Synthesis of Vinaxanthone Analogs

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Abstract

Spinal cord injury is a debilitating injury that affects 12,000 people in the U.S. annually. Current treatment is limited; research in tissue engineering, biomaterials, and gene therapy have dominated neuroregeneration studies. However, an inadequate amount of attention has been dedicated to the development of small molecule therapeutics. Vinaxanthone (SM-345431) and xanthofulvin (SM-216289) are two novel small molecule compounds co-isolated from Penicillium sp. SPF-3059 that demonstrate axonal regenerative properties in both C. elegans and adult rats. Initially, the molecules were thought to inhibit semaphorin 3A, a protein which induces the collapse of neuronal growth cones. Knockout studies of semaphorin 3A indicate that simply shutting off inhibitory signaling does not equate to the pronounced neuroregeneration present from vinaxanthone and xanthofulvin administration, suggesting that the molecules possess alternative modes of action. To uncover the mechanism of action for these two small molecules, analogs of vinaxanthone and xanthofulvin are being developed for structure-activity-relationship studies in C. elegans. Further research into the action of these analogs will provide useful information regarding CNS inhibitory signaling in spinal cord injury models and potential therapeutic options. Currently, the synthesis of vinaxanthone analogs is being pursued. Initial data from G-protein coupled receptor assays (GPCR) indicates that various vinaxanthone analogs have been found to possess either positive or negative allosteric modulation for the succinate receptor 1 protein (SUCNR1 or GPR91). The synthesis of more vinaxanthone analogs will be pursued (with an envisioned vinaxanthone library of 64 compounds) and their biological activity tested.
Introduction

Until the pioneer Albert Aguayo and his co-workers discovered that adult central nervous system (CNS) neurons could grow if offered a peripheral nerve transplant, scientists and physicians believed that neuroregeneration in the CNS was improbable, if not impossible. The inhibitory microenvironment of the CNS following injury prevents successful regeneration of neurons. Aguayo utilized the more flexible microenvironment of the peripheral nervous system through the creation of peripheral nerve grafts to promote neuroregeneration of CNS neurons.²

Upon spinal cord injury (SCI), successive steps lead to the formation of a glial scar in which glial cells are recruited and surround the site of injury. These glial cells (mainly astrocytes) release proteins and chemical signals which prevent the elongation of axons and regeneration of neurons in the associated glial scar. Some of these inhibitory proteins include the semaphorin family of proteins.⁵ Semaphorin 3A (Sema3A) has been shown to promote human neuronal growth cone collapse and is thought to be a guidance cue for developing axons. Sema3A binds to plexin-neuropilin-1 complexes which leads to its inhibitory signaling.⁹ Successful Sema3A inhibitors were thought to be isolated from Penicillium sp. SPF-3059 by Kumagai et al.⁶ The inhibitors, xanthofulvin (1) and vinaxanthone (2), are exciting leads in axonal regeneration. Kaneko et al. published a study in Nature Medicine displaying the remarkable regenerative properties of xanthofulvin following complete spinal cord transection in adult rats, and Omoto et al. published a study showing the neuroregenerative properties of vinaxanthone in corneal transplantation experiments in mice models.⁸,¹¹ However, genetic knockdown of Sema3A does
not garner the pronounced regenerative effects characteristic of xanthofulvin or vinaxanthone, suggesting that the mode of action for xanthofulvin and vinaxanthone (previously identified as Sema3A inhibitors) is unclear. Analog synthesis for vinaxanthone has been delineated by the Siegel group, and efforts are underway to synthesize these analogs. Structure-activity-relation and G-protein coupled receptor studies are being pursued upon synthesis of vinaxanthone analogs to elucidate the mode of action for the natural product and discover enhanced biological activity.

**Background**

*Tatsuta Synthesis*

The first synthesis of vinaxanthone was performed by Tatsuta *et al.* through the intermolecular Diels-Alder (IMDA) reaction of two molecules of a protected vinyl ketone precursor made in 14 steps. The protected vinyl ketone was generated from vanillin and successive oxidation reactions that led to a vinyl iodide precursor, which was then cross-coupled with methyl vinyl ketone using Pd(OAc)$_2$ to generate the protected vinyl ketone intermediate. IMDA between protected vinyl ketone molecules led to the formation of protected vinaxanthone which then underwent de-protection with AlCl$_3$ in toluene at 110° C for 2 hours. This synthesis provided the first biomimetic pathway for vinaxanthone synthesis but produced a mix of products in the final IMDA reaction. The Siegel synthesis improved upon the Tatsuta synthesis, producing vinaxanthone in 2/3 the number of steps and limiting side product formation.

*Tatsuta’s Proposal:*
From sodium [1-$^{13}$C]acetate metabolism studies, Zeeck et al. envisioned the biosynthesis of chaetocyclinone C (4) through a non-enzymatic, twofold aldol condensation of a polyketide intermediate and a highly reactive aldehyde intermediate. The similarity in structure between chaetocyclinone C (4) and vinaxanthone (2) motivated the Siegel group to pursue a dimerization of 5,6-dehydropolivione (5) in the synthesis of vinaxanthone (2).

**Zeeck’s Proposal:**

**Siegel’s Proposal:**

**Siegel First Generation Synthesis**

5,6-dehydropolivione (5) is synthesized from tetronic acid (6) in eight steps (Scheme 1). Tetronic acid (6) undergoes two protection steps, installing a pivaloyl (Piv) and tert-butyldimethylsilyl (TBS) group, to form furan (7). Furan (7) then undergoes a Diels-Alder reaction with keto ester (8) to form the desired bicyclic product (9) in a >20:1 ratio. Keto ester (8) is formed from 3-butyn-2-ol (11) in 4 steps as indicated in Scheme 1 (for more detail, see Experimental section). Treatment with hydrochloric acid induces the bicyclic compound (9) to aromatize and produce acetophenone (13) with migration of the pivaloyl group. The free hydroxyl group from the acetophenone (13) is then protected to generate (14). The enaminone (15) is then produced by using the dimethyl acetal of dimethylformamide in dimethoxyethane at elevated temperatures,
simultaneously cleaving the TBS group. Formation of protected 5,6-dehydropolivione (17) occurs through treatment of enaminone (15) with 5-acetyl Meldrum’s acid (16) in refluxing toluene, yielding the protected 5,6-dehydropolivione (17) in 42 % yield. Cleavage of all protecting groups is achieved with boron trichloride in dichloromethane at room temperature, generating 5,6-dehydropolivione (5). Vinaxanthone (2) was then produced by heating 5,6-dehydropolivione (5) in deionized water to 55˚ C at 61 % yield.\(^\text{10}\)

\textit{Scheme 1:} Siegel synthesis of vinaxanthone
Siegel Second Generation Synthesis

While developing the xanthofulvin synthesis, the Siegel group discovered an alternative synthesis of vinaxanthone through the aldol condensation of an ynone (19) and reactive aldehyde (20) (Scheme 2), similar to Zeeck’s proposal. It was discovered that in the presence of wet acetonitrile and triethylamine, the ynone intermediate (19) used in the xanthofulvin synthesis would dimerize to form protected vinaxanthone. The proposed mechanism for the dimerization is highlighted in Scheme 3. In order to produce the ynone intermediate, the enaminone species (15) from the original synthesis cyclizes with iodine in chloroform to generate the iodochromone species (18). The iodochromone (18) then undergoes a Sonagashira cross-coupling reaction with 3-butyn-2-ol (11) to generate a propargyl alcohol species. The alcohol is then oxidized to the ynone species (19) with pyridinium dichlorochromate (PDC). Placing the ynone (19) in acetonitrile and water (1000 equivalents of H₂O) with .5 eq. of triethylamine at room temperature generated the protected vinaxanthone product at 87% yield through formation of a highly reactive aldehyde species (20). The protected vinaxantone is then deprotected through the use of boron trichloride in dichloromethane at 0˚ C to generate vinaxanthone (2).
**Scheme 2: De novo synthesis of vinaxanthone**

The synthesis of vinaxanthone through the ynone precursor introduces more steps; however, it allows for the synthesis of diverse analogs since different combinations of ynone intermediates

**Scheme 3: Proposed mechanism for formation of vinaxanthone through ynone intermediate**

The synthesis of vinaxanthone through the ynone precursor introduces more steps; however, it allows for the synthesis of diverse analogs since different combinations of ynone intermediates
may undergo cycloaddition. The Siegel group envisions 8 alternative ynone intermediate species, which leads to 64 possible analogs of vinaxanthone (Figure 1).

Figure 1: 64 possible vinaxanthone analogs

Results

Initially, 3 different ynone subunits were synthesized to form several different vinaxanthone analog species. The following ynones were formed:

The formation of ynone (19) proceeded through the scheme shown above in Scheme 2 and below in Scheme 4. Ynone (22) was formed through a similar pathway as ynone (19) (Scheme 4); 2,4-dihydroxyacetophenone (23) was used as the initial starting material instead of forming a
hydroxyacetophenone intermediate from tetronic acid. The protection of 2,4-
dihydroxyacetophenone (23) using chloromethyl methyl ether yielded an acetophenone
intermediate (24) in 69% yield. Enaminone and subsequent iodochromone (25) formation
following procedures previously established yielded the mono-substituted iodochromone (25) in
78% yield over two steps. Sonagashira cross-coupling with commercially available 3-butyn-2-ol
(11) and subsequent oxidation using PDC yielded the desired ynone (22) in 36% over two steps.
Ynone (21) was generated from veratraldehyde (26). Veratraldehyde (26) was reduced to an
alcohol using H₂O₂ and formic acid, and subsequently acylated with boron trifluoride and acetic
anhydride to form intermediate (27). The phenol (27) underwent enaminone and iodochromone
formation as described previously. Removal of the methoxy groups was achieved using boron
tribromide in dichloromethane at 0°C to generate a catechol. The catechol species was protected
to generate the dimethoxy methyl protected iodochromone (28). Iodochromone (28) underwent
Sonagashira cross-coupling with 3-butyn-2-ol (11) and oxidation with PDC to generate ynone
(21).

Scheme 4: Ynone analog synthesis
Ynones (19, 21, 22) were combined to form 9 different analogs of vinaxanthone (including the original vinaxanthone molecule) displayed in Figure 2. The general procedure for combining two ynone analogs is highlighted in Scheme 5. The initial ynone placed in wet acetonitrile (1000 eq. of H₂O) equilibrates to the highly reactive aldehyde intermediate and reacts with subsequent addition of the second ynone. The initial ynone forms the left side of the vinaxanthone product, while the second ynone forms the right side of the vinaxanthone product. Multiple vinaxanthone analog products are formed, unless the same ynone intermediates are used for the dimerization reaction. The desired vinaxanthone analog was purified by column chromatography using a 5:2:1 dichloromethane:ethyl acetate:hexanes solution.

The dimerization reaction yields are displayed in Figure 2 for various combinations of ynones (for specific procedures, see Experimental section); the yields displayed in parenthesis indicate formation of other vinaxanthone analog products. All protected vinaxanthone analogs (2a, 2b, 2c, 2f) generated with ynone (19) underwent de-protection by stirring in boron trichloride in dichloromethane for 1 hour; the protected vinaxanthone analogs (2d, 2e, 2g, 2h) that did not use ynone (19) for any part of the dimerization reaction underwent de-protection through a slightly altered procedure by stirring in methanolic HCl for 8 hours. All of the de-protection reactions yielded the desired vinaxanthone analog at about 90% yield or better.

Scheme 5: General procedure for formation of vinaxanthone analogs from ynone analogs
**Conclusions**

9 vinaxanthone analogs (including the original vinaxanthone molecule) were formed and analyzed through GPCR screening from Millipore Co. Millipore Co. identified that vinaxanthone was an allosteric modulator for GPR91 or succinate receptor 1. The vinaxanthone analogs displayed a mix of positive and negative modulation of GPR91 as indicated in *Figure 2*. Analog (2a) displays enhanced positive allosteric modulation of GPR91 as compared to vinaxanthone (2); analog (2b) displays negative allosteric modulation of GPR91. Allosteric modulation was
quantified through Ca$^{2+}$ fluorescence absorbance signals generated from the activity of GPCRs (a value of 0 indicates no allosteric modulation).

GPR91 enhances angiogenesis of blood vessels during hypoxic conditions.$^{12,13}$ The interplay between angiogenesis and neurogenesis is being further studied; common signaling pathways exist in the development of the nervous and circulatory systems.$^{12}$ Synthesis of the remaining ynone intermediates will allow experimentation on 64 analogs. Further data collection will be pursued regarding the activity of the proposed 64 analogs and structure-activity-relationships of the vinaxanthone molecule will be deduced.
References

Experimental

General Information

All reactions were performed in flame dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise indicated. Air-and moisture-sensitive liquids and solutions were transferred via syringe or canula. Organic solutions were concentrated by rotary evaporation at 20 torr. Methylene chloride (CH$_2$Cl$_2$) and tetrahydrofuran (THF) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Acetonitrile (MeCN) was purified using a Vac 103991 Solvent Purification System (Vacuum Atmospheres). Dimethoxyethane (DME) was purchased from Acros (99+% stabilized with BHT), methanol (MeOH) was purchased from Sigma-Aldrich (99.8%, anhydrous), ethanol (EtOH) was purchased from Pharmco-Aaper (200 proof, absolute). All other reagents were used directly from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical) and visualized using a UV lamp and/or aqueous ceric ammonium molybdate (CAM) or aqueous potassium permanganate (KMnO$_4$) stain. Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film or KBr pellet technique. High-resolution mass spectra (HRMS) were recorded on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion [M+Na]$^+$, [M+H], [M$^+$], or [M-H]. Nuclear magnetic resonance spectra ($^1$H NMR and $^{13}$C NMR) were recorded with a Varian Gemini [(400 MHz, $^1$H at 400 MHz, $^{13}$C at 100 MHz), (500 MHz, $^{13}$C at 125 MHz), (600 MHz, $^{13}$C at 150 MHz)]. For CDCl$_3$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent; CHCl$_3$ δ H (7.26 ppm) and CDCl$_3$ δ D (77.0 ppm). For (CD$_3$)$_2$SO solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; (CD$_3$)(CHD)$_2$SO δ H (2.50 ppm) or (CD$_3$)$_2$SO δ C (39.5 ppm). Coupling constants are reported in Hertz (Hz). Data for $^1$H-NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration). Melting points were measured on a MEL-TEMP device without corrections.

5-oxo-2,5-dihydrofuran-3-yl pivalate

To a stirred solution of tetratic acid (6) (25.0 g, 250 mmol, 1.0 equiv.), 4-dimethylaminopyridine (1.53 g, 12.5 mmol, 0.05 equiv,) and N,N-diisopropylethylamine (45.8 mL, 262 mmol, 1.05 equiv.) in CH$_2$Cl$_2$ (500 mL, 0.5 M) at 0 °C was added neat pivaloyl chloride (25.9 mL, 262 mmol, 1.05 equiv.) dropwise over 40 minutes. Upon complete addition the reaction mixture was allowed to warm to 23 °C. After 16 hours, the reaction mixture was concentrated **in vacuo** to give an amber oil. The oil was dissolved in Et$_2$O (500 mL) and washed with H$_2$O (500 mL). The aqueous layer was extracted with Et$_2$O (5 x 500 mL) and the combined organic layers were dried over MgSO$_4$ and concentrated **in vacuo** to give tetronate X (41.0 g, 223 mmol, 89%) as clear amber crystals (m.p. 46-47 °C).
$R_f = 0.60$ (silica gel, 1:1 hexanes:EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.00 (t, $J = 1.4$ Hz, 1H), 4.91 (d, $J = 1.4$ Hz, 2H), 1.32 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.2, 172.2, 169.1, 100.2, 68.2, 38.3, 26.4; IR (film, v cm$^{-1}$): 1779, 1746, 1072.

**5-((tert-butyldimethylsilyloxy)furan-3-yl pivalate (7)**

To a stirred solution of tetroxane (30.0 g, 163 mmol, 1.0 equiv.) and triethylamine (29.8 mL, 212 mmol, 1.3 equiv.) in CH$_2$Cl$_2$ (226 mL, 0.72 M) at 0 °C was added neat tert-butyldimethylsilyl triflate (37.8 mL, 165 mmol, 1.01 equiv.) dropwise over 10 minutes. Upon complete addition the reaction mixture was allowed to warm to 23 °C. After 1 hour, the reaction mixture was concentrated in vacuo to give an amber oil. The oil was suspended in pentane (200 mL) and stirred for 1 hour at 23 °C. The organic layer was decanted and washed with sat. aq. NaHCO$_3$ (3 x 100 mL), H$_2$O (100 mL) and brine (100 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo to give furan X (37.9 g, 127 mmol, 78%) as an amber oil.

$R_f = 0.55$ (silica gel, 20:1 hexanes:EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.10 (d, $J = 1.2$ Hz, 1H), 5.15 (d, $J = 1.2$ Hz, 1H), 1.29 (s, 9H), 0.96 (s, 9H), 0.24 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.3, 154.3, 139.4, 120.6, 80.1, 39.0, 27.1, 25.4, 18.0, -4.85; IR (film, v cm$^{-1}$): 3202, 3141, 1753, 1627; HRMS (ESI) calc. for C$_{15}$H$_{27}$O$_4$Si [M+H]$^+$: 299.20000, obs. 299.20000.

**3-(1-ethoxyethoxy)but-1-yne (11)**

To a stirred solution of 3-butyne-2-ol (11) (100 g, 1.43 mol, 1.0 equiv.) and ethyl vinyl ether (151 mL, 1.57 mol, 1.1 equiv.) in CH$_2$Cl$_2$ (3 L, 0.48 M) at 23 °C was added solid pyridinium p-toluenesulfonate (35.9 g, 143 mmol, 0.1 equiv.). After 1 hour, the reaction mixture was diluted with Et$_2$O (1 L) and washed with brine (2 L). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo to give a mixture of diastereomeric alkynes (201 g, 1.41 mol, 99%) as a clear amber oil.

$R_f = 0.40$ (silica gel, 1:1 hexanes:EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.96 (q, $J = 5.5$ Hz, 1H), 4.85 (q, $J = 5.5$ Hz, 1H), 4.50 (q, $J = 6.7$ Hz, 1H), 4.35 (q, $J = 6.7$ Hz, 1H), 3.75 (m, 1H), 3.62 (m, 1H), 3.53 (m, 2H), 2.40 (s, 1H), 2.39 (s, 1H), 1.46 (d, $J = 3.1$ Hz, 3H), 1.44 (d, $J = 3.1$ Hz, 3H), 1.35 (d, $J = 2.7$ Hz, 3H), 1.34 (d, $J = 2.7$ Hz, 3H), 1.21 (t, $J = 7.0$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 98.5, 97.5, 84.5, 83.6, 72.4, 72.0, 61.1, 60.5, 60.0, 59.9, 22.3, 21.9, 20.0, 19.9, 15.2, 14.9; HRMS (EC-Cl) calc. for C$_8$H$_{13}$O$_2$ [M+H]$^+$: 141.0916, obs. 141.0918.

**tert-butyl 4-(1-ethoxyethoxy)pent-2-ynoate (12)**

To a stirred solution of diastereomeric alkynes (110 g, 774 mmol, 1.0 equiv.) in THF (4.5 L, 0.17 M) at −78 °C was added a 2.0 M solution of n-butyllithium in hexanes (404 mL, 808 mmol, 1.05 equiv.). After 15 minutes, neat di-tert-butyl dicarbonate (186 mL, 808 mmol, 1.05
equiv.) was added over 10 minutes. Upon complete addition the reaction mixture was allowed to warm to 23 °C. The reaction mixture was diluted with Et₂O (1.5 L) and washed with H₂O (3 L) and brine (3 L). The organic layer was dried over MgSO₄ and concentrated in vacuo to give a mixture of diastereomeric esters (12) (180 g, 743 mmol, 96%) as an amber oil.

\[ R_f = 0.21 \text{ (silica gel, 20:1 hexanes:EtOAc); } \] 
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)}: \delta 4.91 (q, J = 5.1 Hz, 1H), 4.82 (q, J = 5.1 Hz, 1H), 4.56 (q, J = 6.8 Hz, 1H), 4.40 (q, J = 6.8 Hz, 1H), 3.73 (m, 1H), 3.62 (m, 1H), 3.56 (m, 1H), 3.50 (m, 1H), 1.49 (s, 18 H), 1.46 (d, J = 1.7 Hz, 6H), 1.34 (d, J = 1.4 Hz, 6H); \] 
\[ ^13C \text{ NMR (100 MHz, CDCl}_3\text{)}: \delta 152.6, 152.5, 99.3, 98.3, 86.1, 85.2, 82.9, 82.7, 78.3, 77.9, 61.0, 60.4, 60.3, 60.2, 27.8 (2 signals), 21.8, 21.5, 20.1, 20.0, 15.5, 15.3; \] 
\[ \text{IR (film, } \nu \text{ cm}^{-1}\text{): 1710, 1274, 1160; HRMS (ESI) calc. for C}_{13}\text{H}_{22}\text{NaO}_4 \text{[M+Na]}^+: 265.14103, \text{obs. 265.14100}. \] 

tert-butyl 4-hydroxypent-2-ynoate

To a stirred solution of diasteromeric esters (12) (117 g, 483 mmol, 1.0 equiv.) in EtOH (4.8 L, 0.1 M) at 78 °C was added solid pyridinium p-toluenesulfonate (12.1 g, 48.3 mmol, 0.1 equiv.). After 2 hours, the reaction mixture was allowed to cool to 23 °C. The reaction mixture was diluted with Et₂O (2.4 L) and washed with brine (4 L). The organic layer was dried over MgSO₄ and concentrated in vacuo to give alcohol X (73.1 g, 429 mmol, 89%) as an amber oil.

\[ R_f = 0.30 \text{ (silica gel, 3:1 hexanes:EtOAc); } \] 
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)}: \delta 4.62 (m, 1H), 2.13 (s, 1H), 1.51 (m, 12H); \] 
\[ ^13C \text{ NMR (100 MHz, CDCl}_3\text{)}: \delta 152.8, 86.8, 82.9, 77.5, 57.8, 27.8, 23.1; \] 
\[ \text{IR (film, } \nu \text{ cm}^{-1}\text{): 3400, 1709; HRMS (EC-Cl) calc. for C}_{9}\text{H}_{13}\text{O}_3 \text{[M+H]}^+: 171.1021, \text{obs. 171.1019}. \] 

tert-butyl 4-oxopent-2-ynoate (8)

To a stirred solution of alcohol (73.0 g, 429 mmol, 1.0 equiv.) in Me₂CO (1.2 L, 0.43 M) at 0 °C was slowly added ice-cold 1.53 M (67.0 g CrO₃, 58.0 mL conc. H₂SO₄ and 160 mL H₂O) Jones reagent (280 mL, 429 mmol, 1.0 equiv.) over 15 minutes. After 30 minutes, i-PrOH (40 mL) was added to neutralize any excess Jones reagent and the reaction mixture was diluted with CH₂Cl₂ (1 L). The organic layer was decanted and washed with H₂O (1 L), sat. aq. NaHCO₃ (1 L) and brine (1 L). The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give keto ester X (57.5 g, 342 mmol, 80%) as a clear amber oil.

\[ R_f = 0.40 \text{ (silica gel, 10:1 hexanes:EtOAc); } \] 
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)}: \delta 2.41 (s, 3H), 1.52 (s, 9H); \] 
\[ ^13C \text{ NMR (100 MHz, CDCl}_3\text{)}: \delta 182.8, 151.0, 85.4, 79.2, 79.0, 32.3, 27.9; \] 
\[ \text{IR (film, } \nu \text{ cm}^{-1}\text{): 1716, 1689; HRMS (EC-Cl) calc. for C}_{9}\text{H}_{13}\text{O}_3 \text{[M+H]}^+: 169.0865, \text{obs. 169.0866}. \]
tert-butyl 3-acetyl-4-((tert-butyldimethylsilyl)oxy)-6-(pivaloyloxy)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (9)

To a stirred solution of furan (7) (70.4 g, 236 mmol, 1.0 equiv.) in THF (212 mL, 1.1 M) at 0 °C was added keto ester (8) (39.7 g, 236 mmol, 1.0 equiv.). Upon complete addition, the reaction mixture was allowed to warm to 23 °C. After 1 hour, the reaction mixture was concentrated *in vacuo* to give bicycle (9) (110 g, 236 mmol, yield taken after subsequent step) in > 20:1 regioselectivity as a viscous burgundy oil.

R<sub>f</sub>= 0.35 (silica gel, 10:1 hexanes:EtoAc); ¹H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.38 (s, 1H), 5.24 (s, 1H), 2.43 (s, 3H), 1.47 (s, 9H), 1.25 (s, 9H), 0.90 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ¹³C NMR (100 MHz, CDCl<sub>3</sub>): δ 199.3, 174.3, 167.7, 163.7, 161.2, 146.3, 118.5, 113.9, 82.3, 78.2, 39.2, 30.7, 27.9, 26.8, 25.4, 17.7, -3.5, -3.7; IR (film, cm<sup>-1</sup>): 1769, 1712; HRMS (EC-Cl) calc. for C<sub>24</sub>H<sub>38</sub>O<sub>7</sub>Si [M+Na]<sup>+</sup>: 489.22790, obs. 489.22801.

tert-butyl 2-acetyl-3-((tert-butyldimethylsilyl)oxy)-5-hydroxy-6-(pivaloyloxy)benzoate (13)

To a stirred solution of bicycle (9) (110 g, 236 mmol, 1.0 equiv.) in THF (471 mL, 0.5 M) at 0 °C was slowly added a 4.0 M solution of hydrochloric acid in dioxane (47.1 mL, 47.1 mmol, 0.2 equiv.) over 5 minutes. Upon complete addition the reaction mixture was allowed to warm to 23 °C. After 2 hours, the reaction mixture was concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography (20:1 hexanes:EtoAc) to give pure phenol X (82.9 g, 178 mmol, 75% over 2-steps) as a clear light-yellow oil.

R<sub>f</sub>= 0.38 (silica gel, 10:1 hexanes:EtoAc); ¹H NMR (400 MHz, CDCl<sub>3</sub>): δ 10.91 (s, 1H), 6.71 (s, 1H), 2.48 (s, 3H), 1.54 (s, 9H), 1.38 (s, 9H), 0.94 (s, 9H), 0.18 (s, 9H); ¹³C NMR (100 MHz, CDCl<sub>3</sub>): δ 202.3, 176.3, 168.4, 148.7, 142.5, 139.7, 131.9, 119.9, 111.0, 85.7, 39.2, 32.5, 27.8, 27.2, 25.5, 18.0, -4.4; IR (film, cm<sup>-1</sup>): 1763, 1716, 1673; HRMS (EC-Cl) calc. for C<sub>24</sub>H<sub>38</sub>O<sub>7</sub>Si [M+Na]<sup>+</sup>: 489.22790, obs. 489.22813.

**General Procedure for Methoxymethyl Ether Protection**

To a stirred solution of phenol (1.0 equiv.) and N,N-diisopropylethylamine (1.5 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (0.2 M) at 0 °C was added and a 2.1 M solution of methoxymethyl chloride in PhMe/MeOAc (1.5 equiv.). After 1 hour, the reaction mixture was diluted with 0.1 M aq. HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give crude methoxymethyl ether. The crude material was purified via silica gel column chromatography to give pure methoxymethyl ether.
**tert-butyl 2-acetyl-3-((tert-butyldimethylsilyl)oxy)-5-(methoxymethoxy)-6-(pivaloyloxy)benzoate (14)**

Following the general procedure for methoxymethyl ether protection, phenol (13) was transformed into methoxymethyl ether (14). The crude material was purified via silica gel column chromatography (10:1 hexanes:EtOAc) to give pure methoxymethyl ether (14) (61.4 g, 120 mmol, 68%) as a white solid (m.p. 60-62 °C).

\[ R_f = 0.61 \text{ (silica gel, 3:1 hexanes:EtOAc); } \]  
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta 6.76 \text{ (s, 1H), 5.10 (s, 2H), 3.42 (s, 3H), 1.49 (s, 9H), 1.34 (s, 9H), 0.97 (s, 9H), 0.21 (s, 9H); } \]  
\[ ^13C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta 200.9, 175.7, 163.5, 150.9, 150.4, 132.8, 128.1, 125.7, 108.6, 94.6, 82.5, 55.9, 38.9, 31.7, 27.7, 27.1, 25.6, 18.1, -4.4; } \]  
\[ \text{IR (film, } \nu \text{ cm}^{-1}\text{): 1761, 1733, 1703; } \]  
\[ \text{HRMS (ESI) calc. for } C_{26}H_{42}NaO_8Si [M+Na]^+: 533.25412, \text{ obs. } 533.25387. \]

**1-(2-hydroxy-4-(methoxymethoxy)phenyl)ethan-1-one (24)**

Following the general procedure for methoxymethyl ether protection, 2',4'-dihydroxyacetophenone (23) was transformed into methoxymethyl ether (24). The crude material was purified via silica gel column chromatography (10:1 hexanes:EtOAc) to give pure methoxymethyl ether (24) (8.84 g, 45.1 mmol, 69%) as a clear oil.

\[ R_f = 0.45 \text{ (silica gel, 5:1 hexanes:EtOAc); } \]  
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta 12.62 \text{ (s, 1H), 7.66 (d, } J = 8.9 \text{ Hz, 1H), 6.60 (d, } J = 2.4 \text{ Hz, 1H), 6.55 (dd, } J = 8.9, 2.4 \text{ Hz, 1H), 5.21 (s, 2H), 3.48 (s, 3H), 2.57 (s, 3H); } \]  
\[ ^13C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta 202.7, 164.7, 163.5, 132.4, 114.6, 108.1, 103.6, 93.9, 56.3, 26.1; } \]  
\[ \text{IR (film, } \nu \text{ cm}^{-1}\text{): 3406, 1635, 1244, 991; } \]  
\[ \text{HRMS (EC-Cl) calc. for } C_{10}H_{13}O_4 [M+H]^+: 197.0814, \text{ obs. } 197.0814. \]

**3,4-dimethoxyphenol**

To a stirred solution of 3,4-dimethoxybenzaldehyde (26) (30.0 g, 181 mmol, 1.0 equiv.) in CH₂Cl₂ (361 mL, 0.5 M) at 23 °C was added 30% aq. H₂O₂ (46.1 mL, 451 mmol, 2.5 equiv.) and formic acid (27.7 mL, 722 mmol, 4.0 equiv.). The reaction mixture was stirred at 40 °C for 42.5 hours. The reaction mixture was then cooled to 23 °C and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to about 361 mL (0.5 M). 5 M aq. NaOH (251 mL, 1.26 mol, 10 equiv.) was then slowly added and the reaction mixture was stirred at 23 °C for 20 minutes. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 100 mL). The aqueous layer was acidified to pH = 1.0 with conc. HCl and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give pure 3,4-dimethoxyphenol (19.05 g, 124 mmol, 68%) as an amber solid (m.p. 58-60 °C).
$R_f = 0.43$ (silica gel, 1:1 hexanes:EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.71 (d, $J = 8.4$ Hz, 1H), 6.46 (d, $J = 2.7$ Hz, 1H), 6.35 (dd, $J = 8.4$, 2.7 Hz, 1H), 5.93 (bs, 1H), 3.79 (s, 3H), 3.76 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.2, 149.7, 142.8, 112.5, 105.9, 100.6, 56.5, 55.6; IR (film, $\nu$ cm$^{-1}$): 3382, 1513, 1223; HRMS (EC-CI) calc. for C$_8$H$_{11}$O$_3$ [M+H]$^+$: 155.0708, obs. 155.0700.

1-(2-hydroxy-4,5-dimethoxyphenyl)ethan-1-one (27)

To a stirred solution of 3,4-dimethoxyphenol (3.0 g, 19.5 mmol, 1 equiv.) in acetic anhydride (9.75 mL, 103 mmol, 5.3 equiv.) at 0 °C was added neat boron trifluoride diethyl etherate (4.8 mL, 38.9 mmol, 2 equiv.). The reaction mixture was stirred at 90 °C for 1 hour and then allowed to sit at 23 °C for 16 hours. The precipitate was collected and recrystallized from EtOH to give pure hydroxyacetophenone (27) (3.38 g, 17.7 mmol, 89%) as white needles (m.p. 104-105 °C).

$R_f = 0.58$ (silica gel, 1:1 hexanes:EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 12.65 (s, 1H), 7.05 (s, 1H), 6.46 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.56 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 202.0, 160.0, 156.7, 141.8, 111.6, 111.5, 100.5, 56.6, 56.1, 26.3; IR (film, $\nu$ cm$^{-1}$): 1632, 1511, 1265, 1160, 1063; HRMS (EC-CI) calc. for C$_{10}$H$_{13}$O$_4$ [M+H]$^+$: 197.0814, obs. 197.0810.

3-iodo-6,7-bis(methoxymethoxy)-4H-chromen-4-one (28)

Following the general procedure for methoxymethyl ether protection, catechol was transformed into iodochromone (28). In this case, 3.0 equivalents of N,N-diisopropylethylamine and 3.0 equivalents of methoxymethyl chloride were used. The crude material was purified via silica gel column chromatography (2:1 hexanes:EtOAc) to give pure methoxymethyl ether (28) (417 mg, 1.06 mmol, 71%) as a white solid (m.p. 105-106 °C).

$R_f = 0.29$ (silica gel, 2:1 hexanes:EtOAc); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.19 (s, 1H), 7.79 (s, 1H), 7.17 (s, 1H), 5.31 (s, 2H), 5.27 (s, 2H), 3.50 (s, 3H), 3.48 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.2, 157.0, 152.7, 152.4, 145.5, 116.0, 110.8, 103.5, 95.4, 95.1, 86.3, 56.5, 56.3; IR (film, $\nu$ cm$^{-1}$): 1617, 1453, 1284, 1152, 1041; HRMS (ESI) calc. for C$_{13}$H$_{13}$INO$_6$ [M+Na]$^+$: 414.96490, obs. 414.96555.

General Procedure for Enaminone Formation

To a stirred solution of hydroxyacetophenone (1.0 equiv.) in dimethoxymethane (0.5 M) at 85 °C was added N,N-dimethylformamide dimethyl acetal (3.0 equiv.). After 4 hours, the reaction mixture was cooled to 23 °C and then concentrated in vacuo to give crude enaminone of sufficient purity for subsequent reactions.
tert-buty 1(3-((dimethylamino)acryloyl)-3-hydroxy-5-(methoxymethoxy)-6-(pivaloyloxy)benzoate (15)

Following the general procedure for enaminone formation, acetophenone (14) was transformed into enaminone (15) (yield taken after subsequent step), an orange solid (m.p. 118-119°C) of sufficient purity for subsequent reactions.

R_f = 0.26 (silica gel, 1:1 hexanes:EtOAc); _1H NMR (400 MHz, CDCl_3): δ 12.43 (bs, 1H), 7.77 (d, J = 12 Hz, 1H), 6.70 (s, 1H), 5.49 (d, J = 12 Hz, 1H), 5.13 (s, 2H), 3.41 (s, 3H), 3.15 (s, 3H), 2.84 (s, 3H), 1.47 (s, 9H), 1.34 (s, 9H); _13C NMR (100 MHz, CDCl_3): δ 189.4, 175.8, 165.6, 159.3, 154.4, 151.6, 130.1, 128.5, 113.7, 104.0, 95.2, 94.0, 82.4, 56.0, 45.1, 38.7, 37.1, 27.6, 27.0; IR (film, ν cm⁻¹): 1751, 1716, 1632, 1111; HRMS (ESI) calc. for C_{23}H_{33}NNaO_8 [M+Na]⁺: 474.20984, obs. 474.21058.

(E)-3-((dimethylamino)-1-(2-hydroxy-4,5-(methoxymethoxy)prop-2-en-1-one

Following the general procedure for enaminone formation, acetophenone (27) was transformed into enaminone (yield taken after subsequent step), a yellow solid (m.p. 157-158°C) of sufficient purity for subsequent reactions.

R_f = 0.18 (silica gel, 1:1 hexanes:EtOAc); _1H NMR (600 MHz, CDCl_3): δ 14.25 (bs, 1H), 7.84 (d, J = 12 Hz, 1H), 7.10 (s, 1H), 6.44 (s, 1H), 5.60 (d, J = 12 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.16 (bs, 3H), 2.96 (bs, 3H); _13C NMR (150 MHz, CDCl_3): δ 190.3, 160.1, 155.0, 154.1, 141.2, 111.7, 111.1, 100.8, 89.7, 57.1, 55.9, 45.3, 37.3; IR (film, ν cm⁻¹): 1630, 1543, 1376, 1228, 1113; HRMS (ESI) calc. for C_{13}H_{18}NO_4 [M+H]⁺: 252.12303, obs. 252.12258.

(E)-3-((dimethylamino)-1-(2-hydroxy-4-(methoxymethoxy)phenyl)prop-2-en-1-one

Following the general procedure for enaminone formation, acetophenone (24) was transformed into enaminone (yield taken after subsequent step), a yellow solid (m.p. 95-96°C) of sufficient purity for subsequent reactions.

R_f = 0.25 (silica gel, 1:1 hexanes:EtOAc); _1H NMR (400 MHz, CDCl_3): δ 7.85 (d, J = 12 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.4 Hz, 1H), 5.69 (d, J = 12 Hz, 1H), 5.19 (s, 2H), 3.47 (s, 3H), 3.18 (bs, 3H), 2.96 (bs, 3H); _13C NMR (100 MHz, CDCl_3): δ 190.4, 165.0, 161.6, 154.1, 129.6, 114.8, 106.9, 103.8, 93.9, 89.6, 56.1, 45.2, 37.2; IR (film, ν cm⁻¹): 1627, 1535, 1235, 1108; HRMS (ESI) calc. for C_{13}H_{17}NO_4 [M+Na]⁺: 274.10498, obs. 274.10491.

General Procedure for Iodochromone Formation
To a stirred solution of crude enaminone (1.0 equiv.) in CHCl₃ (0.1 M) at 23 °C was added solid iodine (2.0 equiv.). After 1 hour, the reaction mixture was diluted with sat. aq. Na₂S₂O₃ and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give crude enaminone. The crude material was purified via silica gel column chromatography to give pure iodochromone.

**tert-butyl 3-iodo-7-(methoxymethoxy)-4-oxo-6-(pivaloyloxy)-4H-chromene-5-carboxylate (18)**

Following the general procedure for iodochromone formation, enaminone (15) was transformed into iodochromone (18). The crude material was purified via silica gel column chromatography (1:1 hexanes:EtOAc) to give pure iodochromone (18) (9.65 g, 18.1 mmol, 60% over 2-steps) as a white solid (m.p. 189-190 °C).

Rᵣ = 0.32 (silica gel, 3:1 hexanes:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.19 (s, 1H), 7.17 (s, 1H), 5.23, (s, 2H), 3.25 (s, 3H), 1.64 (s, 9H), 1.37 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 175.4, 170.9, 163.2, 156.8, 154.9, 153.3, 136.5, 128.3, 112.8, 103.5, 94.7, 86.7, 83.3, 56.6, 39.2, 28.2, 27.2; IR (film, υ cm⁻¹): 1764, 1731, 1650; HRMS (ESI) calc. for C₂₁H₂₅INaO₈ [M+Na]⁺: 555.04863, obs. 555.04881.

**3-iodo-6,7-dimethoxy-4H-chromen-4-one**

Following the general procedure for iodochromone formation, enaminone ((E)-3-(dimethylamino)-1-(2-hydroxy-4,5-(dimethoxyphenyl)prop-2-en-1-one) was transformed into the iodochromone. The crude material was purified via silica gel column chromatography (2:1 hexanes:EtOAc) to give pure iodochromone (7.01 g, 21.1 mmol, 35% over 2-steps) as a white solid (m.p. 170-172 °C).

Rᵣ = 0.32 (silica gel, 2:1 hexanes:EtOAc); ¹H NMR (400 MHz, CDCl₃): δ 8.24 (s, 1H), 7.55 (s, 1H), 6.86 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 172.2, 156.7, 154.5, 152.1, 147.9, 115.0, 104.8, 99.3, 86.4, 56.4, 56.3; IR (film, υ cm⁻¹): 1615, 1505, 1471, 1289, 1226; HRMS (ESI) calc. for C₁₁H₉INaO₄ [M+Na]⁺: 354.94377, obs. 354.94418.

**6,7-dihydroxy-3-iodo-4H-chromen-4-one**

To a stirred solution of iodochromone (3-iodo-6,7-dimethoxy-4H-chromen-4-one) (500 mg, 1.51 mmol, 1.0 equiv.) in CH₂Cl₂ (15.1 mL, 0.1 M) at 0 °C was slowly added neat boron tribromide (0.86 mL, 9.03 mmol, 6.0 equiv.). The reaction mixture was stirred at 23 °C for 1.5 hours. The reaction mixture was then carefully quenched with 1.25 M methanolic HCl (1.2 mL, 2.08 mmol, 1.0 equiv.) at 0 °C and stirred for 5 minutes. The reaction mixture was purged with
N₂ and concentrated \textit{in vacuo} to give the iodochromone (458 mg, 1.51 mmol, 99/) as a grey solid (m.p. 215 °C (decomp.)) of sufficient purity for subsequent reactions.

\( \text{R}_f = 0.72 \) (silica gel, 20:1 EtOAc:AcOH); \(^1\text{H NMR} \) (400 MHz, CD₃OD): \( \delta \) 8.49 (s, 1H), 7.40 (s, 1H), 6.89 (s, 1H); \(^{13}\text{C NMR} \) (100 MHz, CD₃OD): \( \delta \) 174.8, 159.6, 154.5, 153.4, 146.6, 115.6, 108.9, 103.5, 85.4; \( \text{IR} \) (KBr, \( \nu \text{ cm}^{-1} \)): 3218, 1616, 1471, 1308; \( \text{HRMS} \) (EC-Cl) calc. for C₉H₆O₄ \[M+H\]⁺: 304.9311, obs. 304.9308.

\textbf{3-iodo-7-(methoxymethoxy)-4H-chromen-4-one (25)}

Following the general procedure for iodochromone formation, enaminone ((\(E\))-3-(dimethylamino)-1-(2-hydroxy-4-(methoxymethoxy)phenyl)prop-2-en-1-one) was transformed into iodochromone (25). The crude material was purified via silica gel column chromatography (3:1 hexanes:EtOAc) to give pure iodochromone (25) (11.69 g, 35.2 mmol, 78% over 2-steps) as a white solid (m.p. 101-102 °C).

\( \text{R}_f = 0.28 \) (silica gel, 5:1 hexanes:EtOAc); \(^1\text{H NMR} \) (400 MHz, CDCl₃): \( \delta \) 8.23 (s, 1H), 8.17 (d, \( J = 8.6 \) Hz, 1H), 7.10 (dd, \( J = 8.9, 2.4 \) Hz, 1H), 7.08 (d, \( J = 2.1 \) Hz, 1H), 5.27 (s, 2H), 3.50 (s, 3H); \(^{13}\text{C NMR} \) (100 MHz, CDCl₃): \( \delta \) 172.4, 161.6, 157.4, 157.2, 127.8, 116.2, 116.1, 102.8, 94.2, 86.9, 56.4; \( \text{IR} \) (film, \( \nu \text{ cm}^{-1} \)): 1646, 1624, 1149; \( \text{HRMS} \) (ESI) calc. for C₁₁H₉NaO₄ \[M+Na\]^⁺: 354.94377, obs. 354.94436.

\textbf{General Procedure for Propargyl Alcohol Formation}

To a stirred solution of iodochromone (1.0 equiv.), bis(triphenylphosphine) palladium (II) dichloride (0.02 equiv.) and copper (I) iodide (0.1 equiv.) in freeze pump thawed THF (0.1 M) at 23 °C was added 3-butyn-2-ol (11) (4.0 equiv.). Diisopropylamine (3.0 equiv.) was then added. After 1 hour, the reaction mixture was diluted with pH = 7.0 phosphate buffer and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated \textit{in vacuo} to give crude propargyl alcohol. The crude material was purified via silica gel column chromatography to give pure propargyl alcohol.

\( \text{R}_f = 0.21 \) (silica gel, 1:1 hexanes:EtOAc); \(^1\text{H NMR} \) (400 MHz, CDCl₃): \( \delta \) 8.03 (s, 1H), 7.14 (s, 1H), 5.21 (s, 2H), 4.75 (q, \( J = 6.7 \) Hz, 1H), 3.43 (s, 3H), 3.20 (bs, 1H), 1.63 (s, 9H), 1.51 (d, \( J = 6.7 \) Hz, 3H); \(^{13}\text{C NMR} \) (100 MHz, CDCl₃): \( \delta \) 175.5, 173.3, 163.3, 157.5, 154.6, 153.2, 136.3.
128.1, 114.5, 110.5, 103.8, 97.5, 94.6, 83.2, 73.8, 58.6, 56.6, 39.2, 28.2, 27.2, 23.8; IR (film, \( \nu \) cm\(^{-1} \): 3435, 1763, 1735, 1731, 1461; HRMS (ESI) calc. for \( \text{C}_{25}\text{H}_{30}\text{NaO}_9 \) [M+Na]\(^+\): 497.1782, obs. 497.1785.

3-(3-hydroxybut-1-yn-1-yl)-6,7-bis(methoxymethoxy)-4H-chromen-4-one

Following the general procedure for propargyl alcohol formation, iodochromone (28) was transformed into propargyl alcohol. The crude material was purified via silica gel column chromatography (1:1 to 1:2 hexanes:EtOAc) to give pure propargyl alcohol (970 mg, 2.90 mmol, 81%) as an amber oil.

\[ R_f = 0.12 \text{ (silica gel, 1:1 hexanes:EtOAc); } \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta 8.06 \text{ (s, 1H), 7.82 \text{ (s, 1H), 7.20 \text{ (s, 1H), 5.33 \text{ (s, 2H), 5.30 \text{ (s, 2H), 4.79 \text{ (q, } J = 6.7 \text{ Hz, 1H), 3.52 \text{ (s, 3H), 3.51 \text{ (s, 3H), } 3.30 \text{ (bs, 1H), 1.54 \text{ (d, } J = 6.7 \text{ Hz, 3H); } 13C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta 174.7, 157.6, 152.7, 152.3, 145.5, 117.8, 110.4, 109.9, 103.9, 97.2, 95.5, 95.1, 74.2, 58.6, 56.6, 56.5, 24.0; IR (film, } \nu \text{ cm}^{-1}\text{): 3397, 1621, 1494, 1460, 1266, 1227, 986; HRMS (ESI) calc. for } \text{C}_{17}\text{H}_{18}\text{NaO}_7 \text{ [M+Na]}^+\text{: 357.09447, obs. 357.09487.} \]

3-(3-hydroxybut-1-yn-1-yl)-7-(methoxymethoxy)-4H-chromen-4-one

Following the general procedure for propargyl alcohol formation, iodochromone (25) was transformed into propargyl alcohol. The crude material was purified via silica gel column chromatography (1:1 hexanes:EtOAc) to give pure propargyl alcohol (696 mg, 2.54 mmol, 84%) as an amber oil.

\[ R_f = 0.28 \text{ (silica gel, 1:1 hexanes:EtOAc); } \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta 8.16 \text{ (dd, } J = 7.9, 1.0 \text{ Hz, 1H), 8.09 \text{ (s, 1H), 7.10 \text{ (d, } J = 2.4 \text{ Hz, 1H), 7.09 \text{ (d, } J = 1.0 \text{ Hz, 1H), 5.27 \text{ (s, 2H), 4.79 \text{ (q, } J = 6.8 \text{ Hz, 1H), 3.50 \text{ (s, 3H), 2.43 \text{ (bs, 1H), 1.56 \text{ (d, } J = 6.8 \text{ Hz, 3H); } 13C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta 175.0, 161.7, 157.8, 157.3, 127.5, 117.8, 115.9, 110.6, 103.1, 97.6, 94.3, 73.9, 58.4, 56.4, 23.9; IR (film, } \nu \text{ cm}^{-1}\text{): 3392, 1624, 1249, 1077; HRMS (ESI) calc. for } \text{C}_{15}\text{H}_{14}\text{NaO}_5 \text{ [M+Na]}^+\text{: 297.07334, obs. 297.07349.} \]

**General Procedure for Ynone Formation**

To a stirred solution of propargyl alcohol (1.0 equiv.) and activated 4.0 Å molecular sieves (50% by weight) in CH\(_2\)Cl\(_2\) (0.1 M) at 23 °C was added solid pyridinium dichromate (5.0 equiv.). After 5 hours, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo to give crude ynone. The crude material was purified via silica gel column chromatography to give pure ynone.
**tert-butyl 7-(methoxymethoxy)-4-oxo-3-(3-oxobut-1-yn-1-yl)-6-(pivaloyl oxy)-4H-chromene-5-carboxylate (19)**

Following the general procedure for ynone formation, propargyl alcohol (**tert-butyl 3-(3-hydroxybut-1-yn-1-yl)-7-(methoxymethoxy)-4-oxo-6-(pivaloyl oxy)-4H-chromene-5-carboxylate**) was transformed into ynone (19). The crude material was purified via silica gel column chromatography (1:1 hexanes:EtOAc) to give pure ynone (19) (2.79 g, 5.90 mmol, 56%) as a white solid (m.p. 182-183 °C).

**Rf** = 0.41 (silica gel, 1:1 hexanes:EtOAc); **1H NMR** (400 MHz, CDCl3): δ 8.20 (s, 1H), 7.21 (s, 1H), 5.24 (s, 2H), 3.44 (s, 3H), 2.46 (s, 3H), 1.64 (s, 9H), 1.37 (s, 9H); **13C NMR** (100 MHz, CDCl3): δ 184.2, 175.4, 172.1, 163.1, 160.4, 154.6, 153.7, 136.8, 128.3, 114.6, 108.7, 104.0, 94.7, 93.5, 83.5, 56.7, 39.2, 32.7, 27.2; **IR** (film, υ cm⁻¹): 1762, 1734, 1672, 1620, 1459, 1264, 1246, 1155, 1091; **HRMS** (ESI) calc. for C₂₅H₂₈NaO₹ [M+Na]^+: 495.1626, obs. 495.1632.

**6,7-bis(methoxymethoxy)-3-(3-oxobut-1-yn-1-yl)-4H-chromen-4-one (21)**

Following the general procedure for ynone formation, propargyl alcohol (**3-(3-hydroxybut-1-yn-1-yl)-6,7-bis(methoxymethoxy)-4H-chromen-4-one**) was transformed into ynone (21). The crude material was purified via silica gel column chromatography (5:2:1 CH₂Cl₂:EtOAc:hexanes) to give pure ynone (21) (540 mg, 1.63 mmol, 56%) as a white solid (m.p. 119-120 °C).

**Rf** = 0.51 (silica gel, 5:2:1 CH₂Cl₂:EtOAc:hexanes); **1H NMR** (400 MHz, CDCl3): δ 8.23 (s, 1H), 7.86 (s, 1H), 7.26 (s, 1H), 5.35 (s, 2H), 5.32 (s, 2H), 3.54 (s, 3H), 3.53 (s, 3H), 2.49 (s, 3H); **13C NMR** (100 MHz, CDCl3): δ 184.3, 173.5, 160.7, 153.0, 152.2, 146.0, 117.8, 110.4, 108.1, 104.1, 95.5, 95.2, 93.4, 81.8, 56.7, 56.5, 32.7; **IR** (film, υ cm⁻¹): 1668, 1640, 1615, 1271, 970; **HRMS** (ESI) calc. for C₁₇H₁₇O₇ [M+H]^+: 333.09688, obs. 333.09704.

**7-(methoxymethoxy)-3-(3-oxobut-1-yn-1-yl)-4H-chromen-4-one (22)**

Following the general procedure for ynone formation, propargyl alcohol (**3-(3-hydroxybut-1-yn-1-yl)-7-(methoxymethoxy)-4H-chromen-4-one**) was transformed into ynone (22). The crude material was purified via silica gel column chromatography (3:1 to 2:1 hexanes:EtOAc) to give pure ynone (22) (410 mg, 1.51 mmol, 64%) as a white solid (m.p. 139-141 °C).

**Rf** = 0.65 (silica gel, 1:1 hexanes:EtOAc); **1H NMR** (400 MHz, CDCl3): δ 8.24 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 7.13 (dd, J = 8.6, 2.4 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 5.28 (s, 2H), 3.50 (s, 3H),
2.49 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 183.9, 173.5, 162.0, 160.9, 157.1, 127.3, 117.6, 116.3, 108.3, 103.3, 94.2, 93.2, 81.4, 56.3, 32.5; IR (film, $\nu$ cm$^{-1}$): 1669, 1632, 1255, 1158; HRMS (ESI) calc. for C$_{15}$H$_{12}$NaO$_5$ [M+Na]$^+$: 295.05769, obs. 295.05778.

**tert-butyl 3-formyl-7-(methoxymethoxy)-4-oxo-2-(2-oxopropyl)-6-(pivaloyloxy)-4H-chromene-5-carboxylate (20)**

To a stirred solution of ynone (19) (100 mg, 0.212 mmol, 1.0 equiv.) and H$_2$O (3.81 mL, 212 mmol, 1000 equiv.) in MeCN (21.2 mL, 0.01 M) at 23 °C was added triethylamine (0.3 mL, 2.12 mmol, 10 equiv.). After 1 hour, the reaction mixture was diluted with EtOAc (20 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to give aldehyde (20) (104 mg, 0.212 mmol, 99%) as an amber solid (m.p. 178-179 °C (decomp.)) of sufficient purity for subsequent reactions.

$R_f$ = 0.23 (silica gel, 1:1 hexanes:EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) δ 10.42 (s, 1H), 7.20 (s, 1H), 5.23 (s, 2H), 4.26 (bs, 2H), 3.45 (s, 3H), 2.38 (s, 3H), 1.64 (s, 9H), 1.39 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 200.0, 190.7, 175.4, 175.0, 168.5, 163.3, 154.5, 153.9, 136.7, 128.2, 117.4, 115.5, 104.1, 94.8, 83.4, 56.6, 47.5, 39.2, 30.4, 28.2, 27.2; IR (film, $\nu$ cm$^{-1}$) 3420, 1762, 1730, 1653, 1595, 1458, 1265, 1157, 1095; HRMS (ESI) calc. for C$_{25}$H$_{30}$NaO$_{10}$ [M+Na]$^+$: 513.17312, obs. 513.17312.

**General Procedure A for Ynone Dimerization**

To a stirred solution of ynone (1.0 equiv.) (intended left side of protected vinaxanthone) and H$_2$O (1000 equiv.) in MeCN (0.01 M) at 23 °C was added triethylamine (1.0 equiv.). After 1 hour, the reaction mixture was diluted with EtOAc, dried over Na$_2$SO$_4$ and concentrated in vacuo to give an amber oil. The crude aldehyde was diluted to 0.1 M with MeCN before ynone (1.0 equiv.) (intended right side of protected vinaxanthone) and triethylamine (2 equiv.) were added. The reaction mixture was stirred at 23 °C for 16 hours. The reaction mixture was then concentrated to give crude protected vinaxanthone. The crude material was purified via silica gel column chromatography to give pure protected vinaxanthone.

**General Procedure B for Ynone Dimerization**

To a stirred solution of ynone (1.0 equiv.) in MeCN (0.1 M) at 23 °C was added a 1.0 M solution of H$_2$O in MeCN (0.5 equiv.) and triethylamine (10 equiv.). After 16 hours, the reaction mixture was concentrated in vacuo to give crude protected vinaxanthone. The crude material was purified via silica gel column chromatography to give pure protected vinaxanthone.

**tert-butyl 5,7-diacyethyl-6-(5-(tert-butoxycarbonyl)-7-(methoxymethoxy)-4-oxo-6-(pivaloyloxy)-4H-chromen-3-yl)-3-(methoxymethoxy)-9-oxo-2-(pivaloyloxy)-9H-xanthene-1-carboxylate**

![Diagram of tert-butyl 5,7-diacyethyl-6-(5-(tert-butoxycarbonyl)-7-(methoxymethoxy)-4-oxo-6-(pivaloyloxy)-4H-chromen-3-yl)-3-(methoxymethoxy)-9-oxo-2-(pivaloyloxy)-9H-xanthene-1-carboxylate]
Following general procedure B for ynone dimerization, ynone (19) was transformed into the protected vinaxanthone. The crude material was purified via silica gel column chromatography (5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes) to give pure protected vinaxanthone (85 mg, 0.090 mmol, 87%) as a white-tan solid (m.p. 224–225 °C).

R$_f$ = 0.68 (silica gel, 5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.62 (bs, 1H), 7.84 (bs, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 5.27 (s, 2H), 5.26 (s, 2H), 3.47 (s, 3H), 3.46 (s, 3H), 2.65 (bs, 3H), 2.41 (bs, 3H), 1.68 (s, 9H), 1.58 (s, 9H), 1.39 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.3, 198.8, 175.4 (2 signals), 173.3 (2 signals), 163.4, 163.3, 155.1, 154.6, 154.5, 154.0, 153.6, 152.6, 152.3, 151.8, 151.4, 151.0, 150.5, 145.1, 136.4, 134.1, 131.8, 128.2, 126.9, 121.4, 120.6, 115.8, 115.1, 111.4, 110.5, 103.9, 103.8, 95.7, 95.2, 94.7, 82.8, 56.7, 56.6, 56.5, 39.2, 32.5, 29.6, 28.1, 28.0, 27.2, 27.1; IR (film, $\nu$ cm$^{-1}$) 1763, 1735 1460, 1264, 1157; HRMS (ESI) calc. for C$_{50}$H$_{56}$NaO$_{18}$ [M+Na]$^+$: 967.33589, obs. 967.33632.

tert-butyl 5,7-diacyl-6-(6,7-bis(methoxymethoxy)-4-oxo-4H-chromen-3-yl)-9-oxo-2-(pivaloyloxy)-9H-xanthene-1-carboxylate (X)

Following general procedure A for ynone dimerization, ynone (19) and ynone (21) were transformed into the protected vinaxanthone. The crude material was purified via silica gel column chromatography (5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes) to give pure protected vinaxanthone (37 mg, 0.046 mmol, 23%) as a yellow solid (m.p. 116–118 °C). A side-product protected vinaxanthone (ynone (19) homodimer) (31 mg, 0.047 mmol, 46% with respect to ynone (19)) and another side-product protected vinaxanthone (ynone (21) homodimer) (23 mg, 0.024 mmol, 24% with respect to ynone (21)) were also isolated.

R$_f$ = 0.51 (silica gel, 5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.67 (bs, 1H), 7.98 (s, 1H), 7.84 (bs, 1H), 7.26 (s, 1H), 7.22 (s, 1H), 5.39 (s, 2H), 5.35 (s, 2H), 5.26 (s, 2H), 3.57 (s, 3H), 3.56 (s, 3H), 3.47 (s, 3H), 2.67 (bs, 3H), 2.42 (bs, 3H), 1.58 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.8, 199.0, 175.5, 174.5, 173.5, 163.4, 155.2, 154.2, 153.9, 153.6, 153.1, 152.3, 145.1, 136.4, 134.1, 131.8, 128.2, 126.9, 121.4, 120.6, 115.8, 115.1, 111.4, 110.5, 103.9, 103.8, 95.7, 95.2, 94.7, 82.8, 56.7, 56.6, 56.5, 39.2, 32.5, 28.9, 28.2, 27.3; IR (film, $\nu$ cm$^{-1}$) 1654, 1459, 1268, 1156, 1092; HRMS (ESI) calc. for C$_{42}$H$_{44}$NaO$_{16}$ [M+Na]$^+$: 827.25220, obs. 827.25320.

**tert-butyl 5,7-diacyl-3-(methoxymethoxy)-6-(7-(methoxymethoxy)-4-oxo-4H-chromen-3-yl)-9-oxo-2-(pivaloyloxy)-9H-xanthene-1-carboxylate**

Following general procedure A for ynone dimerization, ynone (19) and ynone (22) were transformed into the protected vinaxanthone. The crude material was purified via silica gel column chromatography (5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes) to give pure protected vinaxanthone (86...
mg, 0.115 mmol, 56%) as a pale off-white solid (m.p. 138-139 °C). A side-product protected vinaxanthone (ynone (19) homodimer) (22 mg, 0.040 mmol, 39 % with respect to ynone (19)) and another side-product protected vinaxanthone (ynone (22) homodimer) (10 mg, 10 µmol, 10% with respect to ynone (22)) were also isolated.

\[ R_f = 0.65 \] (silica gel, 5:2:1 CH₂Cl₂:EtOAc:hexanes); \[^1^H\text{NMR} \text{ (500 MHz, CDCl}_3\text{)} \delta 8.64 \text{ (bs, 1H), 8.24 (d, } J = 8.8 \text{ Hz, 1H), 7.84 (bs, 1H), 7.09 (d, } J = 2.3 \text{ Hz, 1H), 7.06 (dd, } J = 8.8, 2.3 \text{ Hz, 1H), 5.28 (s, 2H), 5.24 (s, 2H), 3.50 (s, 3H), 3.45 (s, 3H), 2.65 (bs, 3H), 2.41 (bs, 3H), 1.56 (s, 9H), 1.36 (s, 9H); } \[^{13}C\text{NMR} \text{ (125 MHz, CDCl}_3\text{)} \delta 201.6, 198.8, 175.4, 174.7, 173.4, 163.3, 163.1, 157.3, 155.1, 153.9, 153.5, 153.1, 136.4, 136.0, 134.1, 132.1, 128.4, 128.1, 126.9, 121.3, 121.0, 116.2, 115.3, 115.0, 103.9, 103.1, 94.7, 94.4, 82.7, 56.5 (2 signals), 39.1, 32.4, 28.8, 28.1, 27.2; } \text{IR (film, } \nu \text{ cm}^{-1} \text{) 1620, 1460, 1262, 1158, 1096; } \text{HRMS (ESI) calc. for C}_{40}H_{40}NaO_{14} [M+Na]^+: 767.23103, obs. 767.23148.]

Following general procedure A for ynone dimerization, ynone (21) and ynone (19) were transformed into the protected vinaxanthone. The crude material was purified via silica gel column chromatography (5:2:1 CH₂Cl₂:EtOAc:hexanes) to give pure protected vinaxanthone (107 mg, 0.140 mmol, 55%) as a yellow solid (m.p. 152-154 °C). A side-product protected vinaxanthone (ynone (19) homodimer) (29 mg, 0.031 mmol, 24% with respect to ynone (19)) was also isolated.

\[ R_f = 0.49 \] (silica gel, 5:2:1 CH₂Cl₂:EtOAc:hexanes); \[^1^H\text{NMR} \text{ (400 MHz, CDCl}_3\text{)} \delta 8.68 \text{ (s, 1H), 7.83 (s, 1H), 7.82 (s, 1H), 7.26 (s, 1H), 7.19 (s, 1H), 5.37 (s, 2H), 5.31 (q, } J = 4.5 \text{ Hz, 2H*}, 5.27 (q, } J = 3.4 \text{ Hz, 2H*}, 3.54 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 2.64 (s, 3H), 2.45 (s, 3H), 1.69 (s, 9H), 1.39 (s, 9H); } \[^{13}C\text{NMR} \text{ (150 MHz, CDCl}_3\text{)} \delta 201.3, 199.3, 175.5, 174.6, 173.4, 163.5, 154.7, 154.6, 153.9, 153.8, 153.1, 136.4, 136.0, 134.1, 132.1, 128.4, 128.1, 126.9, 121.3, 121.0, 116.2, 115.3, 115.0, 103.9, 103.1, 94.7, 94.4, 82.7, 56.5 (2 signals), 39.1, 32.4, 28.9, 28.2, 27.2; } \text{IR (film, } \nu \text{ cm}^{-1} \text{) 1458, 1155, 1090; } \text{HRMS (ESI) calc. for C}_{42}H_{44}NaO_{16} [M+Na]^+: 827.25220, obs. 827.25350.}

*Non-equivalent methylene protons.

Following general procedure B for ynone dimerization, ynone (21) was transformed into the protected vinaxanthone. The crude material was purified via silica gel column...
chromatography (5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes) to give pure protected vinaxanthone (52 mg, 0.078 mmol, 52%) as a yellow solid (m.p. 144-146 °C).

$R_f = 0.24$ (silica gel, 5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.72 (s, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 7.26 (s, 1H), 7.23 (s, 1H), 5.38 (d, $J = 1.0$ Hz, 2H)*, 5.36 (d, $J = 5.1$ Hz, 2H)*, 3.52 (s, 3H), 3.50 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.6, 199.2, 174.7, 174.5, 154.2, 153.8, 153.1, 152.9 (2 signals), 152.3, 145.6, 145.1, 135.8, 134.1, 132.8, 127.4, 121.2, 120.6, 118.1, 115.8, 110.6, 104.1, 103.8, 95.7, 95.6, 95.2, 95.1, 56.5, 56.3 (3 signals), 32.4, 28.9; IR (film, $\nu$ cm$^{-1}$) 1618, 1497, 1458, 1269, 1154; HRMS (ESI) calc. for C$_{34}$H$_{32}$NaO$_{14}$ [M+Na]$^+$: 687.16840, obs. 687.16970.

*Non-equivalent methylene protons.

Following general procedure A for ynone dimerization, ynone (21) and ynone (22) were transformed into the protected vinaxanthone. The crude material was purified via silica gel column chromatography (5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes) to give pure protected vinaxanthone (71 mg, 0.117 mmol, 46%) as a yellow solid (m.p. 210-212 °C). A side-product protected vinaxanthone (ynone (21) homodimer) (19 mg, 0.035 mmol, 27% with respect to ynone (21)) was also isolated.

$R_f = 0.35$ (silica gel, 5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.72 (s, 1H), 8.28 (d, $J = 8.9$ Hz, 1H), 7.82 (s, 1H), 7.81 (s, 1H), 7.11 (s, 1H), 7.08 (d, $J = 1.7$ Hz, 1H), 5.37 (s, 2H), 5.31 (d, $J = 4.5$ Hz, 2H)*, 3.54 (s, 3H), 3.53 (s, 3H), 3.52 (s, 3H), 2.65 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.5, 199.2, 174.8, 174.6, 163.2, 157.4, 153.9, 153.3, 152.9 (2 signals), 145.6, 136.0, 134.1, 133.1, 128.5, 127.4, 121.1 (2 signals), 118.2, 116.3, 115.3, 110.6, 104.1, 103.2, 95.6, 95.1, 94.4, 56.5, 56.3 (3 signals), 32.4, 28.9; IR (film, $\nu$ cm$^{-1}$) 1642, 1621, 1456, 1269, 1154; HRMS (ESI) calc. for C$_{32}$H$_{28}$NaO$_{12}$ [M+Na]$^+$: 627.14730, obs. 627.14770.

*Non-equivalent methylene protons.

Following general procedure A for ynone dimerization, ynone (22) and ynone (19) were transformed into the protected vinaxanthone. The crude material was purified via silica gel column chromatography (5:2:1 CH$_2$Cl$_2$:EtOAc:hexanes) to give pure protected vinaxanthone (117 mg, 0.157 mmol, 46%) as a pale yellow solid (m.p. 148-149 °C). A side-product protected...
vinaxanthone (ynone (19) homodimer) (72 mg, 0.076 mmol, 44% with respect to ynone (19))
and another side-product protected vinaxanthone (ynone (22) homodimer) (23 mg, 0.042 mmol, 25% with respect to ynone (22)) were also isolated.

RF = 0.51 (silica gel, 5:2:1 CH2Cl2:EtOAc:hexanes); 1H NMR (400 MHz, CDCl3) δ 8.68 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.82 (s, 1H), 7.19 (s, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.08 (dd, J = 8.7, 2.4 Hz, 1H), 5.29 (s, 2H), 5.27 (d, J = 3.8 Hz, 2H)*, 3.51 (s, 3H), 3.47 (s, 3H), 2.64 (s, 3H), 2.45 (s, 3H), 1.69 (s, 9H), 1.39 (s, 9H); 13C NMR (125 MHz, CDCl3) δ 201.2, 199.1, 175.5, 174.9, 173.3, 163.5, 161.9, 157.9, 154.7, 154.6, 154.1, 152.7, 136.3, 135.9, 133.9, 133.1, 129.0, 127.7, 127.4, 121.6, 120.7, 118.3, 115.9, 112.7, 103.7, 103.4, 94.8, 94.3, 83.3, 56.4, 39.2, 32.4, 28.9, 28.2, 27.3; IR (film, µ cm⁻¹) 1615, 1463, 1252, 1156, 1091; HRMS (ESI) calc. for C₄₀H₄₀O₁₄ [M+Na]⁺: 767.23103, obs. 767.23034.

*Non-equivalent methylene protons.

Following general procedure A for ynone dimerization, ynones (21) and (22) were transformed into the protected vinaxanthone. The crude material was purified via silica gel column chromatography (5:2:1 CH2Cl2:EtOAc:hexanes) to give pure protected vinaxanthone (94 mg, 0.155 mmol, 45%) as a yellow solid (m.p. 84–85 °C). A side-product protected vinaxanthone (ynone (21) homodimer) (3 mg, 5.15 µmol, 52% with respect to ynone (21)) and protected vinaxanthone (ynone (22) homodimer) (24 mg, 0.044 mmol, 3% with respect to ynone (22)) were also isolated.

RF = 0.33 (silica gel, 5:2:1 CH2Cl2:EtOAc:hexanes); 1H NMR (400 MHz, CDCl3) δ 8.73 (s, 1H), 8.13 (d, J = 8.9 Hz, 1H), 7.99 (s, 1H), 7.81 (s, 1H), 7.23 (s, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.08 (dd, J = 8.9, 2.4 Hz, 1H), 5.38 (s, 2H), 5.35 (s, 2H), 5.28 (s, 2H), 3.56 (s, 3H), 3.57 (s, 3H), 3.51 (s, 3H), 2.66 (s, 3H), 2.46 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 201.6, 199.1, 175.1, 174.5, 161.9, 158.0, 154.2, 154.0, 153.2, 146.1, 145.1, 135.8, 134.1, 132.6, 127.8, 127.4, 121.7, 120.6, 118.4, 115.9 (2 signals), 111.4, 103.8, 103.4, 95.7, 95.2, 94.3, 89.4, 56.7, 56.4, 39.2, 32.4, 28.9, 28.2, 27.3; IR (film, µ cm⁻¹) 1619, 1440, 1270, 1254, 1155; HRMS (ESI) calc. for C₃₂H₂₈O₁₂ [M+Na]⁺: 627.14730, obs. 627.14850.

Following general procedure B for ynone dimerization, ynone (22) was transformed into the protected vinaxanthone. The crude material was purified via silica gel column
chromatography (5:2:1 CH₂Cl₂:EtOAc:hexanes) to give pure protected vinaxanthone (12 mg, 0.022 mmol, 24%) as a pale yellow solid (m.p. 215-216 °C).

R_f = 0.50 (silica gel, 5:2:1 CH₂Cl₂:EtOAc:hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.73 (s, 1H), 8.29 (d, J = 9.2 Hz, 1H), 8.13 (d, J = 8.9 Hz, 1H), 7.82 (s, 1H), 7.12 (d, J = 2.1 Hz, 1H), 7.11 (dd, J = 9.2, 2.1 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 8.9, 2.4 Hz, 1H), 5.31 (s, 2H), 5.29 (s, 2H), 3.52 (s, 3H), 3.51 (s, 3H), 2.66 (s, 3H), 2.47 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 210.5, 199.1, 175.0, 174.7, 163.1, 161.9, 157.9, 157.3, 154.0, 153.2, 135.8, 134.1, 132.9, 128.4, 127.7, 127.4, 121.6, 121.0, 118.3, 116.2, 115.8, 115.3, 103.3, 103.2, 94.4, 94.3, 56.5, 56.4, 32.4; IR (film, υ cm⁻¹): 1684, 1636, 1483, 1153; HRMS (ESI) calc. for C₃₀H₂₄NaO₁₀ [M+Na]⁺: 567.12617, obs. 567.12611.

**General Procedure A for Protected Vinaxanthone Deprotection**
To a stirred solution of protected vinaxant hone (1.0 equiv.) in CH₂Cl₂ at 0 °C was added a 1.0 M solution of boron trichloride in CH₂Cl₂ (2.0 equiv. per protecting group). The reaction mixture was stirred at 23 °C for 1 hour. The reaction mixture was then diluted with EtOAc and washed with brine (5x). The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give crude vinaxanthone. Trituration with pentane:MeOH (ratio varies depending on substrate solubility) gave pure vinaxanthone.

**General Procedure B for Protected Vinaxanthone Deprotection**
A solution of protected vinaxanthone (1.0 equiv.) in 1.25 M methanolic HCl (10 equiv. per protected group) was stirred at 65 °C for 8 hrs. The reaction was followed by aliquot ¹H NMR. The reaction mixture was then purged with N₂ and concentrated in vacuo to give crude vinaxanthone. Trituration with pentane:MeOH (ratio varies depending on substrate solubility) gave pure vinaxanthone.

5,7-diacetyl-6-(5-carboxy-6,7-dihydroxy-4-oxo-4H-chromen-3-yl)-2,3-dihydroxy-9-oxo-9H-xanthene-1-carboxylic acid (vinaxanthone) (2)

Following general procedure A for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2) (155 mg, 0.269 mmol, 98%), a yellow solid (m.p. 280 °C (decomp.)).

R_f = 0.05 (silica gel, 20:1 EtOAc:AcOH); ¹H NMR (400 MHz, (CD₃)₂SO) δ 12.89 (bs, 1H), 12.72 (bs, 1H), 11.69 (bs, 1H), 11.44 (bs, 1H), 9.42 (bs, 2H), 8.53 (s, 1H), 8.18 (s, 1H), 6.96 (s, 1H), 6.94 (s, 1H), 2.55 (s, 3H), 2.53 (s, 3H); ¹³C NMR (125 MHz, (CD₃)₂SO) δ 201.1, 199.1, 172.9, 172.6, 167.4, 167.4, 154.1, 152.7, 152.5, 152.1, 150.7, 150.3, 141.7, 141.0, 136.2, 133.4, 132.6, 126.3, 120.8, 120.5, 119.8, 119.6, 112.4, 110.0, 102.4, 102.3, 32.1, 29.1; IR (KBr, υ cm⁻¹) 3236, 1683, 1653, 1472, 1288; HRMS (ESI) calc. for C₂₈H₁₅O₁₄ [M–H]⁻: 575.04673, obs. 575.04679.
5,7-diacetyl-6-(6,7-dihydroxy-4-oxo-4H-chromen-3-yl)-2,3-dihydroxy-9-oxo-9H-xanthene-1-carboxylic acid (2a)

Following general procedure A for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2a) (9 mg, 0.017 mmol, 97%), a tan solid (m.p. 248-250 °C (decomp.)).

R_f = 0.14 (silica gel, 20:1 EtOAc:AcOH); \(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 12.73 (bs, 1H), 11.47 (bs, 1H), 10.87 (bs, 1H), 9.98 (bs, 1H), 9.44 (bs, 1H), 8.57 (s, 1H), 8.17 (s, 1H), 7.48 (s, 1H), 6.96 (s, 1H), 6.95 (s, 1H), 2.54 (s, 3H), 2.50 (s, 3H); \(^13\)C NMR (125 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 201.2, 199.2, 173.4, 172.8, 167.4, 154.4, 152.7, 152.6, 152.5, 150.8, 150.7, 144.5, 144.7, 136.1, 133.6, 132.4, 126.3, 120.9, 119.8, 119.6, 113.5, 112.5, 108.7, 103.1, 102.3, 32.1, 29.1; IR (KBr, \(\nu\) cm\(^{-1}\)) 3219, 1470, 1196, 803; HRMS (ESI) calc. for C\(_{27}\)H\(_{15}\)O\(_{12}\) [M-H]: 531.05690, obs. 531.05700.

5,7-diacetyl-2,3-dihydroxy-6-(7-hydroxy-4-oxo-4H-chromen-3-yl)-9-oxo-9H-xanthene-1-carboxylic acid (2b)

Following general procedure A for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2b) (8 mg, 0.015 mmol, 96%), a tan solid (m.p. 254-255 °C (decomp.)).

R_f = 0.31 (silica gel, 20:1 EtOAc:AcOH); \(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 12.70 (bs, 1H), 11.42 (bs, 1H), 11.15 (bs, 1H), 9.42 (bs, 1H), 8.57 (s, 1H), 8.17 (s, 1H), 6.98 (d, \(J = 8.9\) Hz, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 2.56 (s, 3H), 2.54 (s, 3H); \(^13\)C NMR (125 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 201.1, 199.2, 173.6, 172.8, 167.3, 164.6, 157.2, 152.7, 152.6, 152.5, 150.7, 141.7, 136.5, 133.6, 132.8, 128.1, 126.2, 120.8, 120.3, 119.6, 114.9, 113.8, 112.4, 102.5, 102.3, 32.1, 29.2; IR (KBr, \(\nu\) cm\(^{-1}\)) 3381, 1618, 1466, 1274; HRMS (ESI) calc. for C\(_{27}\)H\(_{15}\)O\(_{11}\) [M-H]: 515.06198, obs. 515.06245.

3-(2,4-diacetyl-6,7-dihydroxy-9-oxo-9H-xanthene-3-yl)-6,7-dihydroxy-4-oxo-4H-chromene-5-carboxylic acid (2c)

Following general procedure A for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2c) (5 mg, 8.83 µmol, 89%), a tan solid (m.p. 225-226 °C).

R_f = 0.13 (silica gel, 20:1 EtOAc:AcOH); \(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)SO) \(\delta\) 11.71 (bs, 1H), 10.59 (bs, 1H), 9.92 (bs, 1H), 9.44 (bs, 1H), 8.55 (s, 1H), 8.15 (s, 1H), 7.28 (s, 1H), 6.96 (s, 1H),
Following general procedure B for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2d) (48 mg, 0.098 mmol, 97%), a magenta solid (m.p. 290 °C (decomp.)).

\[ R_f = 0.24 \text{ (silica gel, 20:1 EtOAc:AcOH); } \]

\[ ^1H \text{ NMR (400 MHz, (CD}_3\text{)SO) } \delta 10.83 (bs, 1H), 10.55 (bs, 1H), 9.93 (bs, 2H), 8.58 (s, 1H), 8.12 (s, 1H), 7.49 (s, 1H), 7.28 (s, 1H), 6.94 (s, 1H), 6.93 (s, 1H), 2.55 (s, 3H), 2.53 (s, 3H); \]

\[ ^{13}C \text{ NMR (125 MHz, (CD}_3\text{)SO) } \delta 201.1, 199.0, 173.6, 173.3, 154.3, 152.8, 152.4, 151.0, 150.6, 144.9, 144.5, 139.8, 135.8, 133.5, 132.7, 162.3, 120.7, 119.7, 115.7, 113.4, 108.6, 107.9, 102.9, 32.2, 29.1; \]

\[ \text{IR (KBr, } \nu \text{ cm}^{-1} ) 3382, 1617, 1473, 1292; \]

\[ \text{HRMS (ESI) calc. for C}_{26}\text{H}_{15}\text{O}_{10}[M-H]^-: 487.06707, \text{ obs. 487.06709.} \]

Following general procedure B for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2e) (5 mg, 10.58 µmol, 91%), a magenta solid (m.p. 218-220 °C (decomp.)).

\[ R_f = 0.09 \text{ (silica gel, 10:10:1 hexanes:EtOAc:AcOH); } \]

\[ ^1H \text{ NMR (400 MHz, (CD}_3\text{)SO) } \delta 11.17 (bs, 1H), 10.59 (bs, 1H), 9.91 (bs, 1H), 8.58 (s, 1H), 8.14 (s, 1H), 8.09 (d, } J = 8.6 \text{ Hz, 1H), 7.29 (s, 1H), 6.98 (d, } J = 8.6 \text{ Hz, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 2.55 (s, 3H), 2.54 (s, 3H); \]

\[ ^{13}C \text{ NMR (125 MHz, (CD}_3\text{)SO) } \delta 201.0, 199.0, 173.5, 164.5, 157.2, 152.9, 152.8, 152.6, 151.1, 144.9, 136.2, 133.5, 132.8, 128.0, 126.3, 120.6, 120.3, 115.7, 114.9, 113.8, 107.9, 102.9, 102.5, 100.0, 32.2, 32.1; \]

\[ \text{IR (KBr, } \nu \text{ cm}^{-1} ) 3406, 1617, 1560, 1466, 1273; \]

\[ \text{HRMS (ESI) calc. for C}_{26}\text{H}_{15}\text{O}_{9}[M-H]^-: 471.07216, \text{ obs. 471.07279.} \]

Following general procedure B for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2e) (5 mg, 10.58 µmol, 91%), a magenta solid (m.p. 218-220 °C (decomp.)).
Following general procedure A for protected vinaxanthone deprotection, protected vinaxanthone X was transformed into pure vinaxanthone X (20 mg, 0.039 mmol, 96%), a yellow solid (m.p. 208-210 °C (decomp.)).

\[ R_f = 0.09 \] (silica gel, 20:1 EtOAc:AcOH); \(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)SO) \( \delta \) 11.72 (bs, 1H), 10.96 (bs, 1H), 9.42 (bs, 1H), 8.58 (s, 1H), 8.19 (s, 1H), 7.91 (d, \( J = 8.9 \) Hz, 1H), 6.96 (dd, \( J = 8.9, 2.4 \) Hz, 1H), 6.93 (s, 1H), 6.91 (d, \( J = 2.4 \) Hz, 1H), 2.57 (s, 3H), 2.55 (s, 3H); \(^13\)C NMR (125 MHz, (CD\(_3\))\(_2\)SO) \( \delta \) 201.0, 198.9, 173.8, 172.5, 167.3, 163.0, 157.6, 154.0, 153.2, 152.2, 150.2, 140.9, 135.6, 133.3, 132.6, 127.2, 126.6, 121.6, 120.5, 119.8, 115.7, 115.4, 110.0, 102.4, 102.2, 32.2, 29.0; IR (KBr, \( \nu \) cm\(^{-1}\)) 3385, 1624, 1459, 1290, 1101; HRMS (ESI) calc. for C\(_{27}\)H\(_{15}\)O\(_{11}\) \([M-H]\): 515.061989, obs. 515.06236.

1,1’-(3-(6,7-dihydroxy-4-oxo-4H-chromen-3-yl)-6-hydroxy-9-oxo-9H-xanthe-2,4-diyl)bis(ethan-1-one) (2g)

Following general procedure B for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2g) (13 mg, 0.028 mmol, 98%), a magenta solid (m.p. 208-210 °C (decomp.)).

\[ R_f = 0.06 \] (silica gel, 10:10:1 hexanes:EtOAc:AcOH); \(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)SO) \( \delta \) 10.97 (bs, 1H), 10.86 (bs, 1H), 9.98 (bs, 1H), 8.62 (s, 1H), 8.19 (s, 1H), 7.91 (d, \( J = 8.9 \) Hz, 1H), 7.48 (s, 1H), 6.96 (d, \( J = 9.2 \) Hz, 1H), 6.95 (s, 1H), 6.91 (d, 1H), 6.9 (s, 1H), 5.75 (s, 3H), 2.55 (s, 3H); \(^13\)C NMR (125 MHz, (CD\(_3\))\(_2\)SO) \( \delta \) 201.2, 199.0, 173.9, 173.3, 163.1, 157.7, 154.4, 153.2, 152.5, 150.7, 144.5, 135.6, 133.6, 132.4, 127.3, 126.6, 121.7, 119.9, 115.8, 115.4, 113.5, 108.7, 103.1, 102.3, 32.3, 29.1; IR (KBr, \( \nu \) cm\(^{-1}\)) 3299, 1624, 1470, 1295; HRMS (ESI) calc. for C\(_{26}\)H\(_{15}\)O\(_9\) \([M-H]\)+: 471.07216, obs. 471.07231.

1,1’-(6-hydroxy-3-(7-hydroxy-4-oxo-4H-chromen-3-yl)-9-oxo-9H-xanthe-2,4-diyl)bis(ethan-1-one) (2h)

Following general procedure B for protected vinaxanthone deprotection, protected vinaxanthone was transformed into pure vinaxanthone (2h) (8 mg, 0.018 mmol, 99%), a tan solid (m.p. 340 °C (decomp.)).

\[ R_f = 0.16 \] (silica gel, 10:10:1 hexanes:EtOAc:AcOH); \(^1\)H NMR (500 MHz, (CD\(_3\))\(_2\)SO) \( \delta \) 11.14 (s, 1H), 10.93 (s, 1H), 8.61 (s, 1H), 8.19 (s, 1H), 8.10 (d, \( J = 7.2 \) Hz, 1H), 7.91 (d, \( J = 7.2 \) Hz, 1H), 6.91 (s, 1H), 6.91 (s, 1H), 6.98 (ddd, \( J = 11, 7.2, 2.0 \) Hz, 2H), 2.57 (s, 3H), 2.57 (s, 3H); \(^13\)C NMR (125 MHz, (CD\(_3\))\(_2\)SO) \( \delta \) 201.0, 199.0, 173.9, 173.6, 164.5, 163.1, 157.7, 157.2, 153.2, 152.5, 150.7, 144.5, 135.6, 133.6, 132.4, 127.3, 126.6, 121.7, 119.9, 115.8, 115.4, 113.5, 108.7, 103.1, 102.3, 32.3, 29.1; IR (KBr, \( \nu \) cm\(^{-1}\)) 3351, 1619, 1468, 1002; HRMS (ESI) calc. for C\(_{26}\)H\(_{16}\)NaO\(_8\) \([M+Na]^+\): 479.07374, obs. 479.07433.