.; Fuganti, C. *Synlett* **2002**, *10*, 1661-1664. (b) Serra, S.; Fuganti, C. *Synlett* **2005**, *5*, 809-812.
- 17 Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896-6899.
- 18 Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760-3765.
- 19 Capecchi, T.; de Koning, C. B.; Michael, J. P. *J. Chem. Soc., Perkin Trans. I*, **2000**, 2681-2688.
- 20 See Experimental section for additional details on how this substrate was prepared.
- 21 Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871-4874.
- 22 (a) Leinweber, D.; Butenschoen, H. *Tetrahedron Lett.* **1997**, *38*, 6385-6386. (b) Leinweber, D.; Schnebel, M.; Wartchow, R.; Wey, H. G.; Butenschoen, H. *Eur. J. Org. Chem.* **2002**, 2385-2390.
- 23 Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A. *Org. Lett.* **2001**, *3*, 1649-1652.
- 24 Tian, Y.; Chen, C.-Y.; Yang, C.-C.; Young, A. C.; Jang, S.-H.; Chen, W.-C.; Jen, A. K.-Y. *Chem. Mater.* **2008**, *20*, 1977-1987.
- 25 Tisdale, E. J.; Kochman, D. A.; Theodorakis, E. A. *Tetrahedron Lett.* **2003**, *44*, 3281-3284.
- 26 Adapted from procedure to prepare enantiomerically pure (S)-**50**, see: Wagner, J. M.; McElhinny, C. J.; Lewin, A. H.; Carroll, F. I. *Tetrahedron: Asymmetry* **2003**, *14*, 2119-2125.
- 27 Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003**, *32*, 932-933.
- 28 For a related example, see: Sawant, R.; Waghmode, S. B. *Tetrahedron* **2009**, *65*, 1599-1602.
- 29 Fkyerat, A.; Dubin, G.-M.; Tabacchi, R. *Helv. Chim. Acta* **1999**, *82*, 1418-1422.
- 30 Smith, A. B., III; Basu, K. *J. Am. Chem. Soc.* **2009**, *131*, 2348-2358.
- 31 Kwon, H. K.; Kee, Y. E.; Lee, E. *Org. Lett.* **2008**, *10*, 2995-2996.
- 32 Salmond, W. G.; Barata, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057-2059.
- 33 Maier, M. W.; Ritschel, J. *ARKIVOC* **2008**, 314-329.
- 34 Xu, Y.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841-3844.
- 35 For use of molecular sieves to accelerate oxidation, see: Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561-562.
- 36 Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *24*, 2515-2518.
- 37 Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095-5106.