A Concise Approach to Anthraquinone-Xanthone Heterodimers

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b03110 • Publication Date (Web): 05 Apr 2018

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Supporting Information Placeholder

ABSTRACT: A synthetic approach to anthraquinone-xanthone heterodimers is described. The route to the pentacyclic core features an efficient assembly of a benzocycloheptenone via a new intramolecular oxidative arylation of an enol ether and a Hauser-Kraus annulation-aldol reaction sequence to access the characteristic bicyclo[3.2.2]nonene motif. Acremoxanthone A is synthesized in 10 steps from commercially available material to demonstrate the application of this approach.

Anthraquinone-xanthone heterodimers belong to a large family of fungal metabolites derived from aromatic polyketides. These natural products exhibit a diverse set of biological activities, including antiproliferative effects and formation of ion channels through cellular membranes by beticolins, anticoccidial activity of xanthoquinodines, and antibacterial activity of acremonidines and engyodontochones.[1-4] The structures of anthraquinone-xanthone heterodimers contain a unique bicyclo[3.2.2]nonene fragment embedded into the polycarbonyl motif, which is found in various oxidation states in different congeners (e.g. **1**, **2**, and **3**, Figure 1). This fragment is believed to arise from an unusual oxidative heterodimerization of anthraquinone-derived subunits and imparts a characteristic molecular shape, where the two monomers are connected in a nearly perpendicular fashion.[5,6] The bridged polycyclic core of anthraquinone-xanthone heterodimers has become the subject of synthetic studies by several research groups.[7-8] Among those, a recent report of the synthesis of an advanced carbocyclic framework relevant to acremoxanthones by Suzuki and co-workers is particularly noteworthy.[8] Here, we demonstrate an approach to anthraquinone-xanthone heterodimers that allows a 5-step assembly of a functionalized pentacyclic core of these natural products. As a proof of concept, we also report a synthesis of acremoxanthone A (**3**)[9] in 10 steps from commercially available material.

We believed that rapid access to a functionalized pentacyclic core (such as **4**, Figure 1) would allow for concise assembly of the anthraquinone-xanthone heterodimers. The aryl bromide moiety was expected to provide a handle for installation of various xanthone-derived fragments, and the tricarbonyl motif would serve as a starting point for appropriate adjustments of the oxidation states. We envisioned the construction of the pentacyclic core to commence with Hauser-Kraus annulation of a phthalide derivative, represented by **5**, with a substituted benzocycloheptenone, represented by **6**.[10] Formation of the quaternary center at C4a was expected to render C3 of the aliphatic aldehyde fragment available for an intramolecular aldol reaction with C2 of the benzyl ketone fragment.[11] Subsequent elimination of the intermediate secondary alcohol would furnish the alkene bridge, completing assembly of the desired bicyclo[3.2.2]nonene motif.

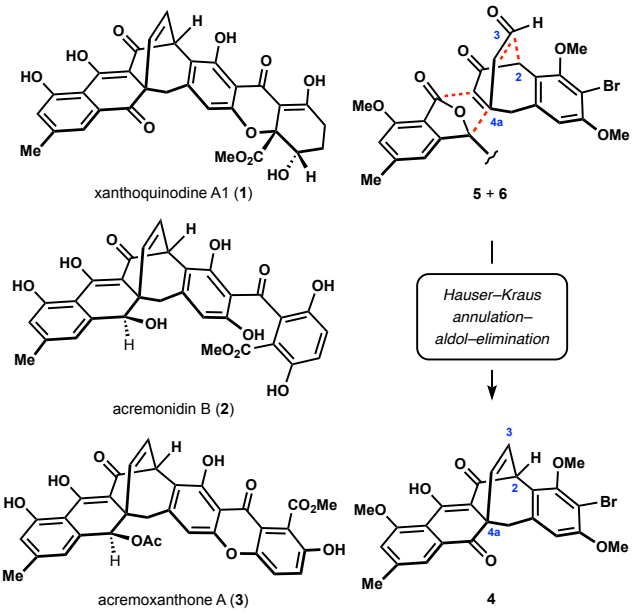
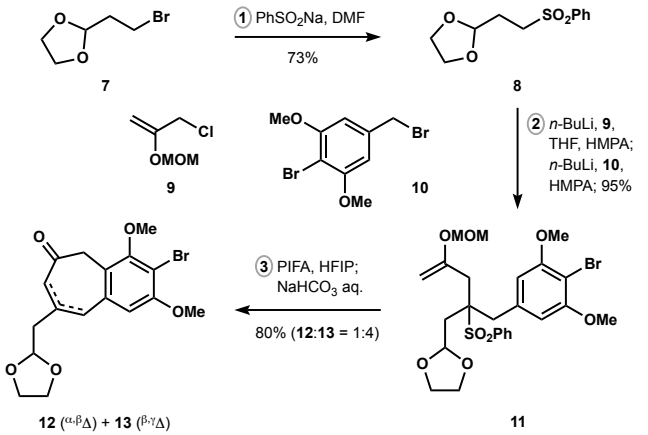


Figure 1. Representative anthraquinone-xanthone heterodimers, and our approach to the pentacyclic core.

The brevity of the proposed route to the pentacyclic core was expected to depend on efficient synthesis of the benzocycloheptenone fragment. In contrast to the phthalide derivatives, which can be readily prepared

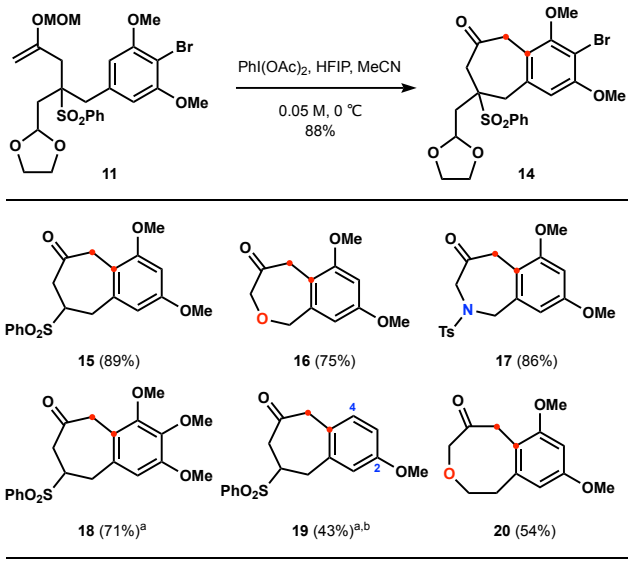
from commercially available materials using established protocols,[10] assembly of the requisite annulation partner finds very little precedent in the current literature.[12] Ring expansions of tetralin derivatives were previously used in the synthesis of relevant benzocycloheptanones,[13] but were plagued by deleterious aromatizations of the properly functionalized precursors in our investigations en route to benzocycloheptenones. We reasoned that an intramolecular oxidative arylation of an enol ether with a pendant arene moiety or an equivalent transformation would allow rapid and expedient access to the desired bicyclic ketone. Application of previously reported conditions was unsuccessful in the current setting,[12,14] and the following solution to the synthesis of a protected version of **6** was devised. Sequential alkylation of sulfone **8** with commercially available allyl chloride **9** and benzyl bromide **10** afforded oxidative arylation precursor **11** in excellent yield (Scheme 1).[15,16] Treatment of

Scheme 1. Synthesis of the Enone Component



enol ether **11** with [bis(trifluoroacetoxy)iodo]benzene (PIFA) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) followed by mild basic work-up resulted in direct formation of a 1:4 mixture of unsaturated ketones **12** and **13**, respectively.[17,18] Although the pronounced preference for the β,γ-unsaturated isomer could be expected to hinder application of this intermediate in our approach, a synthetic sequence that utilized both isomers with apparently equal efficiency was developed (see below). Notably, our oxidative arylation protocol allowed access to gram quantities of the mixture of **12** and **13** in three steps from commercially available bromide **7**. While relevant iodine(III)-mediated arylations of 1,3-dicarbonyl compounds or their equivalents were previously reported,[19] similar transformations of simple enol ethers remain unexplored. In accord with previous observations,[19] we discovered that application of a non-nucleophilic solvent with high hydrogen bond donor ability was crucial to obtaining the desired outcome.[20] Omission of the basic work-up prevented elimination of phenylsulfinate and allowed for the isolation of oxidative arylation product **14** (Table 1). In this setting, (diacetoxyiodo)benzene (PIDA) performed better than PIFA.

Table 1. Oxidative Arylation of Enol Ethers

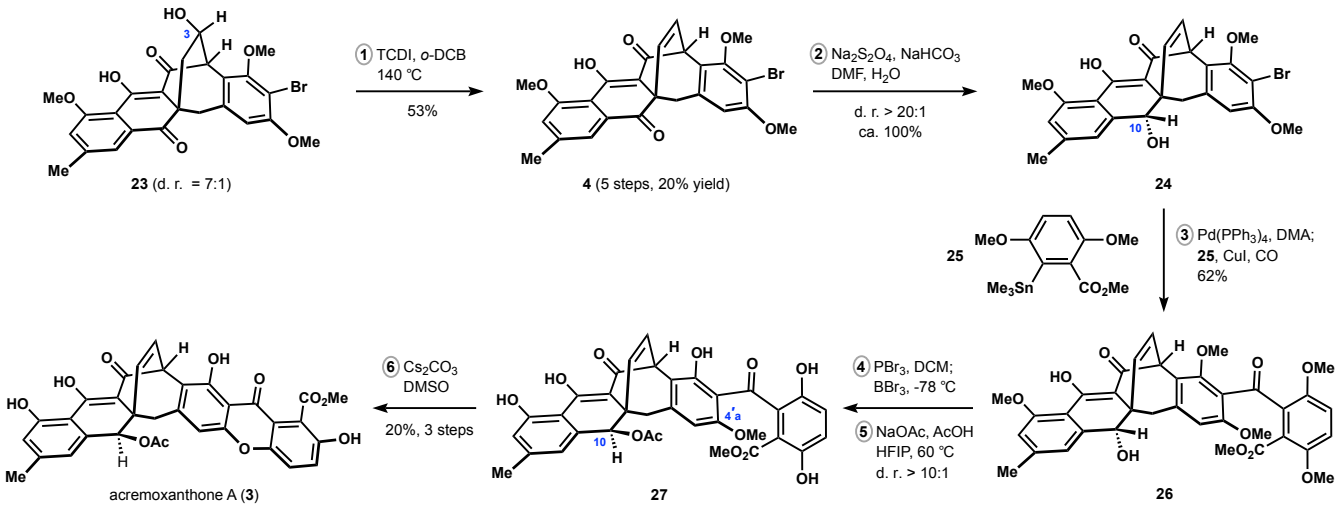


[a]PIFA was used instead of PIDA. [b]r. r. ≈ 15:1.

Preliminary evaluation of the substrate scope indicated that the presence of the fully substituted center was not necessary for the success of the cyclization, and ketone **15** could be obtained in high yield. Furthermore, benzannulated heterocycles **16** and **17** were prepared with comparable efficiency. Modifications of the aromatic substituent were tolerated, but required application of PIFA as an oxidant to minimize formation of the corresponding α-acyloxyketones. Thus, ketone **18** was prepared in good yield and contained a benzosuberone motif found in colchicine.[21] Oxidative arylation en route to ketone **19** proceeded with high regioselectivity, and only traces of the corresponding 4-methoxy-substituted product were observed.[22] It is noteworthy that oxocane derivative **20**, an eight-membered homolog of ketone **16**, could be prepared using our protocol.

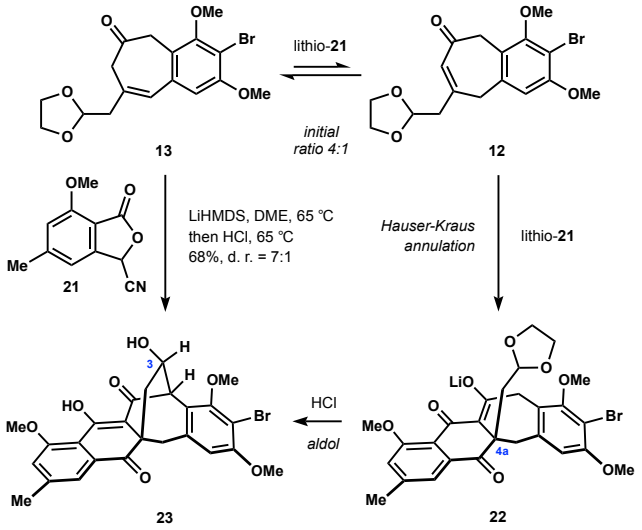
We discovered that treatment of the mixture of ketones **12** and **13** with a lithio derivative of cyanophthalide **21** followed by addition of a strong acid and heating resulted in direct formation of the desired pentacyclic product **23** in good yield (Scheme 2).[23] The process likely involves reversible conversion of styrene derivative **13** to α,β-unsaturated ketone **12**, and lithio-**21** can serve as a catalytic base in the isomerization. Indeed, the value of the initial ratio of **12** to **13** had virtually no effect on the outcome of the transformation. Subsequent Hauser-Kraus annulation of lithio-**21** with ketone **12** produces intermediate **22**.[10] The efficient installation of the quaternary center at C4a is noteworthy as relevant Michael-Claisen cascades find only limited precedent in the current literature.[24] Formation of enolate **22** is supported by observation of the corresponding enol as a major product when subsequent treatment with a strong acid at elevated temperatures was omitted. The latter accomplishes deprotection of the dioxolane moiety and triggers an intramolecular aldol reaction of the resulting aldehyde

Scheme 3. Synthesis of (±)-Acremoxanthone A (3)



with the 1,3-dicarbonyl motif, which could be replicated in a separate experiment with the conjugate acid of **22**. The resulting secondary alcohol at C3 of pentacycle **23** was installed with good stereoselectivity, and the depicted relative configuration of the major diastereomer was supported by the results of the NOE experiments.

Scheme 2. Assembly of the Bridged Polycyclic Motif



Elimination of the secondary alcohol **23** was readily accomplished upon heating with thiocarbonyldiimidazole,[25] completing construction of the desired pentacyclic intermediate **4** in five steps from commercially available material (Scheme 3). To demonstrate the application of our strategy, we synthesized acremoxanthone A (**3**) in five steps from ketone **4**. Thus, reduction with sodium dithionite produced benzyl alcohol **24** in high yield and high diastereoselectivity, albeit with a preference for the undesired configuration at C10. Crystallographic analysis of **24** suggests that the methylene of the benzyl fragment is blocking the approach to the carbonyl group from the same face. Indeed, we were unable to identify conditions that selectively installed the desired configuration at C10. Nevertheless, the problem of stereoselectivity was readily overcome later in the sequence (see below). Carbonylative Stille cross-coupling of aryl bromide **24** with arylstannane **25** was best performed in the presence of stoichiometric quantities of tetrakis(triphenylphosphine)palladium to deliver corresponding benzophenone derivative **26** in good yield.[26–28] Treatment of **26** with phosphorous tribromide followed by addition of a large excess of boron tribromide accomplished conversion of the secondary alcohol moiety to the corresponding alkyl bromide and deprotection of all but one of the aryl methyl ether functionalities. Solvolysis of the crude bromide in a mixture of acetic acid and HFIP delivered acetate **27** bearing the remaining methoxy group at C4′a and the desired stereochemistry at C10.[29] Treatment of crude intermediate **27** with a weak base at elevated temperatures resulted in cyclization to form the xanthone moiety[30] and afforded acremoxanthone A (**3**) in 10 steps from commercially available material.[31]

In summary, we disclose a concise approach to the functionalized pentacyclic core of anthraquinone-xanthone heterodimers featuring an efficient assembly of a benzocycloheptenone via a new intramolecular oxidative arylation of an enol ether and a Hauser-Kraus annulation-aldol reaction sequence to access the characteristic bicyclo[3.2.2]nonene motif. We also demonstrate a short synthesis of (±)-acremoxanthone A, which serves as a proof of concept for our approach. We anticipate that the strategy reported herein will be applicable to the synthesis of other anthraquinone-xanthone heterodimers, implementation of which is currently underway.

ASSOCIATED CONTENT

Experimental procedures and spectroscopic data for new compounds as well as a CIF file for compound **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Funding from the School of Physical Sciences at the University of California, Irvine, Chao Family Comprehensive Cancer Center, and Allergan (graduate fellowship to S.D.H.) is gratefully acknowledged. S.V.P. is a Hellman fellow. We thank Dr. Joseph Ziller and Michael Wojnar for X-ray crystallographic analysis. We also thank Professors Larry Overman, Chris Vanderwal, and Scott Rychnovsky for providing routine access to their instrumentation and helpful discussions.

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(15) Benzyl bromide **10** was prepared in one step from the corresponding commercially available alcohol. See Supporting Information for details.

(16) Performing the alkylations in two separate steps did not offer any advantages and led to a decrease in the overall yield of **11** from **8**.

(17) Isomers **12** and **13** were distinguished by NOE experiments.

(18) Variations in the work-up conditions did not increase the content of **12** in the product mixtures.

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(22) Formation of **19** was accompanied by the corresponding α-(trifluoroacetoxy)ketone: ^{1}H NMR analysis of the crude product mixture indicated ca. 2:1 ratio of **19** and the trifluoroacetate, respectively.

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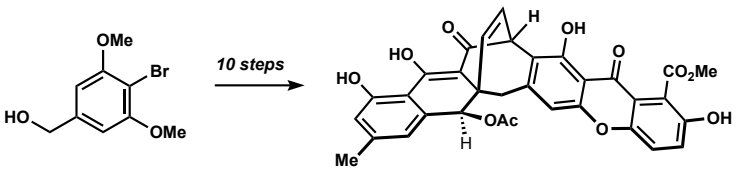
(27) Arylstannane **20** was prepared in two steps from commercially available 2,5-dimethoxybenzoic acid. See Supporting Information for details.

(28) For an example of the use of a preformed arylpalladium(II) complex in the Stille cross-coupling in the context of synthesis see: Zajac, M. A.; Vedejs, E. *Org. Lett.* **2004**, *6*, 237–240.

(29) The stereochemical outcome of the solvolysis can be rationalized following the logic found in the discussion of the reduction en route to alcohol **24**.

(30) For examples of relevant cyclizations see: Hintermann, L.; Masuo, R.; Suzuki, K. *Org. Lett.* **2008**, *10*, 4859–4862.

(31) In this sequence, the bromination/deprotection step accounts for the main loss of the material.



acremoxanthone A