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General and Expedient Synthesis of 1,4-Dioxygenated Xanthones

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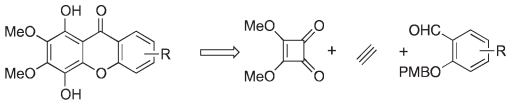
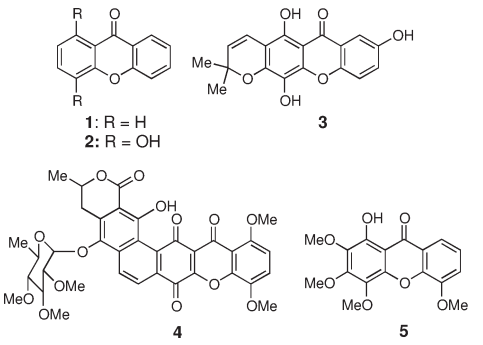
ABSTRACT



A facile entry to 1,4-dioxygenated xanthones having a variety of substitution patterns and substituents was developed that features a novel application of the Moore cyclization using substrates that were readily assembled in a highly convergent fashion by an acetylide stitching process. The practical utility of the methodology was demonstrated by an efficient synthesis of a naturally occurring xanthone and correction of the structure of dulcisxanthone C.

The xanthone core **1** is a common motif found in numerous naturally occurring compounds having biological activity (Figure 1).[1] An important xanthone subclass incorporates oxygenation at the 1- and 4-positions as illustrated in **2**. Many 1,4-dioxygenated xanthones elicit useful biological properties. For example, atroviridin (**3**),[2] which has been synthesized by the groups of Theodorakis[3] and Suzuki,[4] is used in traditional medicine as a remedy for earaches. The more complex IB-00208 (**4**) is a hexacyclic, angularly fused quinone xanthone that has 1 nM activity against the P388D1, A-549, HT-29, and SK-MEL-28 cell lines as well as antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis*.[5] The tetramethoxy xanthone **5** is reported to inhibit the growth of osteoclasts *in vitro*.[6]

Numerous strategies have been developed to prepare xanthones, but there is a relative paucity of methods that are readily applicable to the synthesis of 1,4-dioxygenated xanthones.[7] These typically suffer from a number of significant limitations, including lengthy sequences, low yields, harsh conditions, restricted substitution patterns, narrow substrate scope, and the production of isomeric products.[8] Such procedures are not well-suited for the efficient synthesis of xanthones with diverse substitution patterns or high levels of structural complexity such as **4**. A robust and reproducible method is needed that will enable broad access to 1,4-dioxygenated xanthones found in nature and biologically active compounds.



1: R = H
2: R = OH

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

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(7) For a review of methods to prepare xanthones, see: Sousa, M. E.; Pinto, M. M. M. *Curr. Med. Chem.* **2005**, *12*, 2447–2479.

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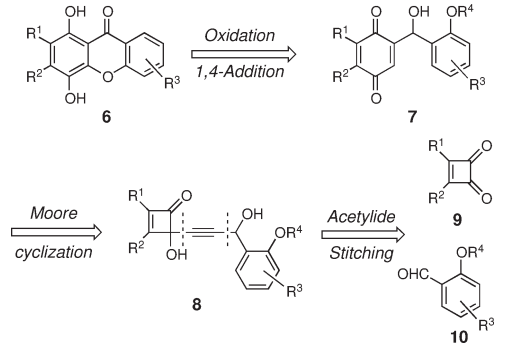
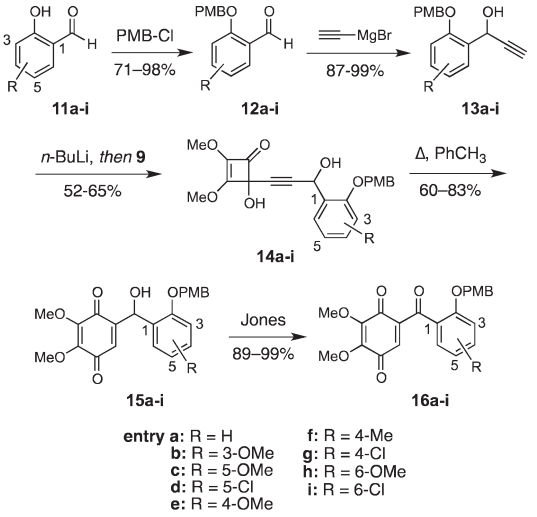
We recently devised an effective strategy to prepare quinone natural products using variants of the Moore cyclization.[9,10] We therefore queried whether the chemistry we had discovered might be more generally applied to synthesizing 1,4-dioxygenated xanthones. The fundamental features of the plan are highlighted in a retrosynthetic format in Scheme 1. The squarate **9** and a readily available aryl aldehyde **10** are first joined together by an acetylide stitching process to give the key intermediate **8**, which is heated to induce a Moore cyclization that produces the quinone **7**. Oxidation of **7** followed by cyclization via 1,4-addition then provided the desired xanthone **6**. We now report the successful implementation of this new methodology for xanthone synthesis and the application to a facile synthesis of the natural product **5**.

Scheme 1. Retrosynthetic Entry to 1,4-Dioxygenated Xanthones



The commercially available salicylaldehydes **11a**–**i** were first protected as their corresponding *p*-methoxybenzyl (PMB) ethers **12a**–**i** in 71–98% yield (Scheme 2). Ethynylation of **12a**–**i** with ethynyl magnesium bromide afforded the propargylic alcohols **13a**–**i** in 87–99% yields. The dianions of **13a**–**i**, which were generated using 2.2 equiv of *n*-BuLi, were then allowed to react with dimethoxysquarate (**9**) to give the adducts **14a**–**i** in 52–65% yield. Because **14a**–**i** were only moderately stable, they were quickly purified and then heated under reflux in toluene to induce the Moore cyclization and give the quinones **15a**–**i** in 60–83% yield. The benzylic alcohols **15a**–**i** were oxidized to furnish ketones **16a**–**i** in 89–99% yield.

Scheme 2. Preparation of Substituted Benzoyl Quinones via Moore Cyclization



The stage was then set for removal of the PMB protecting group so the intermediate phenol could undergo cyclization to deliver the desired xanthone. Although reaction of **16a**–**i** with oxidants such as DDQ and CAN largely returned recovered starting material, treatment of these ketones with TFA in deoxygenated CH_2Cl_2 cleanly removed the PMB group allowing cyclization to occur. The regioselectivity of the cyclization of the intermediate phenol was found to be dependent upon substitution on the aromatic ring. For example, deprotection of **16a** furnished the xanthone **18a** in 95% yield (Scheme 3, entry a). Deprotection/cyclization of **16b**–**d,g** (entries b–d,g) also provided xanthones **18b**–**d,g**. On the other hand, deprotection and cyclization of **16e,f,i** gave inseparable mixtures of spirocyclic ketones **17e,f,i** and xanthones **18e,f,i**, whereas **16h** afforded spirocyclic ketone **17h** as the sole product. Fortunately, we discovered that the spirocyclic ketones **17e,f,h,i** underwent facile rearrangement to the corresponding xanthones **18e,f,h,i** upon treatment with K_2CO_3, conditions much milder than those reported for similar rearrangements.[11]

The disparate behavior of the variously substituted, intermediate phenolic ketones derived from **16a**–**i** toward cyclization to deliver **17** or **18** or mixtures thereof begs rationalization. Based upon the observed substituent effects, we believe a combination of electronic and steric effects are at play, and we have formulated tentative hypotheses that are consistent with the extant experimental observations. For substrates **16a**–**d** lacking substituents at

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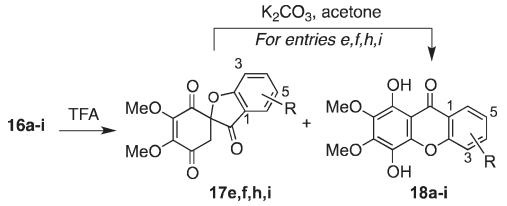
Scheme 3. Phenol Deprotection, Cyclization, and Spirocycle Rearrangement[a–d]



entry	17:18[a]	18a-i (%)[b]
a: R = H	0:1	95
b: R = 3-OMe	0:1	77
c: R = 5-OMe	0:1	81[c]
d: R = 5-Cl	0:1	92
e: R = 4-OMe	1:2	83
f: R = 4-Me	1:4	76
g: R = 4-Cl	0:1	63[d]
h: R = 6-OMe	1:0	61
i: R = 6-Cl	7:2	60

[a] Inseparable mixture; ratios determined by ^{1}H NMR. [b] Overall yield from **15a**–**i**. [c] Reaction required 24 h. [d] Ethyl acetate was used as solvent for rearrangement; yield in acetone was 30%.

C(4) or C(6), xanthones **18a**–**d** are obtained as the only isolable products; there are no significant substituent effects. For 4-substituted compounds **16e**–**g**, the regiochemistry varies with the electron-donating ability of the R-substituent. Electron release by a 4-methoxy group might be expected to decrease the ability of the ketone moiety to activate the double bond in the quinone toward nucleophilic attack through resonance as shown in **19**, thereby leading to increased amounts of the spirocycle **17e** (Figure 2). The inductive effect of a 4-chloro substituent would have the opposite effect, and only the xanthone **18g** is formed. The weak electron-releasing ability of a 4-methyl substituent is reflected by an increased preference for forming the xanthone **18f**. Substituents at the 6-position of **16h,i** appear to exert both electronic and steric effects. The presence of a substituent at the 6-position should disfavor the conformation **20** that is required for cyclization to the xanthone because of unfavorable steric interactions that are relieved in the alternate conformation **21** that is predisposed to cyclize to a spirocyclic ketone. Given that the effective sizes of chlorine and methoxy groups are comparable, electronic effects may also contribute to the observed preference for forming **17h**, as the methoxy group would lessen the activating effect of the ketone moiety toward a mode of 1,4-addition that would generate the xanthone.

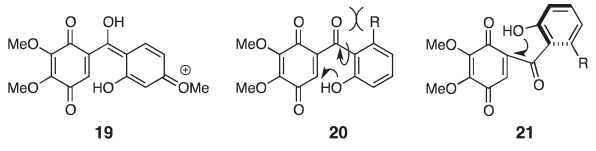
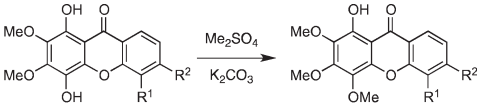


Figure 2. Spirocycle versus fused: Hypothesis for divergent regioselectivity.

We next applied the Moore cyclization approach to the preparation of naturally occurring xanthones (Scheme 4). This goal was readily achieved by the regioselective methylation of xanthones **18b** and **18e** to afford the tetramethoxy xanthones **5** and **22** in 84 and 99% yield, respectively. The present synthesis of **5** in seven steps and in 22% overall yield represents a significant improvement over the prior art.[8b] Although the ^{1}H NMR spectral data for synthetic **5** are consistent with those found in the literature,[8b,12] there are some notable differences in the ^{13}C NMR data that have been reported for **5**. A compound that was named dulcisxanthone C and assigned the structure **22** has been isolated,[13] but the spectral data for synthetic **22**, the structure of which was also verified by X-ray crystallography, do not match those reported.[14] Indeed, the ^{1}H and ^{13}C NMR data reported for dulcisxanthone C are consistent with those of synthetic **5**.

Scheme 4. Regioselective Phenol Methylation



In summary, we have developed a general and efficient strategy for the synthesis of 1,4-dioxygenated xanthones that does not suffer the disadvantages of other known procedures. We established the utility of the method by its application to a significantly improved synthesis of the naturally occurring xanthone **5** and the revision of the structure of a compound that had been previously reported to be dulcisxanthone C and misassigned the structure **22**. We also set forth a hypothesis involving the interplay of electronic and steric factors for the divergent regioselectivity that is observed in cyclizations of 2-hydroxy aroyl quinones of the general structure **16** to form spirocycles or xanthones. Applications of this methodology to the syntheses of more complex 1,4-dioxygenated xanthones are in progress, and the results of these investigations will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM31077), the Robert A. Welch Foundation (F-652) for generous support of this research. We would

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(14) CCDC 830944 contains the supplementary crystallographic data for **22**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

also like to thank Vincent Lynch (The University of Texas) for obtaining X-ray data for compound **22**.

Supporting Information Available. Experimental procedures and spectral data for all new compounds as well as X-ray information for compound **22** and comparison of ^{1}H and ^{13}C NMR spectral data of dulcisxanthone C and synthetic and natural **5**. This material is available free of charge via the Internet at http://pubs.acs.org