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Concise Approach to 1,4-Dioxygenated Xanthenes via Novel Application of the Moore Rearrangement

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Abstract

The rapid synthesis of 1,4-dioxygenated xanthenes and related natural products employing the Moore rearrangement as a key transformation has been developed. The approach features an acetylide stitching step to unite a substituted squaric acid with a protected hydroxy benzaldehyde derivative to provide a key intermediate that undergoes facile Moore rearrangement to deliver a hydroxymethyl aryl quinone. Subsequent oxidation, hydroxy group deprotection and cyclization then affords highly functionalized xanthenes. The utility of the approach was demonstrated by its application to a concise and efficient synthesis of the naturally-occurring xanthone **1**. The structure of a natural product that had been named dulcisxanthone C was also corrected to that of the xanthone **1**.

Keywords

1,4-dioxygenated xanthone; Moore rearrangement; squarate; quinone; total synthesis

1. Introduction

The 1,4-dioxygenated xanthone moiety is an important structural feature that is present in numerous natural products, many of which exhibit significant biological activities and complex structures (Figure 1). Tetramethoxy xanthone **1** is reported to inhibit the formation of osteoclasts *in vitro*.¹ Extracts of the *Garcinia atroviridis* tree contain the xanthone atroviridin (**2**), which is commonly used in traditional medicine as a remedy for earache.² Two elegant syntheses of **2** have been reported recently by Theodorakis³ and Suzuki.⁴ Representative of more complex xanthenes is the angularly-fused, heptacyclic xanthone cervinomycin A⁵ (**3**), which exhibits potent activity against numerous bacterial strains and has been prepared twice by total synthesis.⁶

Given the widespread occurrence of 1,4-dioxygenated xanthenes as well as other substituted analogs, it should not occasion surprise that there are many methods that provide access to this ring system.⁷ However, there are numerous disadvantages that are associated with these methodologies. Many approaches suffer from high step counts and low yielding sequences.

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Supplementary Information

Experimental procedures and characterization for other compounds can be found in the online version at doi:

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Other procedures may require the tedious separation of intermediates, harsh reaction conditions, starting materials that are not readily available, and a limited substrate scope.⁸ In order to develop a practical approach to the xanthenes shown in Figure 1 as well as other naturally occurring 1,4-dioxygenated xanthenes, there is a need for a method that resolves the aforementioned problems. The more general application of such a method would require readily available starting material having a diverse array of functional groups and substitution patterns. During the course of work directed toward the total synthesis of polycyclic xanthenes structurally related to **3**, the problems inherent in the traditional approaches to 1,4-dioxygenated xanthenes became apparent. We thus set to the task of developing a rapid route to the xanthone core.

After a survey of the literature, we designed a general approach to 1,4-dioxygenated xanthenes and related natural products of the form **4** that is outlined in retrosynthetic format in Scheme 1.^{9,10} We envisioned that xanthenes related to **4** would be accessible by the cyclization of phenolic ketones **5** (R = H) that in turn would be prepared by oxidation and *O*-deprotection of **6**. An attractive route to **6** from **7** was inspired by the extensive and elegant work of Moore and coworkers, who showed that the thermal rearrangement of squarate-derived compounds afforded substituted benzoquinones.¹¹ It thus occurred to us that the Moore rearrangement of intermediates such as **7** would provide **6**. Significantly, analogs of **7** would be readily accessible by a convergent approach that involved an acetylide stitching process involving a squarate derivative **8**, an acetylene equivalent **9**, and a protected derivative of a commercially available salicylaldehyde **10**.

2. Results and Discussion

Initial experiments were directed upon identifying a suitable protecting group strategy for the phenolic hydroxyl group on the salicylaldehyde reaction partner and upon establishing the efficacy of the overall plan outlined in Scheme 1. Indeed, selection of the appropriate oxygen-protecting group proved to be one of the more challenging tasks to be confronted. We first explored the possibility that a di-*t*-butylsilyl protecting group would protect both the phenolic and alcohol hydroxy groups in adducts such as **15a,b**.¹² Accordingly, ethynylation of salicylaldehyde (**11**) to afford the corresponding propargylic alcohol **12** occurred in essentially quantitative yield. The hydroxy groups in **12** were then protected by forming the di-*t*-butylsilyl ether **13** in 99% yield. Addition of the lithium acetylide ion of **13** to either **14a** or **14b** then provided the unstable adducts **15 a,b**, which were immediately heated in refluxing toluene to induce the pivotal Moore rearrangement to deliver the quinones **16a,b** in 48–63% overall yield for the two step process from **13**. Removal of the bis-silyl protecting group with HF•pyridine proceeded in quantitative yield to give the quinone alcohols **17a,b**, which were used in subsequent reactions without further purification.

Our original plan was that benzylic oxidation of **17a,b** would give the keto-quinones **18a,b** that would then undergo facile and spontaneous cyclization to give the desired xanthenes **19a,b** (Scheme 3). In the event, treating **17a,b** with a variety of oxidants including chromic acid, IBX, PDC and DDQ gave intermediate ketones that cyclized to the desired xanthone **19a,b**, but the yields varied from 10–70% and were not reproducible. Other oxidants including Dess-Martin periodinane, MnO₂, BaSO₄, TPAP/NMO, TEMPO/BAIB, Pd/C, PCC, Swern-type reagents, Al(O*i*Pr)₃, Ag₂CO₃/celite, *N*-bromoacetamide, and CAN were also screened, but these were also not suitable as they lead to incomplete conversions, formation of side products, or extensive decomposition pathways. During the course of these studies, we discovered that the product xanthenes **19a,b** were often not stable to the conditions of the reaction. For example, when **19a** was exposed to chromic acid in acetone, only 10% of **19a** was recovered from the mixture. It was thus apparent that the phenolic

moiety in the product of the Moore rearrangement was unstable toward oxidation, so it was necessary to modify our original plan and protect this group during the oxidation step.

We first examined the methoxymethyl (MOM) ether as a phenolic protecting group. Salicylaldehyde (**11**) was thus treated with MOM-Cl in the presence of NaH to give **20** in 96% yield (Scheme 4). Ethynylation of **20** gave the propargylic alcohol **21** in 88% yield. The dianion of **21**, which was generated with NaH/*n*-BuLi, was then allowed to react with **14a** to afford the unstable diol **22**, which was heated in a microwave oven to induce the Moore rearrangement and provide the quinone **23** in 94% yield. Jones oxidation of **22** gave the ketone **23** in 99% yield.

The next step required removing the MOM protecting group, but use of standard acidic conditions that are typically employed for this deprotection proved to be somewhat problematic. Namely, exposure of **24** to protic acids such as H₂SO₄, HCl and AcOH provided mixtures of the desired xanthone **19a** together with variable amounts of the hydroquinones **25** and **26**, the formation of which was puzzling. Use of TMSI, I₂/MeOH, and Ph₃CBF₄ were also explored, but in all cases the xanthone **19a** was formed in poor yield and was accompanied with the hydroquinones **25** and **26**.

Reasoning that the conditions required for removing the MOM protecting group were responsible for our difficulties, we decided to switch to a phenolic protecting group that could be removed under milder conditions. After a quick survey of several possibilities, the *p*-methoxybenzyl group (PMB) emerged as the protecting group of choice. In the event, **11** was alkylated with *p*-methoxybenzyl chloride in the presence of K₂CO₃ to give **27** in 91% yield (Scheme 4). Ethynylation of **27** with bromomagnesium acetylide furnished the propargylic alcohol **28** in 99% yield. Reaction of the dianion of **28** with **14a** formed the unstable diol **29**, which was then heated in refluxing toluene to give the quinone **30** in 42% (unoptimized) overall yield. Jones oxidation of the alcohol gave the ketone **31** in 96% yield, thereby setting the stage for the requisite deprotection to give **19a**.

Traditional reagents for cleaving PMB groups such as CAN and DDQ simply returned starting material under mild conditions and mixtures containing unidentifiable products under more forcing conditions. When **31** was treated with aqueous acids, the xanthone **19a** was obtained as well as the unexpected hydroquinone side products **25** and **32**. After considerable experimentation using a variety of protic and Lewis acids and reaction conditions, we discovered serendipitously that treating **31** with CF₃CO₂H (TFA) in CH₂Cl₂ *in the absence of light and/or oxygen* cleanly provided the desired xanthone **19a** in >95% yield without competing formation of the undesired hydroquinones **25** or **32**. Conversely, when the deprotection was conducted in the presence of light *and* oxygen, the hydroquinones **25** and **32** were formed exclusively in high yield. Formation of **25** and **32** was also observed when other acids such as HCl, TMSI and Ph₃CBF₄, and other solvents including dioxane, PhCl and MeOH were used. We currently do not have a satisfactory explanation for this unusual side reaction, although a preliminary experiment suggested that a simple quinone/hydroquinone equilibration was not involved. Namely, when a solution of **31** and **19a** were stirred in the absence of TFA, neither **32** nor **33** were detected.

Having established the underlying efficacy of our approach to 1,4-dioxygenated xanthenes, we explored the scope of the method by changing the substitution pattern and the functional groups on the starting salicylaldehyde reaction partner using commercially available alkyl, methoxy and chloro derivatives. We were delighted to discover that the chemistry outlined in Scheme 4 was generally applicable to the salicylaldehydes **34a–h** shown in Scheme 5. Protection of the phenolic hydroxyl group of **34a–h** to give **35a–h** occurred in 71–98% yield, and the subsequent ethynylation of the aldehyde moiety of **35a–h** proceeded to give

the adducts **36a–h** in 87–99% yield. The dianions generated from **36a–h** were then allowed to react with the squarate **14a** to provide the sensitive diols **37a–h** in 52–65% yield. Although we found that Moore rearrangements can be performed in a microwave oven at elevated temperatures, heating under conventional conditions was more amenable to conducting larger scale reactions. Thus, heating **37a–h** in refluxing toluene furnished the quinones **38a–h** in 60–83% yield. Subsequent Jones oxidation of **38a–h** delivered the ketones **39a–h** in 89–99% yield, setting the stage for the deprotection-cyclization sequence.

In the event, treatment of **39a,b,c,f** with TFA in oxygen-free CH₂Cl₂ cleanly formed the xanthenes **42a,b,c,f** (Scheme 6, Table 1); the intermediate phenols **40a,b,c,f** were not observed. As before, performing the reaction under oxygen free conditions precluded the formation of uncyclized hydroquinone side products related to **25**. Surprisingly, exposure of keto-quinones **39d,e,h** to these same deprotection conditions provided varying mixtures of the spirocycles **41d,e,h** and the xanthenes **42d,e,h**, whereas deprotection of **39g** under identical conditions produced only the spirocycle **41g**. Once again the intermediate phenols **40d,e,g,h** were not observed. It is possible to convert the spirocycles **41d,e,g,h** to their xanthone analogs **42d,e,g,h** either by heating in refluxing DMSO or nitrobenzene or by sublimation at elevated temperature.¹³ However, we discovered a simpler expedient whereby this isomerization could be easily induced by merely stirring the spirocycles **41d,e,g,h** with K₂CO₃ in acetone to give the xanthenes **42d,e,g,h** in 60–83% yield.

The disparate reactivity of phenolic intermediates **40a–h** to give spirocyclic ketones and/or xanthenes deserves comment, and we have formulated a tentative rationalization based upon competing steric and electronic factors. When substituents are located at the C(3) and C(5) positions of the starting aroyl benzoquinone **39** (Entries a–c, Scheme 6), only xanthone products are observed; substituent effects do not appear to play a role in the course of the reaction. However, the presence of substituents at C(4) and C(6) lead to mixtures. Electronic properties of the substituent at C(4) greatly affect the product ratio. For example, the methoxy group at C(4) in **39d** results in a 1:2 ratio of **41d** to **42d**, whereas a methyl group at C(4) (Entry e) provides slightly more xanthone than spirocycle. This observation is consistent with the enhanced capability of a methoxy group to donate electron density via resonance effects into the carbonyl group as shown in the limiting resonance structure **43** (Figure 2). This may reduce the electrophilicity of the carbonyl group, thereby lessening its ability to activate the quinone toward 1,4-addition to give the xanthone and enabling spirocyclization to form a five-membered ring to be competitive. Because a methyl group is less electron releasing than a methoxy group, the initial ratio of products **42e** to **41e** is greater than that of the corresponding methoxy compounds **42d** and **41d**. The inductive electron withdrawing effect of the 4-chloro substituent on **39f** completely suppresses spirocycle formation (Entry f), further supporting our hypothesis that the ketone moiety plays an important role in activating the quinone toward 1,4-cyclization via a 6-*endo* mode to give the xanthone. Substituents at C(6) may influence the course of the reaction through both steric and electronic factors. Because of the severe steric interactions between the keto group and the substituent R in the transition state for cyclization of **44** to a xanthone, the alternate transition state **45**, which avoids this interaction and leads to a spirocycle, is favored. The electron donating ability of a methoxy group apparently reinforces the steric effect, because **41g** is the sole product from **39g**, whereas a mixture (7:2) of spirocycle **41h** and xanthone **42h** are formed when R is an electron withdrawing chloro group and **39h** is the starting material.

Having thus established a new approach for the facile synthesis of 1,4-dioxygenated xanthenes, we sought to apply it to the synthesis of selected xanthone natural products using intermediates that had already been accessed during the methodological studies. Thus, the tetramethoxy xanthenes **1** and **46** were simply prepared by the regioselective methylation of

42a and **42d** under basic conditions in 84 and 99% yields, respectively (Scheme 7). It is noteworthy that the preparation of xanthone **1** in seven steps and in 22% overall yield represents a major improvement over the previously reported synthesis.^{8b} The ¹H NMR spectral data of **1** are in close accord with those reported for the isolated natural product, but there are some significant differences in the ¹³C NMR data.¹⁴ A xanthone that has been referred to as dulcisxanthone C was reported to have the structure of **46**;¹⁵ however, the ¹H and ¹³C NMR spectral data reported for dulcisxanthone C do not match those for synthetic **46**, the structure of which was verified by single crystal x-ray crystallography.¹⁶ Comparison of the ¹H and ¹³C NMR spectral data of dulcisxanthone C actually correspond well to those obtained for synthetic **1**. Accordingly, we believe that the structure of dulcisxanthone C should be reassigned to that of the known **1**.

3. Summary and Conclusions

In summary, we have developed a general and concise route to 1,4-dioxygenated xanthenes that would be otherwise difficult to access. Preliminary experiments with several different protecting groups for the hydroxyl group that would eventually become the oxygen atom in the xanthone ring system led to the identification of a PMB group as a preferred protecting group. We then discovered that successful, acid-catalyzed removal of the PMB protecting group required that the reaction be conducted in the absence of either light or oxygen because when the reaction was performed under ambient conditions, the benzoquinone moiety was reduced to a hydroquinone by an unknown mechanism. This unexpected side reaction is currently under investigation. The intermediate phenols **40a–h** may then cyclize by divergent pathways to give spirocyclic ketones or the desired xanthenes, depending upon the nature and the position of the substituent R. The regiochemistry of this cyclization appears to arise from an interplay of electronic and steric effects. This new approach to 1,4-dioxygenated xanthenes was then applied to a more concise and efficient synthesis of **1**, a known natural product. We have also shown that the proposed structure for dulcisxanthone C is incorrect and likely to be **1** based upon a comparison of its spectral data with synthetic **1**. The application of this methodology to the synthesis of other natural products containing 1,4-dioxygenated xanthenes is the subject of several ongoing investigations, the results of which will be reported in due course.

4. Experimental

4.1 General

Solvents and reagents were reagent grade and used without purification unless otherwise specified. THF was passed through two columns of neutral alumina. CH₃CN and DMF were passed through two columns of molecular sieves. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon or nitrogen in glassware that had been oven dried. Reaction temperatures refer to bath temperatures. Melting points are uncorrected. Infrared (IR) spectra were recorded neat on sodium chloride plates and are reported in wave numbers (cm⁻¹). ¹H and ¹³C NMR spectra were obtained as solutions in CDCl₃ unless otherwise noted, and chemical shifts are reported in parts per million (ppm) in reference to CDCl₃ (7.26 ppm and 77.0 ppm, respectively). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; app, apparent; br, broad; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons. 2-(1-Hydroxyprop-2-yn-1-yl)phenol (**12**) was prepared according to literature procedure.¹⁷

4.2 Experimental Procedures

2,2-Di-*tert*-butyl-4-ethynyl-4*H*-benzo[*d*][1,3,2] dioxasiline (13): Freshly distilled 2,6-lutidine (2.7 mL, 2.5 g, 24 mmol) was added to a solution of **12** (1.4 g, 9.4 mmol) in CH₂Cl₂ (25 mL) at 0 °C. After 5 min, di(*tert*-butyl)silyl bis(triflate) (3.6 mL, 4.9 g, 11 mmol) was added, and the reaction was stirred for 3 h at 0 °C. The reaction was diluted with saturated NH₄Cl (15 mL), the ice bath was removed and the aqueous mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with brine (1 × 15 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes:EtOAc (20:1) to give 2.7 g (99% yield) of **13** as a yellow oil; ¹H NMR (400 MHz, C₆D₆) δ 7.39 (d, *J* = 8.0 Hz, 1 H), 7.02-6.94 (comp, 2 H), 6.78 (td, *J* = 8.0, 1.2 Hz, 1 H), 5.89 (d, *J* = 2.0 Hz, 1 H), 2.19 (d, *J* = 2.0 Hz, 1 H), 1.08 (s, 9 H), 1.04 (s, 9 H); ¹³C NMR (100 MHz) δ 153.3, 129.6, 126.8, 126.1, 121.0, 119.5, 82.7, 74.4, 64.7, 26.94, 26.87, 21.6, 20.9; IR (CH₂Cl₂) 3073, 2936, 2126, 1186 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₇H₂₄O₂Si (M⁺), 288.1546; found, 288.1539.

5-(2,2-Di-*tert*-butyl-4*H*-benzo[*d*][1,3,2]dioxasilin-4-yl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (16a): *n*-BuLi (2.1 M in hexanes, 1.3 mL, 2.7 mmol) was added to a solution of **13** (0.78 g, 2.7 mmol) in THF (15 mL) at -78 °C. After stirring for 30 min, a solution of **14a** (0.32 g, 2.3 mmol) in THF (8 mL) at -78 °C was transferred via cannula to the acetylide solution. After stirring for 1 h, AcOH (1 M in THF, 10 mL) was added, the cooling bath was removed, and the reaction was warmed to room temperature over 30 min. The reaction was concentrated, diluted with Et₂O (30 mL), vacuum filtered, and then concentrated under reduced pressure. The crude **15a** was dissolved in PhCH₃ (20 mL), sparged with Ar for 20 min, and then heated under reflux for 4 h. The reaction was cooled to room temperature and then concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes:EtOAc (20:1 to 10:1) to afford 0.59 g (61% yield) of **16a** as a red oil; ¹H NMR (400 MHz) δ 7.20 (t, *J* = 14.0 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 6.83 (t, *J* = 14.0 Hz, 1 H), 6.62 (s, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 6.20 (s, 1 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 1.10 (s, 9 H), 0.96 (s, 9 H); ¹³C NMR (100 MHz) δ 184.3, 183.5, 154.2, 147.5, 145.0, 144.7, 132.1, 129.5, 128.0, 126.6, 119.7, 68.6, 61.4, 61.3, 27.1, 27.0, 21.7, 21.1; IR (CH₂Cl₂) 2931, 2858, 1658, 1603, 1481, 1454, 1247 cm⁻¹; HRMS (CI) *m/z* calculated for C₂₃H₃₁O₆Si (M+1), 431.1890; found, 431.1892.

5-(2,2-Di-*tert*-butyl-4*H*-benzo[*d*][1,3,2]dioxasilin-4-yl)-2,3-dimethylcyclohexa-2,5-diene-1,4-dione (16b): Identical procedure to that of **16a**. Hexanes:EtOAc (30:1), 63% yield over two steps, red oil; ¹H NMR (500 MHz) δ 7.17 (td, *J* = 8.0, 1.7 Hz, 1 H), 6.95-6.93 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.79 (td, *J* = 8.0, 1.2 Hz, 1 H), 6.74 (d, *J* = 1 Hz, 1 H), 6.50 (d, *J* = 7 Hz, 1 H), 6.22 (s, 1 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.09 (s, 9 H), 0.95 (s, 9 H); ¹³C NMR (125 MHz) δ 187.8, 186.9, 154.3, 148.7, 141.0, 140.9, 133.7, 129.3, 128.4, 126.6, 120.9, 119.6, 68.7, 27.1, 27.0, 21.8, 21.1, 12.5, 12.2; IR (CH₂Cl₂) 2924, 2855, 1651, 1618.2, 1483, 1454, 827 cm⁻¹; HRMS (CI) *m/z* calculated for C₂₃H₃₁O₄Si (M+1), 399.1992; found, 399.1992.

1,4-Dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (19a): HF•pyridine (70% HF, 0.004 mL, 0.2 mmol) was added to a solution of **16a** (0.031 g, 0.072 mmol) and pyridine (0.017 mL, 0.017 g, 0.22 mmol) in THF (4 mL). After 1 h, the reaction was diluted with Et₂O (10 mL), and the aqueous layer was washed with brine (1 × 10 mL). The brine was further extracted with Et₂O (3 × 10 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude **17a** was dissolved in acetone (10 mL) and cooled to 0 °C. Jones' reagent (0.14 mL, 0.21 mmol) was added and the reaction was stirred for 1 h at which time 2-propanol (1 mL) and saturated aqueous NaHCO₃ (10 mL) were added. The product was extracted with Et₂O (3 × 12 mL), and the combined organic layers

were washed with brine (1 × 15 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by filtering through a plug of silica gel eluting with CH₂Cl₂:MeOH (10:1) to give 0.014 g (67% yield) of **19a** as a yellow solid (Et₂O/hexanes): mp 180–181 °C; ¹H NMR (400 MHz) δ 12.39 (s, 1 H), 8.27 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.75 (td, *J* = 8.0, 2.0 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 5.43 (s, 1 H), 4.19 (s, 3 H), 3.98 (s, 3 H); ¹³C NMR (100 MHz) δ 181.7, 156.0, 148.0, 147.1, 139.4, 135.4, 134.8, 128.7, 126.0, 124.1, 120.1, 117.9, 105.2, 61.7, 61.1; IR (CH₂Cl₂) 3385, 2922, 2851, 1651, 1464 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₅H₁₃O₆ (M+1), 289.0712; found, 289.0713.

1,4-Dihydroxy-2,3-dimethyl-9H-xanthen-9-one (19b): Identical procedure to that of **19a**. Hexanes:EtOAc (3:1), 57% over two steps, yellow solid (Et₂O/hexanes): mp 265–266 °C (dec.); ¹H NMR (400 MHz) δ 12.39 (s, 1 H), 8.30 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.75 (t, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 5.26 (s, 1 H), 2.37 (s, 3 H), 2.24 (s, 3 H); ¹³C NMR (150 MHz) δ 181.6, 155.6, 151.5, 140.5, 135.2, 133.9, 133.5, 126.4, 124.1, 120.8, 118.4, 117.5, 106.3, 13.1, 10.8; IR (CH₂Cl₂) 3361, 2923, 2853, 1650 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₅H₁₃O₄ (M+1), 257.0809; found, 257.0809.

Representative procedure for phenol protection

2-(4-Methoxybenzyloxy)benzaldehyde (27): Anhydrous K₂CO₃ (39.0 g, 283 mmol) was added to a stirred solution of **11** (11.5 g, 10.0 mL, 94.2 mmol) and PMB-Cl (19.2 g, 16.6 mL, 122 mmol) in DMF (95 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then warmed to room temperature. The mixture was stirred for 20 h, whereupon the reaction was partitioned between H₂O (200 mL) and PhCH₃ (100 mL). The layers were separated, and the aqueous layer was washed with PhCH₃ (2 × 50 mL). The combined organic layers were washed with brine (1 × 100 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure to afford 20.7 g (91% yield) of **27** (colorless solid from hexanes/EtOAc): mp 86–87 °C; ¹H NMR (400 MHz) δ 10.52 (s, 1 H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.54 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.08–6.94 (comp, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 5.12 (s, 2 H), 3.83 (s, 3 H); ¹³C NMR (100 MHz) δ 189.8, 161.1, 159.6, 135.8, 129.1, 128.3, 128.0, 125.1, 120.9, 114.1, 113.0, 70.3, 55.3; IR (CH₂Cl₂) 2837, 1687, 1598, 1245 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₅H₁₄O₃ (M⁺), 242.0942; found, 242.0942.

Representative procedure for preparation of propargyl alcohols

1-(2-(4-Methoxybenzyloxy)phenyl)prop-2-yn-1-ol (28): A solution of ethynyl magnesium bromide (24 mL, 12 mmol, 0.5 M in THF) was added to a solution of **27** (2.4 g, 10 mmol) in THF (100 mL) at 0 °C. After stirring for 3 h at 0 °C, saturated aqueous NH₄Cl (50 mL) was added, the ice bath was removed, and the reaction was warmed to room temperature. The aqueous layer was washed with Et₂O (3 × 30 mL), and the combined organic layers were washed with brine (1 × 30 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The resulting oil was purified by passing through a plug of silica gel, eluting with hexanes:EtOAc (1:1) to afford 2.6 g (99% yield) of **28** as a yellow oil; ¹H NMR (500 MHz) δ 7.55 (dd, *J* = 7.3, 1.7 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.29 (dt, *J* = 7.7, 2.0 Hz, 1 H), 7.00–6.97 (m, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 5.69 (dd, *J* = 6.6, 2.0 Hz, 1 H), 5.08, 5.06 (ABq, *J* = 11.2 Hz, 2 H), 3.80 (s, 3 H), 3.10 (d, *J* = 6.6 Hz, 1 H), 2.60 (d, *J* = 2.2 Hz, 1 H); ¹³C NMR (125 MHz) δ 159.5, 155.9, 129.7, 129.1, 128.6, 128.4, 128.3, 127.9, 121.1, 114.1, 112.3, 83.2, 74.0, 70.1, 61.3, 55.3; IR (CH₂Cl₂) 3434, 2936, 2112, 1515, 1029 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₇H₁₆O₃ (M⁺), 268.1099; found, 268.1099.

Representative procedure for addition of acetylide nucleophiles to squarates and subsequent Moore rearrangement

5-(Hydroxy(2-(4-methoxybenzyloxy)phenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (30): A solution of *n*-BuLi (2.37 M in hexanes, 3.5 mL, 8.2 mmol) was added to a stirred solution of **28** (1.0 g, 3.7 mmol) in THF (25 mL) at 0 °C. The solution was stirred for 4 min at which time a solution of **14a** (0.69 g, 4.8 mmol) in THF (10 mL) was transferred via cannula to the dianion solution. The reaction was stirred at 0 °C for 1.5 h, whereupon saturated aqueous NH₄Cl (30 mL) was added, and the reaction was warmed to room temperature over 10 min. The aqueous layer was diluted with H₂O (20 mL), and then washed with Et₂O (3 × 30 mL). The combined organic layers were washed with H₂O (1 × 20 mL), brine (1 × 20 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was rapidly purified by silica gel chromatography, eluting with hexanes:EtOAc (2:1) to afford 0.79 g (54% yield) of **29** as a red oil. The diol **29** (0.79 g, 1.9 mmol) was dissolved in PhCH₃ (19 mL), sparged with argon for 15 min, placed in a preheated oil bath (~130 °C) and heated under reflux for 4 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with hexanes:EtOAc (3:1) to afford 0.65 g (78% yield) of **30** as a red oil; ¹H NMR (500 MHz, CD₃OD) δ 7.37 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.28-7.23 (comp, 3 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.3 (d, *J* = 1.3 Hz, 1 H), 6.06 (s, 1 H), 4.97, 4.95 (AB q, *J* = 11.2 Hz, 2 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 3.76 (s, 3 H); ¹³C NMR (125 MHz, CD₃OD) δ 185.8, 184.5, 161.0, 156.9, 150.2, 146.3, 146.0, 130.9, 130.7, 130.4, 130.3, 130.2, 128.7, 121.8, 114.9, 113.6, 71.2, 65.0, 61.7, 61.6, 55.7; IR (CH₂Cl₂) 3487, 2950, 1656, 1603, 1515, 1245, 755 cm⁻¹; HRMS (CI) *m/z* calculated for C₂₃H₂₃O₇ (M+1), 411.1444; found, 411.1450.

Representative procedure for oxidation of benzyl alcohols

2,3-Dimethoxy-5-[2-(4-methoxybenzyloxy)benzoyl]-[1,4]benzoquinone (31): A solution of Jones' reagent (0.061 mL, 0.16 mmol) was added to a stirred solution of **30** (0.056 g, 0.14 mmol) in acetone (4 mL) at 0 °C. The solution was stirred for 1 h, at which time 2-propanol (~1 mL) was added, and the reaction was warmed to room temperature over 5 min. The reaction was diluted with H₂O (5 mL) and brine (10 mL). The aqueous layer was washed with Et₂O (2 × 20 mL), and the combined organic layers were washed with brine (1 × 10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure to afford 0.053 g (96% yield) of **31** as a red oil; ¹H NMR (400 MHz) δ 7.95 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.03 (d, *J* = 8.2 Hz, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.46 (s, 1 H), 4.89 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.77 (s, 3 H); IR (CH₂Cl₂) 2951, 1653, 1596, 1517, 1454, 1246 cm⁻¹; HRMS (ESI) *m/z* calculated for C₂₃H₂₀O₇ (M+Na), 431.1107; found, 431.1102.

Representative procedure of xanthone formation

1,4-Dihydroxy-2,3-dimethoxy-9H-xanthen-9-one (19a): The unpurified keto-quinone **31** (0.053 g, 0.13 mmol) was dissolved in CH₂Cl₂ (5 mL) and sparged with Ar for 3 min at which time TFA (0.099 mL, 0.15 g, 1.3 mmol) was added. The Ar sparge was continued for 1 min, and the reaction was allowed to stir at room temperature under Ar for 1 h. The reaction was quenched with saturated aqueous NaHCO₃ (10 mL), and the aqueous layer was washed with Et₂O (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography, eluting with hexanes:EtOAc (3:1) to afford 0.037 g (99% yield) of **19a** as a yellow solid.

Representative procedure for rearrangement of spirocycle to xanthone

1,4-Dihydroxy-2,3,6-trimethoxy-9H-xanthen-9-one (42d): A solution of unpurified **39d** (0.066 g, 0.15 mmol) in CH₂Cl₂ (3 mL) was sparged with Ar for 3 min. TFA (0.12 mL, 0.17 g, 1.5 mmol) was added, and sparging was continued for 1 min. The solution was then stirred under Ar for 1 h, at which time the reaction was quenched with saturated aqueous NaHCO₃ (6 mL). The aqueous layer was washed with Et₂O (3 × 10 mL), and the combined organic layers were washed with brine (1 × 10 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The mixture (**1:2**) of **41d:42d** was dissolved in acetone (6 mL) and stirred in the presence of K₂CO₃ (0.10 g, 0.75 mmol) for 1.5 h. The mixture was filtered through a celite plug eluting with acetone, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes:EtOAc (5:1 to 3:1) to afford 0.041 g (84% yield) of **42d** as a yellow solid; yellow cubes from hexanes/Et₂O: mp 194–195 °C; ¹H NMR (500 MHz) δ 12.52 (s, 1 H), 8.16 (d, *J* = 8.8 Hz, 1 H), 6.97–6.93 (m, 2 H), 5.43 (s, 1 H), 4.17 (s, 3 H), 3.97 (s, 3 H), 3.92 (s, 3 H); ¹³C NMR (125 MHz) δ 180.9, 165.6, 158.1, 148.0, 146.6, 139.4, 134.9, 128.5, 127.4, 113.9, 113.8, 105.0, 100.1, 61.7, 61.1, 56.0; IR (CH₂Cl₂) 2924, 1607, 1573, 956 cm⁻¹; HRMS (CI) *m/z* calculated for C₁₆H₁₃O₇ (M-1), 317.1025; found, 317.1023.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
1,4-Dioxygenated xanthone natural products.

Figure 2.
Proposed rationale for formation of the spirocycle.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Table 1Deprotection of **39a–h**

Entry (R =)	41:42 ^a	42a–h (%) ^b
a : 3-OMe	0:1	77
b : 5-OMe	0:1	81
c : 5-Cl	0:1	92 ^c
d : 4-OMe	1:2	83
e : 4-Me	1:4	76
f : 4-Cl	0:1	63
g : 6-OMe	1:0	61 ^d
h : 6-Cl	7:2	60

^a Isolated as an inseparable mixture; ratios determined by ¹H NMR spectroscopy;^b overall yield from **38a–h**;^c reaction required 24 h;^d ethyl acetate was used as solvent for rearrangement; yield in acetone was 30%.