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Graphical Abstract

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Toward the Total Synthesis of Citreamicin η: Synthesis of the Pentacyclic Core and GAB-Ring Annelation Model Studies

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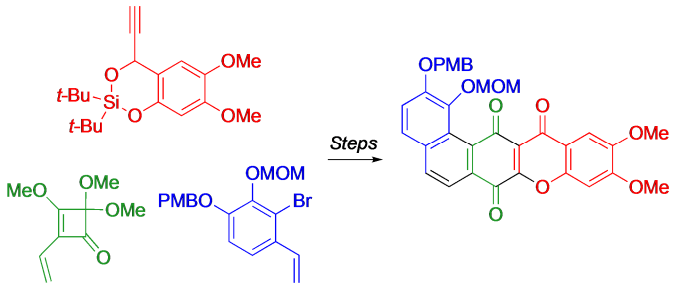

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Toward the Total Synthesis of Citreamicin: Synthesis of the Pentacyclic Core and GAB-Ring Annelation Model Studies

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ABSTRACT

A short 11-step synthesis of the pentacyclic core of the polycyclic xanthone antibiotic citreamicin η has been completed. Although the basic approach was inspired by our previous explorations of polycyclic xanthone chemistry, the present report features some new insights into the Moore rearrangement and offers some improvements to our original methodology that include additions of aryllithiums to squarate esters, additions of cerium acetylides to hindered ketones utilizing PDA as an internal indicator, and the use of cyclic di-*tert*-butylsilyl (DTBS) ethers to protect electron-rich benzyl alcohols toward ionization under acidic conditions. We also developed an improved protocol for selective *o*-bromination of phenols utilizing *N*-bromosuccinimide (NBS) and tetramethylguanidine (TMG) that promises to be generally useful. Finally, we developed a modular approach for the synthesis of isoquinolones and dihydro-5H-oxazolo[3,2-b]isoquinoline-2,5(3H)-diones that features a novel sequence of alkoxycarbonylation, acetone arylation, transamidation.

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1. Introduction

The first member of the citreamicin family of antibiotics,[1] which constitutes a novel subclass of polycyclic xanthone natural products, was isolated by Lechevalier in 1989 from a culture of *Micromonospora citrea* that was taken from lake Manyara in Tanzania.[1a] Shortly after this initial discovery, additional members of this family were isolated and characterized by Carter[1b] and others.[1c,d] The citreamicins generally display potent inhibitory activity against a broad spectrum of Gram-positive aerobic and anaerobic bacteria, but given the current problems of increasing antibiotic resistance, it is especially notable that the citreamicins are active against multidrug-resistant vancomycin-resistant *Enterococcus faecalis* (VRE) and *Staphylococcus aureus* (MDRSA).[1c] With a minimum inhibitory concentration (MIC) of 26 nM against several Gram-positive strains, citreamicin η (**1**) is one of the most potent members of this family (Figure 1).[1b] Coupled with their impressive antibiotic activity, several members of the citreamicin family exhibit cytotoxic activity against HeLa and Hep62 cells.[1e] The feature that differentiates the citreamicins from other polycyclic xanthones natural products such as cervinomycin A_2 (**2**),[2] IB-00208 (**3**),[3] kibdelone C (**4**),[4] kigamicin (**5**),[5] xantholipin (**6**),[6] and others,[7] is a dihydrooxazolo-[3,2-b]-isoquinolinone tricyclic subunit that comprises the GAB rings (Figure 1). In view of the potent biological activities of the citreamicin antibiotics, it is surprising that no member of this family has succumbed to synthesis. On the other hand, the total syntheses of representative cervinomycins[8] and kibdelones[9] have been reported, and we recently disclosed the synthesis of the aglycone of IB-00208 (**3**).[10] Synthetic efforts directed toward a number of other polycyclic xanthones have also been described.[11] We now disclose the details of our recent efforts to synthesize citreamicin η, including the preparation of the pentacyclic core as well as exploratory studies to annelate the G and A rings.[12]

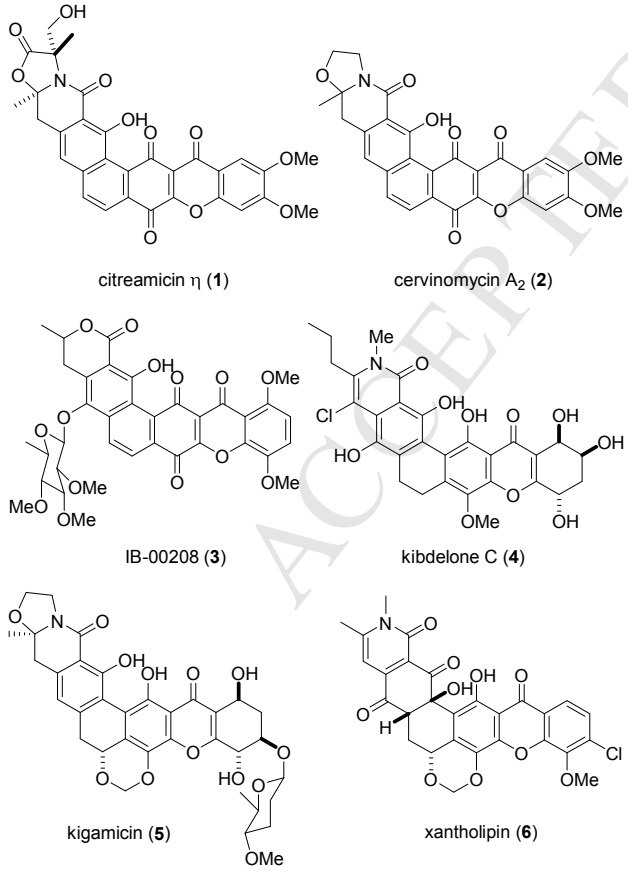
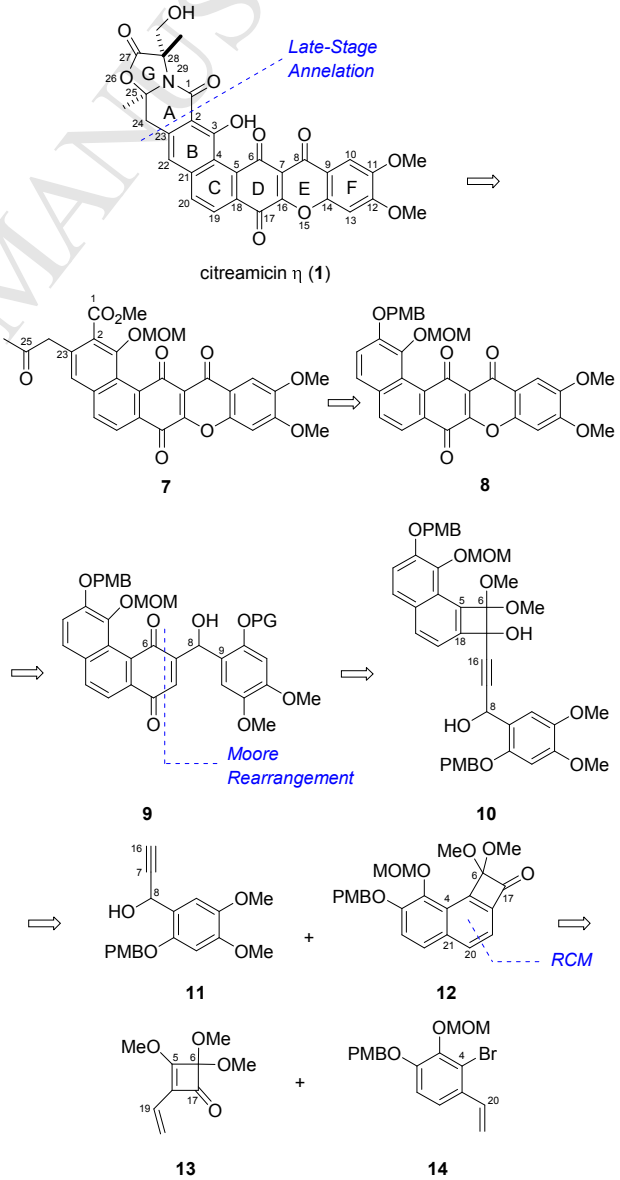


Figure 1. Polycyclic xanthone natural products.

2. Retrosynthetic analysis

Naturally-occurring polycyclic xanthones captured our attention several years ago because of their complex molecular architectures coupled with their potent biological activities. The unique challenges associated with the synthesis of the citreamicins appealed to us, so we initiated efforts toward the total synthesis of citreamicin η (**1**). Drawing upon our successful invention of a novel approach to 1,4-dioxygenated xanthones and its application to the synthesis of IB-00208 aglycone,[7,13] we initially formulated the plan for the synthesis of citreamicin η (**1**) that is outlined in Scheme 1. We envisioned final assembly of **1** by annelating the G and A rings onto the hexacyclic precursor **7** via a thermodynamically-controlled, diastereoselective condensation of **7** with (*S*)-α-methylserine.[14] Formation of **7** from **8** requires a cross-coupling to

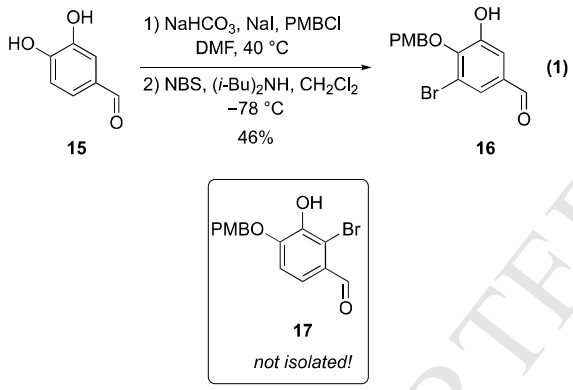


Scheme 1. Retrosynthetic analysis.

introduce the ester and the acetonyl groups. Compound **8** might then be accessible from the quinone **9** via sequential oxidation and cyclization, whereas generation of **9** features a variant of the Moore rearrangement of **10**,[15] which would be formed by the union of an acetylide anion derived from **11** and the naphthocyclobutenone **12**. There are no general methods for the syntheses of substituted naphthocyclobutenones like **12**, but we reasoned that **12** might be prepared by coupling of bromostyrene **14** with the vinyl squarate **13** followed by a ring closing metathesis (RCM) to create the arene ring.[16]

3. Synthesis of BCD ring precursor

In our first approach to the napthocyclobutenone fragment **12**, which was required for the acetylide stitching step, the C4 phenolic moiety of 3,4-dihydroxybenzaldehyde (**15**) was selectively protected as its *p*-methoxybenzyl (PMB) ether (Equation 1).[17] To our surprise, however, the amine-mediated, regioselective bromination of the intermediate phenol did not proceed at the 2-position to give **17** as expected,[18] but rather at C5 to furnish **16** exclusively (Equation 1). To our knowledge, this is the first example of selective bromination of an isovanillin derivative at the 5-position.[19] Conversely, the corresponding benzyl ether analog underwent regioselective bromination to give a C2-bromo derivative in 55% yield. Apparently the PMB-protecting group influences the regiochemistry in this bromination, but the origin of this effect remains unknown.



Our overall plan suggested that the *O*-PMB protecting group would likely be better than a benzyl group. Hence, we had to solve the problem and develop a procedure that enabled regioselective bromination *ortho* to the phenolic hydroxyl group in **18** at the 2-position. Accordingly, we explored other conditions for the amine-mediated bromination. We hypothesized that more basic amines would favor the desired pathway to form **17**, so we selected four amines with varying basicity to evaluate their effect on the regioselectivity in the bromination of **15** (Table 1).[20] Consistent with expectations, we found that the selectivity of *ortho*-bromination of the phenol increased with basicity of the amine, with tetramethylguanidine (TMG) providing **17** with >20:1 selectivity (Table 1, entry 4) using a solvent mixture (2:3) of toluene and CH_2Cl_2; use of toluene as a cosolvent proved critical to this success.

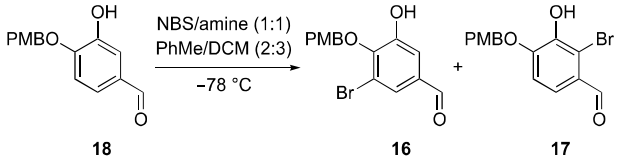
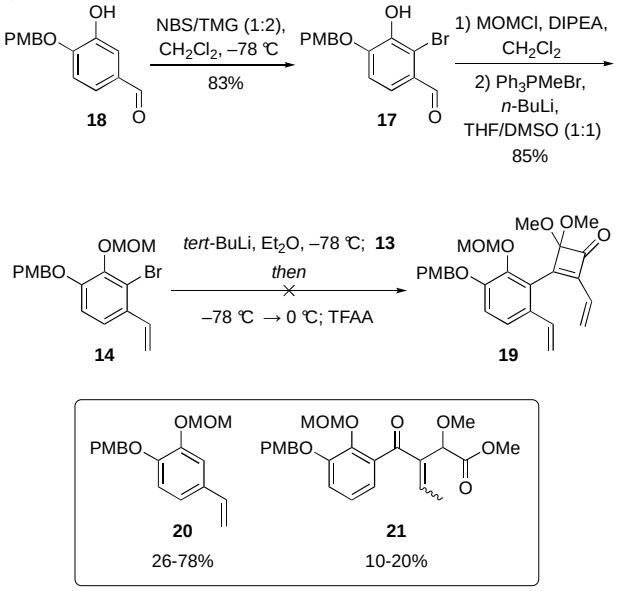


Table 1. Effect of amines on regioselectivity of bromination of **18**.

Entry	Amine	Ratio of 16:17[a]
1	*tert-BuNH$_2$*[18a]	*1:3.75*
2	*(i-Bu)$_2$NH*[18b]	*1:11.5*
3	*DBU*	*1:13.5*
4	*TMG*	*1:>20*

a) Ratios determined by NMR.

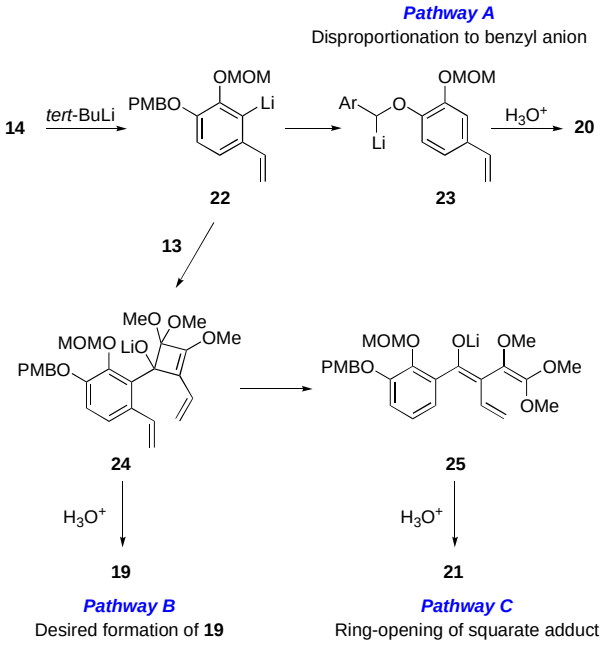
Although the conditions identified in Table 1 for brominating **18** to give **17** worked well on a small scale, it was necessary to change the stoichiometry of NBS to TMG from 1:1 to 1:2 in order to selectively produce **17** on a multigram scale because increased quantities of **16** were observed when a 1:1 ratio was employed (Scheme 2). Protection of the phenolic hydroxy group in **18** as a methoxymethyl (MOM) ether followed by a Wittig olefination in a mixture (1:1) of THF and DMSO provided bromostyrene **14** in 85% overall yield. Unfortunately, initial attempts to couple the aryllithium reagent derived from **14** by metal-halogen exchange with the vinyl squarate **13** led to the isolation of the debrominated product **20**, and an unexpected side-product that was tentatively identified as **21** (Scheme 2).



Scheme 2. Synthesis of bromostyrene **14** and attempted coupling with squarate **13**.

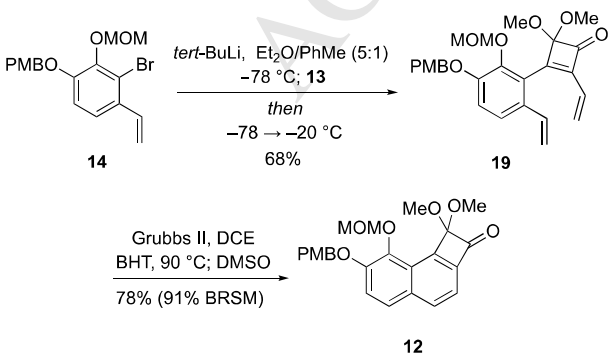
Debrominated starting material **20** formed even in the presence of NaH, suggesting that the something in the reaction mixture, not an adventitious protic impurity such as water, served as the proton source. Some exploratory studies implicated the benzylic protons on the PMB group as a probable proton source. We surmise that the aryllithium **22** is transformed by proton transfer into the benzyl

anion **23**, which forms **20** upon aqueous workup (Scheme 3, Pathway A). Alternatively, the reaction of vinyl squarate **13** with aryllithium **22** produces the adduct **24**, which is protonated to furnish the desired **19** (Scheme 3, Pathway B). The side-product **21** likely originates from protonation of dienolate **25**, which could be generated via an oxy-anion accelerated electrocyclic ring opening of **24** (Scheme 3, Pathway C).[21]



Scheme 3. Putative pathways forming side-products.

We postulated that the presence of non-polar co-solvents could favor more aggregated forms of aryllithium **22** that might be less prone to suffer proton transfers.[22] After some experimentation, we discovered that performing the metal-halogen exchange in a mixture (5:1) of Et_2O and toluene at –78 ºC, followed by addition of **13** and warming the reaction mixture to 0 ºC led to the isolation of **19** in 40% yield while suppressing the formation of **20**. However, the ring-opened side-product **21** was still isolated in yields up to 20%. We reasoned that the oxy-anionic electrocyclic ring-opening reaction of **24** would be suppressed at lower temperatures and eventually found that raising the bath temperature to –20 ºC after the addition of **13** enabled us to isolate **19** in 68% yield with only traces of **21** being observed. Heating **19** in degassed dichloroethane in the presence of Grubbs II catalyst led ring closing metathesis and the formation of the naphthocyclobutenone **12** in 78% (91% BRSM) yield (Scheme 4).[23,24]

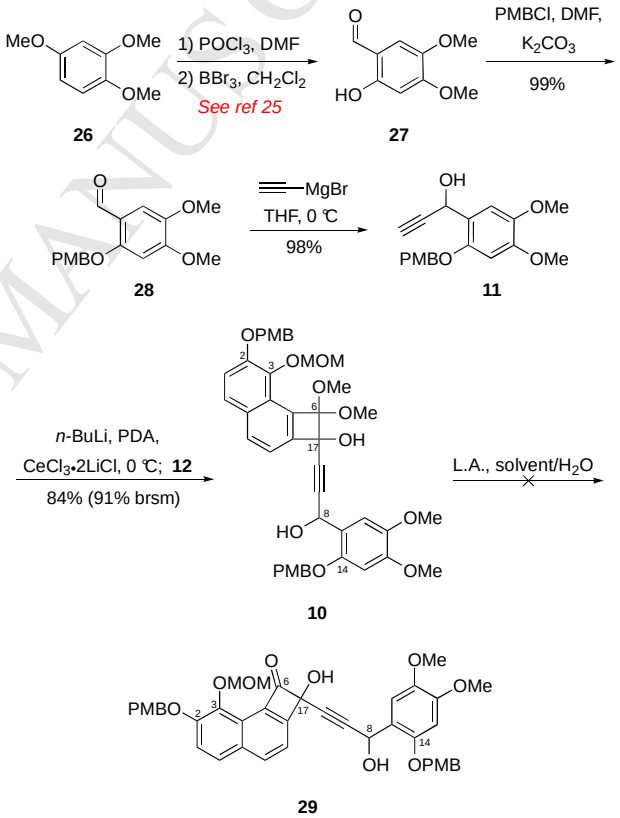


Scheme 4. Completion of the naphthocyclobutenone fragment.

4. Setting the stage for the Moore rearrangement

4.1. First generation approach to precursor of Moore rearrangement

With the naphthocyclobutenone fragment **12** in hand, we turned to the synthesis of a suitable substrate for the Moore rearrangement. In our first approach, the salicylaldehyde **27**, which was readily prepared from 1,2,4-trimethoxybenzene (**26**) by a known procedure,[25] was *O*-protected with a PMB moiety to give **28** in nearly quantitative yield (Scheme 5). Addition of ethynylmagnesium bromide to **28** then furnished the F-ring fragment **11**. Using conditions we previously developed during our synthesis of IB-00208 aglycone,[10] **11** was treated with tetramethylpiperidinomagnesium bromide (TMPMgBr) to form an intermediate magnesium acetylide that was coupled with **12** to provide **10**, albeit in only 40% yield. We screened a number of other bases and solvents to improve the yield of this reaction, but these efforts were to no avail.



Scheme 5. Synthesis of F-ring fragment, acetylide coupling and attempted hydrolysis.

Organocerium reagents may add more efficiently to ketones than Grignard reagents.[26] However, initial attempts to generate the cerium reagent from **11** were complicated by adventitious proton sources in the $CeCl_3$•2LiCl solution.[27] Because we wanted to combine **11** and **12** in 1:1 stoichiometry, a suitable indicator was needed so we could closely monitor formation of the cerium acetylide anion from **11**. Serendipitously, we had employed 4-(phenylazo)diphenylamine (PDA)[28] as an indicator to titrate the solutions of TMPMgBr used to deprotonate **11** (*vide supra*). We were impressed by the vivid endpoints, so we queried whether PDA might be useful as an internal indicator to monitor generation of the organocerium reagent from **11**. Gratifingly, we found that adding *n*-BuLi to a mixture of **11**, $CeCl_3$•2LiCl, and PDA produced a vivid

purple endpoint showing that complete deprotonation of the benzylic alcohol moiety of **11** had occurred. Addition of another equivalent of *n*-BuLi ensured quantitative formation of the acetylide anion, whereupon **12** was added to deliver **10** in 84% yield. Subsequent to these experiments, we demonstrated that PDA is generally an excellent indicator for titrating a variety bases, Lewis acids and reducing agents.[29]

With compound **10** in hand, it remained to selectively hydrolyze the dimethyl ketal moiety to furnish **29**, the requisite substrate for the Moore rearrangement. However, all attempts to convert **10** into **29** using a variety of Lewis and Brønsted acid catalysts invariably led to complex mixtures of compounds. This finding was surprising because we had previously hydrolyzed a number of related substrates without difficulty.[10,13] We eventually found that **11** was unstable to the acidic conditions, whereas **12** could be recovered unscathed, suggesting that the benzyl alcohol moiety at C8 in **10** might be the offending functionality. This discovery signaled that we needed a synthon for the F-ring subunit having a benzyl alcohol that would be less prone to solvolysis under acidic conditions.

4.2. Second generation approach to precursor of Moore rearrangement

A plausible explanation for the observed instability of **10** is that the benzylic C–OH bond at C8 in the putatively preferred conformation of **10** is aligned with the π-system of the arene as shown in **10a** (Figure 2). We reasoned that constraining this C–O bond in approximately the plane of the aromatic ring might allow selective hydrolysis of the dimethyl ketal without concomitant solvolysis of the benzyl alcohol moiety. This goal might be achieved through the agency of a cyclic protecting group that incorporated both the benzylic hydroxyl group and the *ortho* oxygen atom.

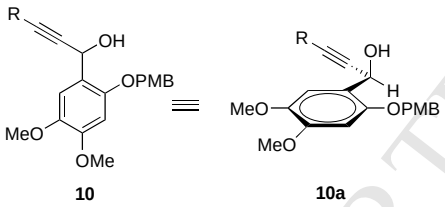
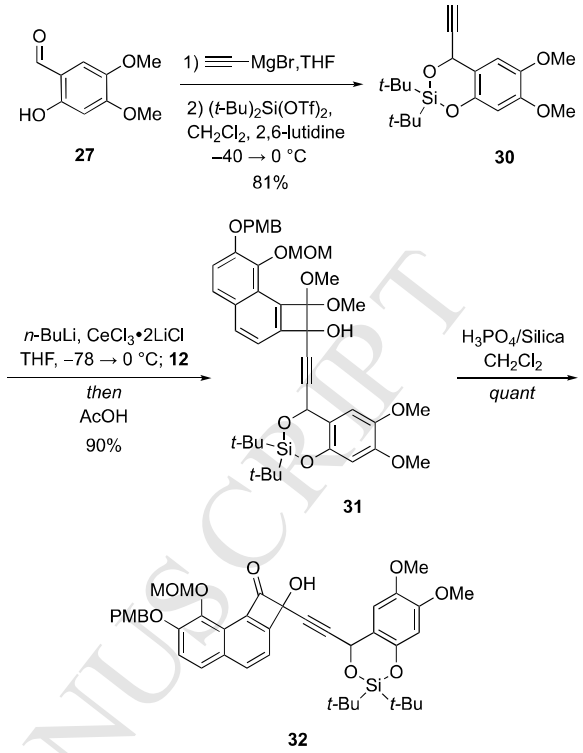


Figure 2. Putative origin of solvolytic instability of **10**.

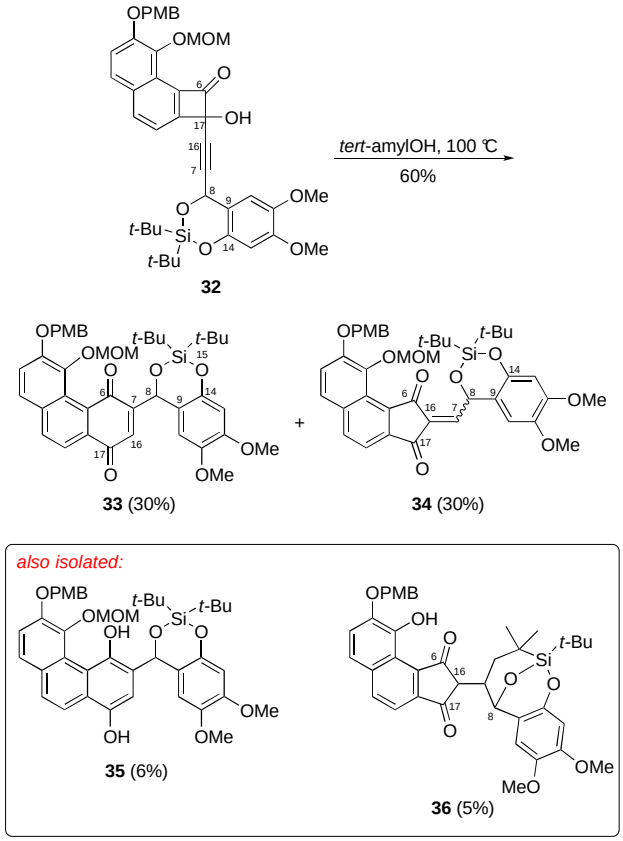
Based upon this hypothesis, we turned to the cyclic silylether protecting group in **30**, which was prepared in 82% yield by addition of ethynylmagnesium bromide to **27** and reaction of the unstable intermediate alcohol with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) DTBS(OTf)$_2$ in analogy with our previous work (Scheme 6).[13] Application of the acetylide coupling conditions developed previously furnished **31** in 90% yield on multigram scale. Gratifyingly, hydrolysis of **31** with H_3PO_4-doped hydrated silica gel provided **32** in virtually quantitative yield. The stage was now set for the pivotal Moore rearrangement.



Scheme 6. Synthesis of **32**

5. Moore rearrangement and synthesis of the pentacyclic core

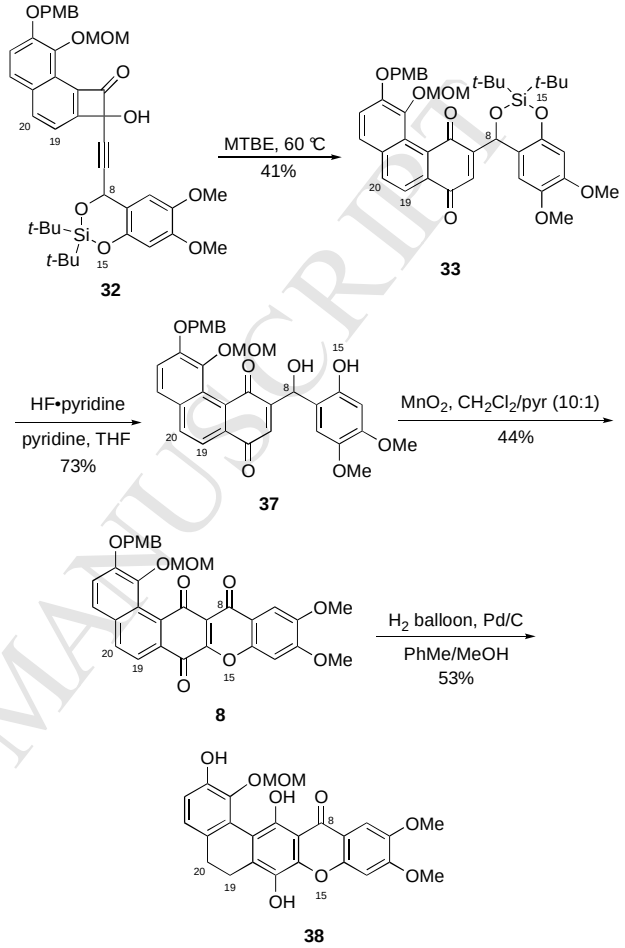
When **32** was heated at 100 °C in DMSO according to the protocol developed during our synthesis of IB-00208 aglycone,[10] only trace amounts of the desired quinone **33** were observed (Scheme 7). In previous studies of the Moore rearrangement, we observed that solvent could influence the outcome. Accordingly, we screened a number of solvents and discovered that heating **32** in *tert*-amyl alcohol at 100 ºC gave a mixture (~1:1) of the desired **33** and the 5-*exo* cyclization product **34** (*E/Z*-ratio *ca.* 1.1:1) together with smaller quantities of compounds that were tentatively identified as the hydroquinone **35** and the C-H insertion adduct **36**. The formation of products as **34** from 5-*exo*-cyclizations in the Moore reaction were known, but the isolation of **36** suggested the possible intermediacy of compounds with carbene-like character at C7. Although carbenoid mechanisms for the Moore rearrangement have been predicted computationally,[30] isolation of **36** offers some experimental evidence for this mechanistic pathway.



Scheme 7. Initial studies of Moore rearrangement.

Recent studies of the Moore rearrangement reveal that protic solvents can affect the course of the reaction. For example, when 1% H_2O is present, mixtures (1:1) of 5-*endo* and 6-*exo* products are formed, rather than products expected from a radical cyclization.[31] We thus surmised that use of *tert*-amyl alcohol as solvent might have a similar effect, so we queried whether improved ratios of **33** to **34** might be obtained in an aprotic solvent. We eventually discovered that the Moore rearrangement of **32** in methyl-*tert*-butylether (MTBE) proceeds at 60 ºC to give a mixture (1.4:1, 70% combined yield) of **33** and **34**, the latter of which was isolated as a single diastereomer (Scheme 8); only trace amounts of **36** were detected. With a reliable procedure for forming **33** in hand, the cyclic silyl ether protecting group was removed with HF•pyridine to furnish **37** in 73% yield. Compound **37** proved to be sensitive to acids, bases and a variety of oxidants, so options to selectively oxidize the benzylic alcohol were limited. Following a comprehensive examination of numerous oxidants, MnO_2 emerged as the oxidant of choice,[32] although some experimentation with Lewis basic additives was necessary.[33] We eventually discovered that the combination of pyridine and MnO_2 furnished **8**, which comprises the pentacyclic core of citreamicin η, in reproducible 44% yield.[34]

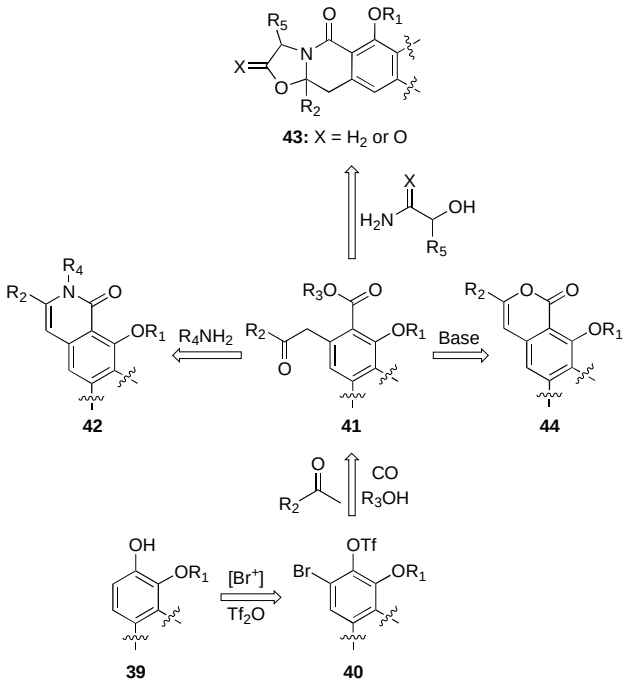
We then turned to the task of removing the PMB group. However, exposure of **8** to several oxidative conditions known to remove PMB groups resulted in rapid decomposition of **8**,[35] whereas use of Lewis acids selectively removed the MOM group, perhaps owing to its close spatial proximity to the quinone carbonyl oxygen atom.[36] Although we were able to selectively remove the PMB group from **8** by hydrogenolysis, the quinone and the C19-C20 double bond were also unavoidably reduced to provide **38** in 53% yield. This was unexpected, but not unprecedented as the double bond in the central ring of phenanthrenes are known to undergo facile reduction by catalytic hydrogenation.[37] This result has interesting implications for the synthesis of other polycyclic xanthones, such as kibdelone C (**4**), which lacks the double bond in the C ring.



Scheme 8. Synthesis of pentacyclic core of citreamicin η

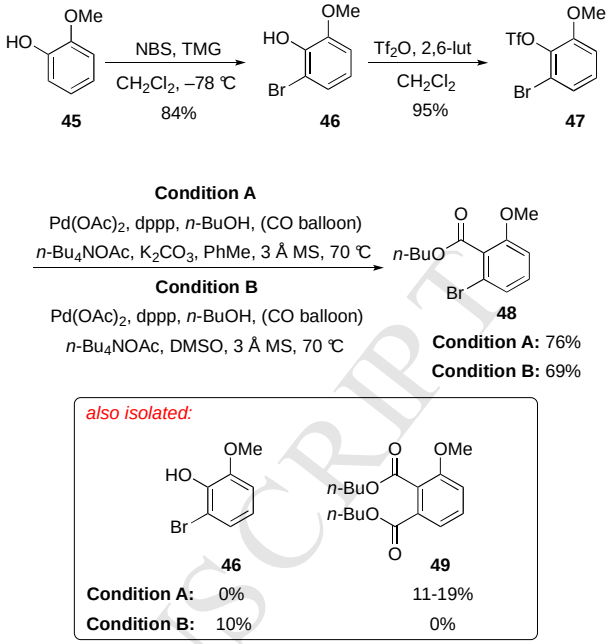
6. GAB ring model studies

The polycyclic xanthone natural products, which are exemplified in Figure 1, bear one or two additional rings fused to the pentacyclic BCDEF core. Accordingly, we wanted to develop a unified and modular strategy that could be used to append these different heterocyclic rings at a late stage in the synthesis of these natural products. We envisioned that the dihydrooxazolo-[3,2-b]-isoquinolinone **43**, the isoquinolinone **42**, and the isocoumarin **44** could all be accessed from the keto ester **41** (Scheme 9). Although there are a number of routes to keto-esters such as **41** from *o*-halo,[38] methyl,[39] or alkynyl benzoate derivatives,[40] there was no general methodology that enabled the elaboration of substituted phenols such as **39** into the pivotal intermediate **41**. We thus sought to develop a reliable approach to **41** and the derived annelated ring systems **42**–**44** from phenols **39** by sequential palladium-catalyzed alkoxycarbonylation and ketone arylation of the differentially functionalized arene **40**, which could be prepared with our new procedure for selective *o*-bromination of phenols (see Table 1).



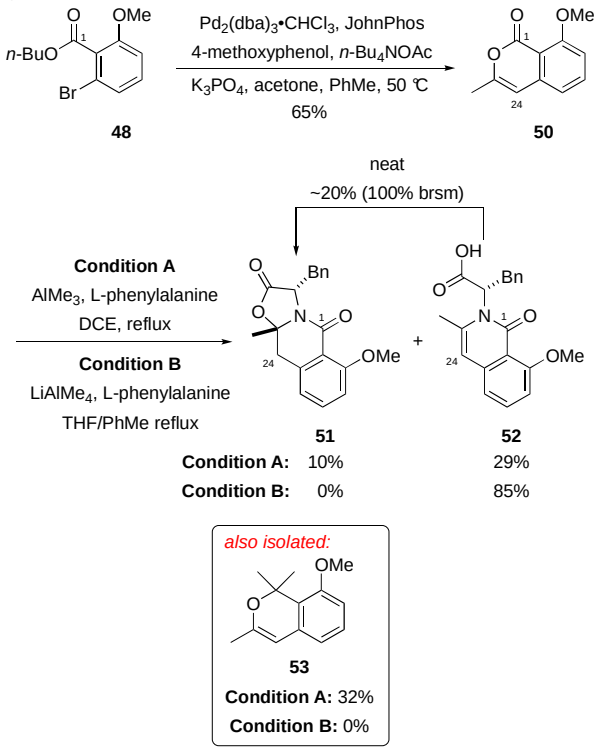
Scheme 9. A unified methodology strategy for the GAB rings.

We initiated a model study by brominating guaiacol (**45**) using NBS and TMG to furnish **46** in 84% yield, (Scheme 10), and subsequent reaction with triflic anhydride provided **47** in 95% yield. In preliminary experiments to convert **47** into **48**, hydrolysis to return **46** was problematic. Toward addressing this issue, we modified conditions that had been originally reported by Buchwald[41] and found that use of molecular sieves, 1,3-bis(diphenylphosphino)propane (dppp), and dry *n*-Bu_4NOAc in toluene gave **48** in 76% yield together; however, the phthalate **49** was also isolated (11–19%) (Scheme 10, condition A). Because polar aprotic solvents can favor palladium-catalyzed reactions of a triflate moiety versus a halide,[42] we screened several polar aprotic solvents and discovered that use of DMSO gave only trace amounts of **49**, although **46** was also formed in about 10% yield.



Scheme 10. Synthesis of model system and alkoxycarbonylation.

There are several methods for coupling aryl halides with acetone,[43] but we eventually adopted a procedure reported by Buchwald.[43a] ,In the event, **48** was coupled with acetone using JohnPhos and $Pd_2(dba)_3$•$CHCl_3$ in the presence of *n*-Bu_4NOAc and 4-methoxyphenol, and the putative keto ester intermediate cyclized spontaneously to furnish the known isocoumarin **50**,in 65% yield (Scheme 11).[44,45]



Scheme 11. Acetone arylation and amino acid coupling.

Although we had hoped to isolate the intermediate keto ester instead of **50**, the reaction of amino alcohols with isocoumarins

related to **50** was known to form dihydrooxazolo-[3,2-b]-isoquinolinones or isoquinolinones.[8a,d] Toward inducing this condensation, we turned to a method we had previously developed i which for $AlMe_3$ was used to couple amino acids with amino esters to form peptides.[46] When **50** was allowed to react with L-phenylalanine in the presence of $AlMe_3$, a mixture of **51**–**53** was in about 70% combined yield (Condition A, Scheme 11). The formation of **53** was unexpected, and we reasoned that a less Lewis acidic promoter might suppress methylation of the coumarin carbonyl group. Accordingly, we first combined L-phenylalanine and $LiAlMe_4$, which was generated *in situ* from $AlMe_3$ and MeLi, in a mixture of THF and toluene under reflux.[47] After adding isocoumarin **50**, the isoquinolone **52** was isolated in 85% yield (Condition B, Scheme 11); neither **51** nor **53** was observed. We attempted to convert **52** into **51** using Brønsted and Lewis acids, but these efforts were unavailing. Serendipitously, we discovered that merely storing the isoquinolone **52** at room temperature for several days gave the dihydro-5H-oxazolo[3,2-b]isoquinoline-2,5(3H)-dione **51** as a single diastereomer with a conversion of about 20%. Further studies on the cyclization of isoquinolones to dihydro-5H-oxazolo[3,2-b]isoquinoline-2,5(3H)-diones are underway.

7. Summary

In summary, we completed a short 11-step synthesis of the pentacyclic core of citreamicin η by an approach that exploits a novel variant of the Moore rearrangement inspired by our previous methodological work[13] and our synthesis of the aglycone of IB-00208.[10] In order to solve a problem involving the regioselective bromination of a vanillin derivative, we discovered a way to induce selective *ortho* bromination of phenols using TMG and NBS. The use of TMG as an alternative to other amines as a means of promoting such brominations may be generally useful. In another key step, we exemplified the utility of a new route to angular aryl cyclobutendiones that exploits a RCM reaction. We also showed that PDA can be exploited as an internal indicator to enable the quantitative generation of cerium acetylides uncontaminated with excess nucleophilic bases. Finally, our exploratory studies to develop tactics for the annelation of the G and A rings of citreamicin η led to the discovery of a potentially general, four step approach to the synthesis of isocoumarins and isoquinolones from phenols.

8. Experimental section

8.1. General

Unless otherwise noted, solvents and reagents were used without purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through two columns of activated neutral alumina. Methanol (CH_3OH), acetonitrile (CH_3CN), and N,N-dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves.[48] Toluene was dried by sequential passage through a column of activated neutral alumina followed by a column of Q5 reactant. Methylene chloride (CH_2Cl_2), benzene, triethylamine (Et_3N), and diisopropylethylamine (DIPEA) were distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO), and tert-amyl alcohol were stored over 4Å molecular sieves for 48 h prior to use. All solvents were determined to contain less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis, unless otherwise noted. All reactions were performed in flame-dried glassware under argon or nitrogen unless otherwise indicated. Volatile solvents were removed under reduced pressure using a Buchi rotary evaporator. Solutions of *n*-BuLi, and *tert*-BuLi were titrated according to our published procedure.[29] Reaction mixtures were degassed by putting the reaction vessel under vacuum until the solvent effervesced, and backfilling with nitrogen (3 x). Infrared (IR) spectra were obtained using a FT IR 1600 spectrophotometer using sodium chloride plates and reported as wave numbers. Low resolution chemical ionization mass spectra were obtained with a TSQ-70 instrument. High resolution measurements were made with a VG Analytical ZAB2-E instrument. Thin layer chromatography (TLC) was performed on glass-backed precoated silica gel plates (0.25 mm thick with 60 F254) and were visualized using one or both of the following manners: UV light (254 nm) and staining with basic aqueous $KMnO_4$ or Cerium ammonium molybdate (CAM). Flash chromatography was performed according to Still's procedure using ICN Silitech 32-67 D 60A silica gel.[49] ^{1}H nuclear magnetic resonance (NMR) spectra were obtained at either 600, 500, or 400 MHz as indicated as solutions in $CDCl_3$ with 0.05% v/v tetramethylsilane (TMS) unless indicated otherwise. ^{13}C-NMR was obtained at either 125, 100 or 75 MHz as shown in the indicated deuterated solvent. Chemical shifts are reported in parts per million (ppm, δ), and referenced to TMS, and coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint, quintuplet; sex, sextet; sept, septuplet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; and app, apparent.

8.2. Synthetic procedures

3-Hydroxy-4-((4-methoxybenzyl)oxy) benzaldehyde (**18**). Prepared according to a modified procedure used by Plourde,[17] A mixture of 3,4-dihydroxybenzaldehyde (**15**) (10.0 g, 65.6 mmol), $NaHCO_3$ (8.2 g, 98.4 mmol) and sodium iodide (NaI) (3.0 g, 19.6 mmol) in anhydrous DMF (40 mL) was heated at 40 °C for 2 h. *p*-Methoxybenzyl chloride (PMBCl) (20.6 g, 17.8 mL, 131.2 mmol), prepared according to Sosa's procedure,[50] was added, and the reaction was stirred at 40 °C for 24 h, whereupon the reaction was cooled to room temperature and H_2O (80 mL) was added. The mixture was extracted with EtOAc (3 x 30 mL), and the combined organic extracts were washed with 13% aqueous brine solution (4 x 10 mL) and dried (Na_2SO_4). Hexanes (50 mL) were added, and the combined organic extracts were filtered through a silica plug and eluted with EtOAc/Hexanes (2:1; 1 x 300 mL), and the combined organic layers were concentrated under reduced pressure. The crude material was crystallized from toluene (40 mL) to yield 13.4 g (79%) pure **18** as a white solid: mp 117-120 °C.

The mother liquors were washed with 5% aqueous NaOH solution (3 x 60 mL), the combined aqueous extracts were neutralized with saturated aqueous NH_4Cl (*ca.* 32 mL) until the pH was 5-7 (pH paper), and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The solids were purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 3.4 g (20%) more **18** as an off-white solid (99% total): ^{1}H-NMR (400 MHz) δ 9.83 (s, 1 H), 7.52 (d, J = 2.0 Hz, 1 H), 7.44 (dd, J = 2.0, 8.0 Hz, 1 H), 7.36 (d, J = 8.8, 2 H), 7.05 (d, J = 8.0 Hz, 1 H), 6.95 (d, J = 8.8 Hz, 2 H), 5.10 (s, 2 H), 3.84 (s, 3 H); ^{13}C-NMR (100 MHz) δ 191.0, 160.0, 151.1, 146.3, 130.7, 129.8, 127.2, 124.3, 114.3, 114.2, 111.5, 71.1, 55.3; IR (film) 3213, 1668, 1612, 1504, 1274, 1128 cm^{-1}; HRMS (ESI) *m/z* calc for $C_{15}H_{14}O_4^-$, 257.0819; found, 257.0826.

2-Bromo-3-hydroxy-4-((4-methoxybenzyl)oxy) benzaldehyde (**17**). A suspension of aldehyde **18** (3.73 g, 14.44 mmol) in CH_2Cl_2 (144 mL) was cooled to – 78 °C. In a separate flask, TMG (3.32 g, 3.62 mL, 28.88 mmol) was added to a slurry of NBS (2.57 g, 14.44 mmol) in CH_2Cl_2 (43 mL) at 0 °C. The mixture was stirred until it became homogenous (*ca.* 5 min), whereupon it was added in one portion to the slurry of **18** at – 78 °C. The reaction mixture was stirred for 30 min at – 78 °C, whereupon AcOH (0.87 g, 0.83 mL, 28.88 mmol) was added, and the reaction was warmed to room temperature. The mixture was filtered through a silica plug (300 mL) eluting with EtOAc/Hexane (1:1, 1 x 1.5 L). The eluent was concentrated under reduced pressure to provide 4.05 g (83%) **17** as a pale yellow solid: mp 154-156 °C (IPA). The crude material can be purified by flash chromatography eluting with a gradient of acetone/hexanes with 1% Et_3N (1:7 → 3:7), but the material was sufficiently pure for use in the next step; ^{1}H-NMR (400 MHz) δ 10.26 (s, 1 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 6.99 (d, *J* = 8.2 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.13 (s, 1 H), 5.17 (s, 2 H), 3.84 (s, 3 H); ^{13}C-NMR (100 MHz) δ 190.9, 160.1, 143.5, 137.9, 129.8, 127.3, 126.8, 122.5, 114.3, 113.0, 110.6, 71.5, 55.4; IR (film) 3388, 2927, 1680, 1588, 1516, 1487, 1464, 1282, 1251, 1176, 1130 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{15}H_{13}{}^{79}BrO_4{}^+$ (M+Na), 358.9889; found, 358.9010.

2-Bromo-4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy) benzaldehyde A solution of the crude aldehyde **17** (6.76 g, 20.05 mmol) and diisopropylethylamine (DIPEA) (3.89 g, 5.25 mL, 30.07 mmol) in CH_2Cl_2 (140 mL) was cooled to 0 °C. Chloromethyl methyl ether (MOMCl) (1.18 M, 25.5 mL, 30.07 mmol), prepared according to Chong's procedure,[51] was added, and the cooling bath was removed. The solution was stirred at room temperature for 3 h, whereupon a solution of saturated aqueous $NaHCO_3$ (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide crude material as a white solid: mp 88-90 °C. The crude material can be purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:3), but the material was sufficiently pure for use in the next step; ^{1}H-NMR (400 MHz) δ 10.27 (s, 1 H), 7.72 (d, *J* = 8.6 Hz, 1 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 8.6 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 5.19 (s, 2 H), 5.11 (s, 2 H), 3.82 (s, 3 H), 3.58 (s, 3 H); ^{13}C-NMR (100 MHz) δ 191.0, 159.8, 157.4, 143.6, 129.4, 127.5, 127.2, 126.4, 123.2, 114.1, 112.2, 98.8, 71.0, 58.1, 55.3; IR (film) 2968, 1674, 1515, 1382, 1250, 931 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{17}H_{17}{}^{79}BrO_5{}^+$ (M+Na), 403.0152; found, 403.0147.

2-Bromo-4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy)-1-vinylbenzene (**14**). A slurry of methyltriphenylphosphonium bromide (Ph_3PMeBr) (14.12 g, 40.10 mmol) in THF (35 mL) was cooled to 0 °C and degassed. A solution of *n*-BuLi in hexanes (1.61 M, 25 mL, 40.10 mmol) was slowly added over 10 min. The mixture was stirred for an additional 5 min, whereupon DMSO (70 mL) was added followed by a solution of crude aldehyde **17** in THF (35 mL). The reaction was stirred for 10 min, whereupon a solution of saturated aqueous $NaHCO_3$ (50 mL) and water (100 mL) was added. The mixture was extracted with EtOAc (3 x 100 mL), and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:4) to provide 6.51 g (86% from **17**) of **14** as a white waxy solid: mp 41-43 °C; ^{1}H-NMR (400 MHz) δ 7.34 (d, *J* = 8.8 Hz, 2 H), 7.26 (d, *J* = 8.8 Hz, 1 H), 7.02 (dd, *J* = 11.2, 17.2 Hz, 1 H), 6.90 (comp, 3 H), 5.56 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.25 (dd, *J* = 1.2, 11.2 Hz, 1 H), 5.17 (s, 2 H), 5.03 (s, 2 H) 3.82 (s, 3 H), 3.59 (s, 3 H); ^{13}C-NMR (100 MHz) δ 159.8, 151.8, 143.7, 135.7, 131.7, 129.3, 128.3, 121.9, 119.6, 115.2, 114.0, 113.2, 98.7, 71.0, 58.1, 55.3; IR (film) 2934, 2835, 1614, 1587, 1515, 1484, 1465, 1382, 1287, 1251, 1214, 1174, 1159, 1033, 985 cm^{-1}; HRMS (CI) *m/z* calc for $C_{18}H_{19}{}^{79}BrO_4{}^+$, 377.0388; found, 377.0391.

4,4-Dimethoxy-3-(3-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)-6-vinylphenyl)-2-vinylcyclobut-2-en-1-one (**19**). Compound **14** (500 mg, 1.32 mmol) was dried by dissolving in toluene (2 mL) and concentrating under reduced pressure (2 x), whereupon it was stored under vacuum for 2 h. 3,4,4-Trimethoxy-2-vinylcyclobut-2-en-1-one (**13**), prepared according to Moore's procedure,[15b] was freshly purified via flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2), and the oil thus obtained was stored under vacuum for 2 h. Toluene (9 mL), Et_2O (44 mL) and NaH (60 % dispersion in mineral oil, 16 mg, 0.26 mmol) were added to the flask containing **14**, and the mixture was stirred for 10 min before cooling to – 78 °C. This mixture was degassed, and a solution of *tert*-BuLi in pentanes (1.85 M, 1.64 mL, 3.03 mmol) was added dropwise at – 78 °C. Stirring was continued for an additional 5 min, whereupon a solution of **13** in Et_2O (2 mL) that had been slurried over NaH (60 % dispersion in mineral oil, 8 mg, 0.13 mmol) for at least 5 min was added. The reaction mixture was warmed to –20 °C and stirring continued for 15 min, whereupon a solution of saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 364 mg (61%) of **19** as a yellow oil that slowly turns solid upon standing: mp 75-77 °C; ^{1}H-NMR (600 MHz) δ 7.37 (d, *J* = 8.6 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 8.6 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.77 (dd, *J* = 10.8, 17.6 Hz, 1 H), 6.16 (dd, *J* = 2.8, 17.6 Hz, 1 H), 6.08 (dd, *J* = 10.4, 18.0 Hz, 1 H) 5.60 (dd, *J* = 1.2, 17.6 Hz, 1 H), 5.56 (dd, *J* = 2.8, 10.4 Hz, 1 H), 5.18 (dd, *J* = 1.2, 10.8 Hz, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H) 3.81 (s, 3 H), 3.47 (s, 6 H), 3.38 (s, 3 H); ^{13}C-NMR (150 MHz) δ 191.1, 170.9, 159.6, 152.8, 151.1, 142.5, 134.2, 129.3, 129.3, 128.4, 126.0, 125.8, 124.1, 121.3, 116.7, 115.1, 114.5, 114.0, 99.0, 70.7, 57.3, 55.3, 52.7; IR (film) 2945, 1765, 1515, 1465, 1251, 1028, 992 cm^{-1}; HRMS (CI) *m/z* calc for $C_{26}H_{28}O_7{}^+$ (M+), 452.1835; found, 452.1837.

1,1-Dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)cyclobuta[a]naphthalen-2(1H)-one (**12**). A solution of **19** (1.14 g, 2.513 mmol), Grubbs II (149 mg, 0.176 mmol) and butylated hydroxytoluene (BHT) (111 mg, 0.502 mmol) in dichloroethylene (DCE) was degassed and then heated under reflux for 8 h. The reaction mixture was cooled to room temperature, whereupon DMSO (0.564 g, 0.62 mL, 8.795 mmol) was added, and the mixture was stirred for 16 h. The solvent was removed under reduced pressure, and the crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 836 mg (78%) of **12** as a brownish green solid: mp 83-85 °C and 214 mg (13%) **19** (91% brsm); ^{1}H-NMR (500 MHz) δ 7.90 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.35 (s, 2 H), 5.20 (s, 2 H), 3.82 (s, 3 H), 3.57 (comp, 9 H); ^{13}C-NMR (125 MHz) δ 193.2, 160.3, 159.6, 150.4, 147.5, 140.6, 133.8, 132.7, 129.4, 128.4, 125.8, 125.2, 120.1, 118.2, 114.7, 114.0, 99.6, 71.7, 57.7, 55.3, 53.7; IR (film) 2942, 2836, 1760, 1614, 1584, 1515, 1462, 1334, 1251, 1174, 1108, 1033, 937 cm^{-1}; HRMS (CI) *m/z* calc for $C_{24}H_{25}O_7{}^+$ (M+), 425.1600; found, 425.1596.

2-Hydroxy-4,5-dimethoxy benzaldehyde (**27**). A solution of 2,4,5-trimethoxybenzaldehyde (**26**) (3.3 g, 16.78 mmol),[25a] in CH_2Cl_2 (84 mL) was cooled to 0 °C, whereupon BBr_3 (freshly distilled from CaH_2, 4.59 g, 1.74 mL, 18.45 mmol) was added, and the mixture was warmed to room temperature and stirred for 24 h. H_2O (20 mL) was added, and stirring was continued for an additional 10 min. The mixture was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide 2.60 g (85%) crude **27** as a dark green solid: mp 104-106 °C (MeOH). The crude material can be purified by flash chromatography eluting with a gradient of acetone/hexanes (1:3 → 1:1), but in most cases the material is sufficiently pure for the next step; 1H-NMR (400 MHz) δ 11.41 (s, 1 H), 9.71 (s, 1 H), 6.91 (s, 1 H), 6.48 (s, 1 H), 3.94 (s, 3 H), 3.89 (s, 3 H); 13C-NMR (100 MHz) δ 194.0, 159.3, 152.2, 142.9, 113.1, 112.8, 100.1, 56.4, 56.3; IR (film) 2838 (C-H), 1625 (C=O), 1506, 1475, 1443, 1369, 1339, 1280, 1251, 1198, 1147, 998 cm^{-1}; LRMS (CI) *m/z* found, 183.0.

4,5-Dimethoxy-2-((4-methoxybenzyl)oxy)benzaldehyde (**28**). A mixture of crude aldehyde **27** (0.50 g, 2.74 mmol), K_2CO_3 (0.76 g, 5.48 mmol) and NaI (0.12 g, 0.82 mmol) in DMF (1.7 mL) was heated at 40 °C for 2 h.Paramethoxybenzyl chloride (PMBCl)[50] (0.64 g, 0.56 mL, 4.12 mmol) was added, and the mixture was stirred at 40 °C for 24 h. H_2O (10 mL) was added, and the reaction mixture was cooled to room temperature. The mixture was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic extracts were washed with 5% NaOH solution (1 x 10 mL), 13% aqueous brine solution (4 x 3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 820 mg (99%) **28** as a white solid: mp (IPA) 98-99 °C; ^{1}H-NMR (500 MHz) δ 10.34 (s, 1 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.32 (s, 1 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.56 (s, 1 H), 5.10 (s, 2 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 3 H); ^{13}C-NMR (125 MHz) δ 188.1, 159.8, 157.8, 155.6, 144.0, 129.2, 128.1, 118.2, 114.2, 108.8, 98.1, 71.7, 56.2, 55.3; IR (film) 2958 (C-H), 2937 (C-H), 2837, 1655 (C=O), 1606, 1468, 1454, 1276, 1216, 1127, 1037, 1021, 915 cm^{-1}; HRMS (CI) *m/z* calc for $C_{17}H_{18}O_5^+$ (M+), 302.1154; found, 302.1159.

1-(4,5-Dimethoxy-2-((4-methoxybenzyl)oxy)phenyl)prop-2-yn-1-ol (**11**). A solution of aldehyde **28** (354 mg, 1.17 mmol) in THF (7 mL) was degassed. A solution of ethynyl magnesium bromide (0.5 M, 5.8 mL, 2.93 mmol) in THF was added and the reaction mixture was stirred for 2 h at 5 °C, whereupon a solution of saturated aqueous $NaHCO_3$ (1 mL) was added. The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with EtOAc/hexanes (1:2) to provide 375 mg (98%) of **11** as a waxy solid: ^{1}H-NMR (600 MHz) δ 7.36 (d, *J* = 8.8 Hz, 2 H), 7.13 (s, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.60 (s, 1 H), 5.68 (dd, *J* = 2.4, 6 Hz, 1 H), 5.05 (dd, *J* = 4, 10.6 Hz, 2 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 2.79 (d, *J* = 6 Hz, 1 H), 2.62 (d, *J* = 2.4 Hz, 1 H); ^{13}C-NMR (150 MHz) δ 159.6, 150.1, 149.7, 143.5, 129.1, 128.7, 120.8, 114.1, 111.5, 99.5, 83.6, 73.9, 71.7, 66.3, 56.5, 56.2, 55.3; IR (film) 3469 (O-H), 3282, 3001, 2936 (C-H), 2836 (C-H), 1612, 1515, 1464, 1405, 1383, 1304, 1249, 1209, 1175, 1114, 1019, 941 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{19}H_{20}O_5^+$ (M+Na), 351.1203; found, 351.1200.

2-(3-(4,5-Dimethoxy-2-((4-methoxybenzyl)oxy)phenyl)-3-hydroxyprop-1-yn-1-yl)-1,1-dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)-1,2-dihydrocyclobuta[a]naphthalen-2-ol (**10**). A solution of **12** (143 mg, 0.337 mmol) in toluene (2 mL) was concentrated under reduced pressure (3 x), put under vacuum for 2 h and dissolved in THF (2.7 mL). A separate round-bottomed flask containing **11** (221 mg, 0.674 mmol) was dissolved in toluene (2 mL), concentrated under reduced pressure (3 x) and put under vacuum for 2 h. 4-(Phenylazo)diphenylamine (PDA) (5 mg, 0.017 mmol) was added to the flask containing **11**, followed by a solution of $CeCl_3$•2LiCl in THF (0.33 M, 4.1 mL, 1.35 mmol), prepared by Knochel's method,[27] and the reaction mixture was cooled to – 78 °C and degassed. The cooling bath was removed, and the mixture was warmed to 0 °C, whereupon a solution of *n*-BuLi (1.21 M, 1.5 mL, 1.81 mmol) in hexanes was added until the reaction mixture turned a persistent purple color. After the purple endpoint had been seen, an additional amount of *n*-BuLi in hexanes (1.21 M, 0.56 mL, 0.67 mmol) was added, and the reaction mixture was stirred for 10 min at 0 °C. The solution of **12** in THF (1 mL) was slurried over NaH (60 % dispersion in mineral oil, *ca.* 6 mg, 0.150 mmol) before adding to the reaction mixture containing **11**, and stirring was continued for 1 h at 0 °C. A solution of saturated aqueous $NaHCO_3$ (5 mL) was then added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:2 → 3:4) to provide 212 mg (84%) of **10** and 10 mg (7%) of **12** (91% brsm): ^{1}H-NMR (600 MHz) δ 7.81 (d, *J* = 8.6 Hz, 1 H), 7.78 (d, *J* = 8.6 Hz, 1 H), 7.60 (d, *J* = 6.9 Hz, 1 H), 7.58 (d, *J* = 6.9 Hz, 1 H), 7.40-7.35 (Comp, 6 H), 7.30 (d, *J* = 9.0 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 7.084 (s, 1 H), 7.07 (s, 1 H), 6.55 (s, 1 H), 6.53 (s, 1 H) 5.74 (app. d, 2 H), 5.29 (d, *J* = 5.3 Hz, 1 H), 5.25 (d, *J* = 5.3 Hz, 1 H), 5.16 (app qd, 4 H), 5.09 (d, *J* = 5.3 Hz, 1 H), 5.04 (d, *J* = 5.3 Hz, 1 H), 4.96 (app qd, 4 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 6 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.67 (s, 3 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 3.58 (s, 3 H), 3.53 (s, 3 H), 3.52 (app. d, 6 H); ^{13}C-NMR (150 MHz) δ 159.5, 159.4, 150.3, 150.1, 150.0, 149.5, 149.4, 146.3, 143.4, 138.7, 136.7, 132.6, 131.0, 129.4, 129.2, 128.8, 128.7, 126.3, 126.2, 121.4, 117.2, 117.1, 116.6, 114.0, 113.9, 111.8, 111.6, 107.6, 99.8, 99.7, 87.1, 83.9, 83.7, 77.6, 71.8, 71.6, 60.9, 60.6, 57.6, 56.3, 56.2, 56.1, 55.3, 55.2, 53.2, 51.9, 51.8; IR (film) 3466 (O-H), 2939 (C-H), 2838 (C-H), 2251 (C≡C), 1728, 1613, 1515, 1463, 1405, 1382, 1303, 1251, 1209, 1113, 1032, 912 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{43}H_{44}O_{12}^+$ (M+Na), 775.2725; found, 775.2722.

2,2-Di-tert-butyl-4-ethynyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasiline (**30**). A solution of aldehyde **27** (1.56 mg, 8.57 mmol),[25] in THF (16 mL) was cooled to – 78 °C, and the reaction vessel was degassed. A solution of ethynyl magnesium bromide (0.5 M, 42.8 mL, 21.41 mmol) was then added at – 78 °C. The cooling bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h, whereupon a solution of dilute NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude oil was purified by silica plug eluting with 1:1 mixture acetone/hexanes (500 mL) to provide 1.44 g of the acetylide adduct as a brown solid that used directly in the next step.

A solution the acetylide adduct (1.44 g, 6.92 mmol) and 2,6-lutidine (1.85 g, 2.0 mL, 17.3 mmol) in CH_2Cl_2 (18 mL) was cooled to – 40 °C, (*tert*-Bu)$_2$Si(OTf)$_2$ (3.65 g, 2.7 mL, 8.30 mmol) was added, and the reaction mixture was warmed to 0 °C by replacing the cooling bath with an ice/water bath. The mixture was stirred for

4 h, whereupon a solution of saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:10) to provide 1.98 g (82% from **27**) of **30** as a waxy white solid: mp 78-80 °C; ^{1}H-NMR (500 MHz) δ 6.82 (s, 1 H), 6.49 (s, 1 H), 5.84 (dd, *J* = 0.7, 2.3 Hz, 1 H), 3.85 (s, 1 H), 3.83 (s, 3 H), 2.66 (d, *J* = 2.3 Hz, 1 H), 1.06 (s, 9 H), 1.03 (s, 9 H); ^{13}C-NMR (125 MHz) δ 149.8, 147.1, 143.2, 116.5, 109.8, 103.6, 83.1, 74.1, 64.5, 56.4, 55.9, 26.9, 26.9, 21.5, 20.9; IR (film) 3287, 2936, 2896, 2860, 2120, 1616, 1512, 1471, 1471, 1450, 1405, 1364, 1326, 1291, 1264, 1218, 1200, 1195, 1175, 1126, 1084, 1012, 940 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{19}H_{28}O_4Si^+$ (M+Na), 371.1649; found, 371.1652.

2-((2,2-Di-tert-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-1,1-dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)-1,2-dihydrocyclobuta[a]naphthalen-2-ol (**31**). A solution of **12** (1 g, 2.36 mmol) in toluene (5 mL) was concentrated under reduced pressure (1 X), put under vacuum for 2 h, and dissolved in THF (5 mL). A separate round-bottomed flask containing **30** (1.64 mg, 4.72 mmol) was dissolved in toluene (5 mL), concentrated under reduced pressure (1 X), and put under vacuum for 2 h. 4-(Phenylazo)diphenylamine (PDA) (32 mg, 0.12 mmol), THF (24 mL) and a solution of $CeCl_3$•2LiCl in THF (0.33 M, 17.8 mL, 5.89 mmol)[27] was added to the flask containing **30** and the mixture was cooled to – 78 °C and the reaction vessel was degassed, whereupon a solution of *n*-BuLi in hexanes was added until the reaction mixture turned a persistent purple color. After the purple endpoint had been seen, an additional amount of *n*-BuLi in hexanes (2.47 M, 1.91 mL, 4.72 mmol) was added, the cooling bath was removed, and the reaction mixture was warmed to 0 °C. The solution of **12** in THF was slurried over NaH (60 % dispersion in mineral oil, *ca.* 60 mg, 1.5 mmol) before adding to the reaction mixture containing **9**, and stirring continued for an additional 1 h.The reaction was quenched with neat AcOH (7.07 mL, 1.36 g, 23.6 mmol) followed by de-ionized H_2O (50 mL), and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 1.64 g (90%) of **31** as a golden foam; ^{1}H-NMR (600 MHz) δ 7.81 (d, *J* = 8.3 Hz, 2 H), 7.60 (d, *J* = 8.9 Hz, 2 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 7.40 (d, *J* = 8.3 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 4 H), 7.31 (d, *J* = 9.0 Hz, 2 H), 6.90 (d, *J* = 9.7 Hz, 4 H), 6.78 (s, 1 H), 6.69 (s, 1 H), 6.44 (s, 1 H), 6.43 (s, 1 H), 5.89 (d, *J* = 6.4 Hz, 2 H), 5.31 (dd, *J* = 5.3, 6.8 Hz, 2 H), 5.18 (dq, *J* = 2.4, 11.4 Hz, 4 H), 5.10 (dd, *J* = 5.3, 8.3 Hz, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.61 (s, 3 H), 3.56 (s, 3 H), 3.53 (s, 3 H), 3.52 (s, 3 H), 3.51 (s, 3 H), 3.50 (s, 3 H), 1.51 (s, 9 H), 1.03 (s, 9 H), 0.96 (s, 9 H), 0.90 (s, 9 H); ^{13}C-NMR (150 MHz) δ 159.5, 150.1, 150.0, 149.5, 149.4, 147.0, 146.3, 143.0, 142.9, 138.7, 136.8, 136.7, 132.5, 131.0, 129.4, 128.8, 128.7, 126.3, 126.2, 117.1, 117.0, 116.6, 113.9, 109.9, 109.8, 107.6, 107.5, 103.4, 99.8, 86.7, 83.8, 77.5, 71.6, 64.8, 57.6, 56.1, 55.9, 55.3, 53.2, 51.9, 51.8, 26.9, 21.5, 21.0, 20.8; IR (film) 3498, 2937, 2860, 2353, 1732, 1615, 1594, 1513, 1464, 1405, 1337, 1252, 1200, 1175, 1121, 1080, 1035, 1012, 938 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{19}H_{28}O_4Si^+$ (M+Na), 795.3171; found, 795.3163.

2-((2,2-Di-tert-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-2-hydroxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)cyclobuta[a]naphthalen-1(2H)-one (**32**). H_3PO_4 (85%, 7 mg, 4 µL, 0.0697 mmol) and H_2O (28 mg, 28 µL, 1.2546 mmol) was added to a slurry of silica (280 mg) in CH_2Cl_2 (2.1 mL). The mixture was stirred vigorously for 1 h, whereupon **31** (54 mg, 0.0697 mmol) and CH_2Cl_2 (1 mL) were added, and the mixture was stirred for 1 h. Et_3N (35 mg, 49 µL, 0.3485 mmol) was added, and the mixture was filtered through a silica plug (~10 mL). The plug was eluted with EtOAc/hexanes (1:1, 1 x 100 mL) and the eluant was concentrated under reduced pressure (bath temp 30 °C) to provide 48 mg (95%) of **32** as an orange oil. The material was unstable, so it was used directly in the next step without further purification; ^{1}H-NMR (600 MHz) δ 8.04 (d, *J* = 8.3 Hz, 1 H), 8.03 (d, *J* = 8.5 Hz, 1 H), 7.66 (d, *J* = 9.0 Hz, 1 H), 7.65 (d, *J* = 9.0 Hz, 1 H), 7.63 (d, *J* = 8.2 Hz, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 7.41-7.37 (comp, 6 H), 6.91 (d, *J* = 8.7 Hz, 4 H), 6.72 (s, 1 H), 6.68 (s, 1 H), 6.46 (s, 1 H), 6.44 (s, 1 H), 5.90 (d, *J* = 0.7 Hz, 1 H), 5.87 (d, *J* = 0.7 Hz, 1 H), 5.40-5.36 (m, 4 H), 5.20 (d, *J* = 3.2 Hz, 4 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.54 (s, 3 H), 3.52 (s, 3 H), 1.04 (s, 9 H), 1.03 (s, 9 H), 0.99 (s, 9 H), 0.97 (s, 9 H); ^{13}C-NMR (150 MHz) δ 182.9, 160.4, 160.3, 159.6, 151.6, 149.8, 149.7, 147.0, 146.9, 143.2, 142.1, 140.4, 138.6, 130.9, 129.3, 128.3, 126.1, 124.1, 118.1, 116.6, 116.4, 116.3, 114.0, 109.5, 103.6, 103.5, 99.6, 99.5, 90.0, 89.9, 85.5, 82.2, 82.1, 71.5, 64.7, 57.7, 56.3, 56.2, 56.0, 55.9, 55.3, 27.0, 26.9, 26.8, 21.5, 20.8; IR (neat) 3435, 2935, 2860, 1765, 1615, 1587, 1512, 1465, 1406, 1336, 1251, 1216, 1200, 1175, 1120, 1080, 1034, 941 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{41}H_{46}O_{10}Si^+$ (M+Na), 749.2752; found, 749.2739.

3-(2,2-Di-tert-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)-6-((4-methoxybenzyl)oxy)-5-(methoxymethoxy)phenanthrene-1,4-dione (**33**). A solution of crude **32** (35 mg, 0.0472 mmol) in degassed MTBE (14 mL) was heated to 60 °C for 1 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the crude oil was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:10 → 3:10) to provide 61 mg (37%) of **33** as an amorphous red solid and 48 mg (29%) of **34** as a yellow solid: ^{1}H-NMR (600 MHz) δ 8.00 (d, *J* = 8.5 Hz, 1 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 7.63 (d, *J* = 8.9 Hz, 1 H), 7.48 (d, *J* = 8.9 Hz, 1 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 6.73 (s, 1 H), 6.56 (s, 1 H), 6.47 (s, 1 H), 6.37 (s, 1 H), 5.29-5.16 (comp, 4 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.66 (s, 3 H), 3.31 (s, 3 H), 1.09 (s, 9 H), 1.02 (s, 9 H); ^{13}C-NMR (150 MHz) δ 186.9, 185.4, 159.6, 154.8, 150.9, 149.8, 148.3, 143.3, 142.8, 133.6, 133.1, 133.0, 132.9, 132.0, 129.4, 128.5, 125.3, 125.0, 120.1, 119.6, 117.8, 114.0, 110.6, 103.7, 98.9, 71.9, 69.4, 57.6, 56.5, 56.0, 55.3, 27.1, 27.1, 21.9, 20.8; IR (film) 2934, 2859, 1662, 1614, 1588, 1513, 1448, 1407, 1336, 1299, 1251, 1199, 1135, 1058, 919 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{41}H_{46}O_{10}Si^+$ (M+Na), 749.2752; found, 749.2747.

3-(Hydroxy(2-hydroxy-4,5-dimethoxyphenyl)methyl)-6-((4-methoxybenzyl)oxy)-5-(methoxymethoxy)phenanthrene-1,4-dione (**37**). One drop of HF•Pyridine was added to a solution of **33** (41 mg, 0.0565 mmol) and pyridine (49 mg, 50 µL, 0.6210 mmol) in THF (2 mL), and the reaction was stirred for 30 min at room temperature. The mixture was diluted with EtOAc (5 mL), and the solution was washed with NH_4Cl (1 x 2 mL) and de-ionized H_2O (1 x 2 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:2 → 3:4) to provide 24 mg (72%) of **37** as an amorphous red solid: ^{1}H-

NMR (600 MHz) δ 7.97 (d, *J* = 8.5 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.68 (bs, 1 H), 7.63 (d, *J* = 8.9 Hz, 1 H), 7.47 (d, *J* = 8.9 Hz, 1 H), 7.39 (d, *J* = 8.7 Hz, 2 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 6.67 (s, 1 H), 6.55 (s, 1 H), 6.47 (d, *J* = 1.6 Hz, 1 H), 6.17 (bs, 1 H), 5.19 (s, 2 H), 5.13 (d, *J* = 4.8 Hz, 1 H), 5.19 (d, *J* = 4.8 Hz, 1 H), 4.40 (bs, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.19 (s, 3 H); ^{13}C-NMR (150 MHz) δ 188.8, 185.0, 159.7, 152.7, 150.9, 150.3, 150.0, 143.0, 141.4, 133.8, 133.2, 132.9, 132.7, 130.0, 129.4, 128.3, 125.3, 125.1, 119.6, 114.1, 114.0, 113.6, 111.2, 102.4, 98.2, 71.7, 70.3, 57.6, 56.6, 56.0, 55.3; IR (film) 3431, 2933, 2837, 1659, 1614, 1588, 1514, 1449, 1335, 1302, 1250, 1197, 1137, 1112, 1055, 1035, 916 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{33}H_{39}O_{10}^{+}$ (M+Na), 609.1731; found, 609.1722.

10,11-Dimethoxy-2-((4-methoxybenzyl)oxy)-1-(methoxymethoxy)-13H-naphtho[1,2-b]xanthene-7,13,14-trione (**8**). Activated manganese dioxide (MnO_2) (667 mg, 7.670 mmol) was added to a solution of **37** (30 mg, 0.051 mmol) in CH_2Cl_2 (6.1 mL) and pyridine (0.3 mL) at room temperature and stirred for 4 h. The mixture was then filtered through a silica plug, eluting with a mixture (1:1) of acetone/hexanes (20 mL) and the combined filtrates were concentrated under reduced pressure. The crude material was then purified by flash chromatography eluting with a gradient of acetone/hexanes (7:20 → 1:2) to provide 13 mg (44%) of **8** as an amorphous orange solid: ^{1}H-NMR (500 MHz) δ 8.04 (d, *J* = 8.5 Hz, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.65 (s, 1 H), 7.61 (d, *J* = 9.1 Hz, 1 H), 7.50 (d, *J* = 9.0 Hz, 1 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 7.15 (s, 1 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.26 (s, 2 H), 5.23 (s, 2 H), 4.03 (s, 3 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 3.44 (s, 3 H); ^{13}C-NMR (125 MHz) δ 182.1, 179.1, 172.6, 159.6, 155.6, 153.8, 151.2, 150.6, 148.8, 143.7, 135.2, 133.7, 133.3, 130.4, 129.4, 128.5, 125.2, 124.7, 121.6, 121.0, 119.8, 119.1, 114.0, 105.1, 100.6, 99.2, 77.1, 57.8, 56.8, 56.5, 55.3; IR (film) 2928, 1688, 1641, 1620, 1600, 1512, 1467, 1450, 1428, 1402, 1334, 1272, 1249, 1175, 1126, 1081, 1048, 992 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{33}H_{26}O_{10}^{+}$ (M+Na), 605.1418; found, 605.1410.

2,7,14-Trihydroxy-10,11-dimethoxy-1-(methoxymethoxy)-5,6-dihydro-13H-naphtho[1,2-b]xanthen-13-one (**38**). Pd/C (*ca.* 1-2 mg) was added to a solution of **8** (7 mg, 0.12 mmol) in a mixture (1:1) of MeOH/PhMe (1 mL). The reaction mixture was sparged with a balloon of H_2 for 5 min then stirred at room temperature for 24 h under a hydrogen atmosphere. The reaction mixture was filtered through a silica plug, eluting with a mixture (1:1) acetone/hexanes (5 mL). The solution was concentrated under reduced pressure and the crude material was purified by flash chromatography eluting with a gradient of acetone/hexanes (7:20 → 1:2) to provide 3 mg (53%) of **38** as an amorphous yellow solid: ^{1}H-NMR (500 MHz) δ 13.06 (s, 1 H), 8.25 (s, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H), 6.944 (s, 1 H), 6.941 (d, *J* = 8.0 Hz, 1 H), 5.39 (bs, 1 H), 5.29 (bs, 2 H), 4.07 (s, 3 H), 4.03 (s, 3 H), 3.62 (s, 3 H), 1.57 (bs, 4 H); ^{13}C-NMR (125 MHz) δ 180.9, 156.1, 151.9, 151.3, 148.1, 147.2, 143.9, 142.9, 136.5, 131.9, 131.5, 124.6, 123.4, 115.8, 114.8, 113.4, 106.8, 104.7, 99.7, 99.3, 57.0, 56.6, 56.4, 29.2, 23.9; IR (film) 3396 (O-H), 2955 (C-H), 1644 (C=O), 1615, 1588, 1509, 1479, 1453, 1434, 1382, 1361, 1299, 1277, 1237, 1211, 1175, 1147, 1115, 1073, 1030, 1003, 988 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{25}H_{22}O_{9}^{+}$ (M+Na), 489.1156; found, 489.1154.

2-Bromo-6-methoxyphenol (**46**). Guiacol (**45**) (2.0 g, 16.11 mmol) was dissolved in CH_2Cl_2 (160 mL) and cooled to – 78 °C. In a separate flask, TMG (4.45 g, 4.85 mL, 38.66 mmol) was added to a slurry of NBS (3.44 g, 19.33 mmol) in CH_2Cl_2 (43 mL) at 0 °C. The mixture was stirred until it became homogenous (~5 min), then it was added to the solution containing guiacol (**45**) at – 78 °C over 10 min. The reaction mixture was stirred for 30 min at – 78 °C whereupon AcOH (1.1 mL, 1.15 g, 19.33 mmol) was added, and the reaction was warmed to room temperature. The mixture was washed with H_2O (1 x 100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:4 → 1:2) buffered with 1% Et_3N to provide 2.74 g (84%) of **46** as a white solid: mp 49-53 °C; ^{1}H-NMR (600 MHz) δ 7.09 (dd, *J* = 1.4, 8.1 Hz, 1 H), 6.81 (dd, *J* = 1.4, 8.1 Hz, 1 H), 6.74 (t, *J* = 8.1 Hz, 1 H), 3.90 (s, 3 H); ^{13}C-NMR (150 MHz) δ 147.4, 143.2, 124.8, 120.7, 109.9, 108.4, 56.3; IR (film) 3409 (O-H), 2953 (C-H), 2848 (C-H), 1601, 1490, 1471, 1442, 1354, 1287, 1263, 1234, 1201, 1147, 1072, 1027 cm^{-1}; HRMS (CI) *m/z* calc for $C_7H_7O_2{}^{79}Br^{+}$ (M+), 201.9629; found, 201.9632.

2-Bromo-6-methoxyphenyl trifluoromethanesulfonate (**47**). A solution of phenol **46** (4.38 g, 21.57 mmol) and pyridine (3.41 g, 3.47 mL, 43.14 mmol) in CH_2Cl_2 (120 mL) was cooled to 0 °C. Neat triflic anhydride (Tf_2O) (7.31 g, 4.35 mL, 25.88 mmol) was added, and the reaction mixture was stirred for 1 h. H_2O (100 mL) was added, and the layers were separated. The organic layer was washed with aqueous $CuSO_4$ (1 M, 1 x 100 mL) dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with EtOAc/hexanes (1:10) to provide 6.83 g (94%) of **47** as a clear oil: ^{1}H-NMR (600 MHz) δ 7.22 (dd, *J* = 1.5, 8.2 Hz, 1 H), 7.18 (t, *J* = 8.2 Hz, 1 H), 6.97 (dd, *J* = 2.5, 8.2 Hz, 1 H), 3.91 (s, 3 H); ^{13}C-NMR (150 MHz) δ 152.6, 137.0, 129.3, 125.3, 118.6 (q, *J* = 321 Hz), 116.9, 112.0, 56.4; IR (film) 1595, 1475, 1300, 1282, 1210, 1136, 1036, cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_8H_6{}^{79}BrF_3O_4S^{+}$ (M+Na), 356.9014; found, 356.9026.

Butyl 2-bromo-6-methoxybenzoate (**48**).

Using PhMe: $Pd(OAc)_2$ (75 mg, 0.33 mmol), 1,3-bis(diphenylphosphino)propane (DPPP) (270 mg, 0.65 mmol), K_2CO_3 (1.81 g, 13.08 mmol) and tetrabutylammonium acetate (TBAA) (1.97 g, 6.54 mmol) were weighed in a glove-box and added to a flame dried round bottomed flask. Pulverized 3 Å molecular sieves (1.1 g) were added, and the flask was put under vacuum and backfilled with N_2 (3 x). Toluene (20 mL) was added and the reaction mixture was stirred for 10 min before adding **47** (2.19 g, 6.54 mmol) and *n*-BuOH (1.46 g, 1.80 mL, 19.61 mmol). The reaction mixture was heated to 70 °C for 16 h. The mixture was cooled to room temperature and filtered through a silica plug. The plug was washed with 1:1 EtOAc/hexanes (200 mL), and the combined eluant was concentrated and purified by flash chromatography eluting with a gradient of CH_2Cl_2/hexanes (1:4 → 3:4) to provide 1.26 g (67%) of **48** as a clear oil.

Using DMSO: Pd(OAc)2 (34 mg, 0.149 mmol), 1,3-bis(diphenylphosphino)propane (DPPP) (123 mg, 0.298 mmol), and tetrabutylammonium acetate (TBAA) (900 mg, 2.98 mmol) were weighed in a glove-box, and added to a flame dried round bottomed flask. Pulverized 3 Å molecular sieves (1.5 g) were added and the flask was put under vacuum and backfilled with N_2 (3 x). Degassed DMSO (20 mL) was added, and the reaction mixture was stirred for 10 min before adding **47** (500 mg, 1.49 mmol) and *n*-BuOH (0.33 g, 0.41 mL, 4.47 mmol). The mixture was heated to 70 °C for 16 h. The mixture was cooled to room temperature and filtered through a silica plug. The plug was washed with 1:1 EtOAc/hexanes (1 x 100 mL), and the combined eluant was washed with H_2O (1 x 50 mL), dried (Na_2SO4), filtered and concentrated under reduced pressure and the crude oil was purified by flash

chromatography eluting with a gradient of CH_2Cl_2/hexanes (1:4→ 3:4) to provide 272 mg (69%) of **48** as a clear oil. 1H-NMR (500 MHz) d 7.18 (dd, J = 8.1, 8.0 Hz, 1 H), 7.13 (dd, J = 1.0, 8.3 Hz, 1 H), 6.85 (dd, J = 1.0, 8.0 Hz, 1 H), 4.36 (t, J = 6.6 Hz, 2 H), 3.81 (s, 3 H), 1.74 (quin, J = 6.6 Hz, 2 H), 1.47 (sex, J = 7.6 Hz, 2 H), 0.96 (t, J = 7.3 Hz, 3 H); 13C-NMR (125 MHz) d 166.3, 157.2, 131.1, 126.4, 124.5, 119.7, 110.0, 65.6, 56.1, 30.6, 19.1, 13.7; IR (film) 2960 (C-H), 2873 (CH), 1731 (C=O), 1591, 1573, 1464, 1433, 1267, 1187, 1157, 1107, 1066, 1035, 839 cm-1; HRMS (ESI) *m/z* calc for $NaC_{12}H_{15}{}^{79}BrO_3{}^+$ (M+Na), 309.0097; found, 309.0102.

8-Methoxy-3-methyl-1H-isochromen-1-one (**50**). $Pd_2(dba)_3{\bullet}HCCl_3$ (45 mg, 0.043 mmol), (2-biphenyl)di-*tert*-butylphosphine (52 mg, 0.174 mmol), K_3PO_4 (923 mg, 4.35 mmol), *para*-methoxyphenol (43 mg, 0.348 mmol) and tetrabutylammonium acetate (TBAA) (525 mg, 1.74 mmol) were weighed in a glove-box and added to a flame dried round bottomed flask. Pulverized 3 Å molecular sieves (250 mg) was added and the flask was put under vacuum and backfilled with N_2 (3 x). Toluene (5 mL) was added, and the reaction mixture was stirred for 10 min before adding a degassed solution of **48** (2.19 g, 6.54 mmol) in toluene (4 mL) and acetone (freshly distilled from CaH_2, 0.61 g, 0.77 mL, 10.44 mmol) and the mixture was heated to 60 °C for 16 h. The mixture was then cooled to room temperature, and filtered through a silica plug. The plug was washed with 3:1 EtOAc/hexanes (100 mL) and the combined eluant was concentrated and purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 197 mg (59%) of **50** as a brown amorphous solid: ^{1}H-NMR (600 MHz) δ 7.57 (dd, *J* = 7.77, 7.78 Hz, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 6.86 (d, *J* = 7.77 Hz, 1 H), 6.15 (app d, *J* = 1 Hz, 1 H), 3.99 (s, 3 H), 2.23 (d, *J* = 1 Hz, 3 H); ^{13}C-NMR (150 MHz) δ 161.6, 159.8, 155.1, 140.7, 135.7, 117.0, 109.3, 108.0, 103.6, 56.3, 19.5; IR (film) 3436, 1729 (C=O), 1666, 1599, 1571, 1478, 1434, 1319, 1282, 1262, 1163, 1089, 1039, 980 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{11}H_{10}O_3{}^+$ (M+Na), 213.0522; found, 213.0523.

(S)-2-(8-Methoxy-3-methyl-1-oxoisoquinolin-2(1H)-yl)-3-phenylpropanoic acid (**52**). A solution of $AlMe_3$ (2 M, 3.44 mL, 6.89 mmol) in toluene was added to THF (10 mL), followed by a solution of MeLi (1.26 M, 5.5 mL, 6.89 mmol) in Et_2O. The mixture was stirred for 10 min before adding to a degassed flask containing solid L-phenylalanine (487 mg, 2.95 mmol). The mixture was stirred for 10 min before heating to 50 °C and heating for an additional 30 min or until the mixture became homogeneous. A solution of **50** (187 mg, 0.98 mmol) in toluene (10 mL) was then added and the mixture was stirred for 1 h at 50 °C, whereupon the reaction was cooled to room temperature and poured into cold 1 M HCl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of MeCN/$HCCl_3$ (1:20 → 1:10) buffered with 2% AcOH to provide 262 mg (79%) of **52** as a yellow oil: ^{1}H-NMR (600 MHz) δ 7.50 (m, 1 H), 7.16 (comp, 3 H), 7.01 (m, 2 H), 6.92 (m, 1 H), 6.85 (m, 1 H), 6.09 (app d, 1 H), 4.65 (m, 1 H), 3.98 (app d, 3 H), 3.67-3.60 (comp, 2 H), 2.64 (s, 3 H); ^{13}C-NMR (150 MHz) δ 175.9, 161.8, 160.9, 140.1, 140.0, 138.3, 133.4, 129.5, 128.6, 126.7, 117.5, 113.8, 107.3, 106.6, 61.3, 56.0, 34.4, 20.8; IR (film) 3443 (O-H), 2924 (C-H), 1730 (C=O), 1653 (C=O), 1602, 1561, 1481, 1455, 1399, 1335, 1296, 1267, 1212, 1180, 1154, 1115, 1084, 1065 cm^{-1}; HRMS (ESI) *m/z* calc for $NaC_{20}H_{19}NO_4{}^+$ (M+Na), 360.1206; found, 360.1208.

(3S,10aS)-3-Benzyl-6-methoxy-10a-methyl-10,10a-dihydro-5H-oxazolo[3,2-b]isoquinoline-2,5(3H)-dione (**51**). Isolated from a sample of **52** which was left on the bench at room temperature for ~ 1 week. Purified via preparative TLC (50% EtOAc/hexanes) to provide 9 mg (20%) of **51** as an amorphous white solid: ^{1}H-NMR (600 MHz) δ 7.40 (dd, *J* = 7.5, 8.5 Hz, 1 H), 7.27-7.20 (comp, 5 H), 6.96 (d, *J* = 8.6 Hz, 1 H), 6.76 (d, *J* = 7.4 Hz, 1 H), 4.97 (dd, *J* = 2.6, 6.4 Hz, 1 H), 3.95 (s, 3 H), 3.52 (dd, *J* = 6.4, 13.9 Hz, 1 H), 3.42 (dd, *J* = 2.6, 13.9 Hz, 1 H), 3.16 (d, *J* = 14.6 Hz, 1 H), 3.05 (d, *J* = 14.7 Hz, 1 H), 0.53 (d, *J* = 1.0 Hz, 3 H); ^{13}C-NMR (150 MHz) δ 171.3, 161.0, 159.9, 136.3, 136.0, 133.7, 130.5, 128.6, 127.3, 120.2, 116.5, 111.9, 94.2, 69.6, 58.0, 56.3, 53.8, 24.6; IR (film) 3436, 1729 (C=O), 1666 (C=O), 1599, 1571, 1478, 1434, 1319, 1282, 1262, 1163, 1089, 1039, 980 cm^{-1}; HRMS (CI) *m/z* calc for $C_{20}H_{19}NO_4{}^+$ (M+), 337.1314; found, 337.1310.

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