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Total Syntheses of Graphisin A and Sydowinin B

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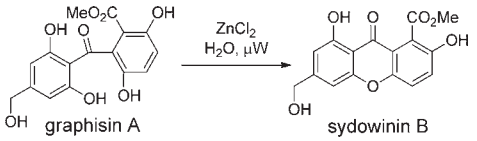
ABSTRACT



Efficient syntheses of the highly substituted benzophenone graphisin A and the xanthone sydowinin B are described. Key steps involve aryl anion addition to substituted benzaldehyde derivatives, subsequent methyl ester installation, and dehydrative cyclization. Oxidation of graphisin A led to a spirodienone derived from a highly substituted benzoquinone intermediate.

Acremoxanthone A[2] (**1**), xanthoquinodin A[3] (**2**), and acremonidin A (**3**)[4] (Figure 1) are members of a class of heterodimeric natural products originally isolated from *Acremonium* sp. BCC31806, *Humicola* sp. FO888, and *Acremonium* sp. *LL*-Cyan 416, respectively. These natural products share structurally related anthraquinone and xanthone-derived monomer units which are linked by a unique bicyclo[3.2.2] ring system.[5] We have initiated synthetic studies toward these targets with syntheses of the requisite xanthone and benzophenone fragments present in the natural product frameworks. In our initial studies, we have targeted the highly functionalized, tetra-*ortho*-substituted benzophenone graphisin A[6] (**4**) and the corresponding cyclized xanthone sydowinin B[7] (**5**). Herein, we report the total synthesis of the highly substituted benzophenone[8] graphisin A using a suitably functionalized benzophenone as well as preparation of the derived xanthone sydowinin B *via* dehydrative cyclization.

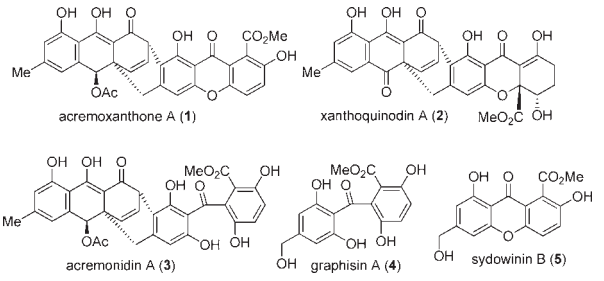


Figure 1. Acremoxanthone A and related natural products.

Our initial plan (Figure 2) was to prepare benzophenone nitrile **6** *via* aryl anion addition to a substituted benzaldehyde according to literature precedent.[9] We envisioned that acidic methanolysis[10] of aryl nitrile **6** followed by

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global deprotection should provide graphisin A (**4**). Sydowinin B (**5**) could then be accessed through dehydrative cyclization.[11]

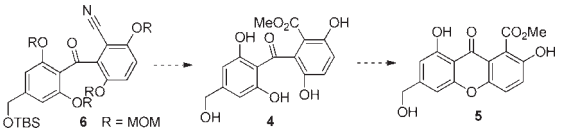
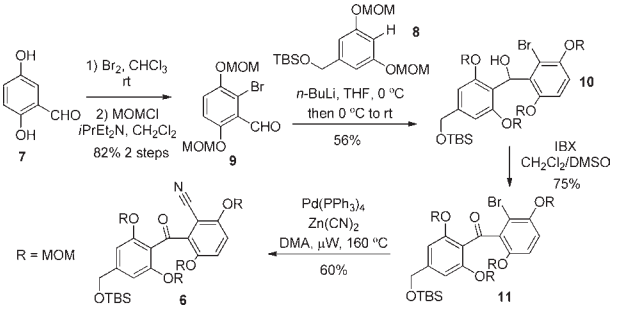


Figure 2. Initial synthetic plan.

In our forward synthesis, benzaldehyde **7** was regioselectively brominated and protected as a *bis*-MOM ether in 82% yield over two steps (Scheme 1). Regioselective deprotonation of **8** with *n*-BuLi, followed by addition of aldehyde **9** at 0 °C, provided benzylic alcohol **10** in 56% yield with the remainder of the mass balance consisting of byproducts derived from competitive lithium−halogen exchange of the *ortho* aryl bromide. Oxidation of **10** with 2-iodoxybenzoic acid (IBX) provided bromobenzophenone **11** (75%). We had initially planned to utilize **11** directly in palladium-catalyzed carbonylative methyl ester formation ($Pd(dppf)Cl_2$, CO, NEt_3, DMF/MeOH);[12] however, this substrate was found to be unreactive likely due to the highly electron-rich and *bis-ortho*-substituted aryl ring. Efforts to install the methyl ester on either bromobenzaldehyde **9** or its corresponding acetal-protected derivatives were also unsuccessful. Similarly, anion chemistry (e.g., lithium−halogen exchange, Grignard formation) of aryl bromide substrates was also found to be unproductive.[8c] However, compound **11** was found to undergo smooth cyanation using $Pd(PPh_3)_4$ and $Zn(CN)_2$ under microwave heating to afford aryl nitrile **6** in 60% yield.[13]

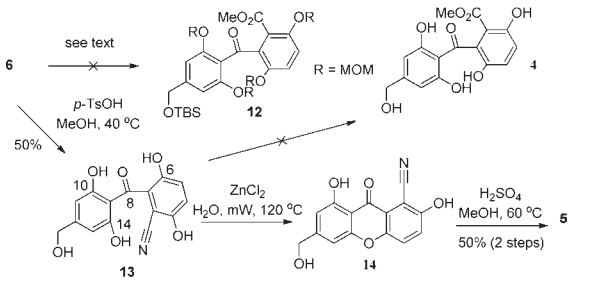
Initial attempted hydrolysis of aryl nitrile **6** to the derived acid or ester **12** (aq NaOH or H_2SO_4) resulted in either decomposition or partial MOM deprotection (Scheme 2). Attempted partial hydrolysis of the primary amide with K_2CO_3 and H_2O_2[14] resulted in no reaction. Similarly, treatment of **6** with methyl triflate in CH_2Cl_2 followed by a methanolysis to access the imidate in a Ritter-type reaction was also unsuccessful.[15] Attempts to hydrolyze the nitrile in the presence of methanol (BF_3,[16] $FeCl_3$,[17] TMSCl,[18] and H_2SO_4[19]) resulted in mixtures of partially and fully MOM-deprotected compounds with the aryl nitrile remaining intact.

Scheme 1. Synthesis of Aryl Nitrile **6**



In light of the apparent incompatibility of the MOM protecting groups with nitrile hydrolysis conditions, we elected to fully deprotect benzophenone **6** to tetraphenol **13** prior to hydrolysis (Scheme 2). Accordingly, treatment of nitrile **6** with *p*-TsOH in MeOH at 40 °C produced a deep red solution whereby the protecting groups were globally removed to afford benzophenone **13** in 50% yield. Purification of polyphenol **13** on silica gel was found to be difficult due its high polarity and propensity to form an intractable, red-colored salt with residual *p*-TsOH. An example of a highly substituted benzophenone nitrile hydrolysis has been reported.[20] However, standard acidic hydrolysis[9] (H_2SO_4 or HCl, MeOH, 60 °C) of **13** resulted in recovered starting material and minor formation of xanthone **14**, whereas standard basic conditions[21] (NaOH) resulted in decomposition.

Scheme 2. Synthesis of Sydowinin B *via* an Aryl Nitrile



At this juncture, we elected to optimize the xanthone formation/nitrile methanolysis sequence. We observed dehydrative cyclization to the xanthone when attempting

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to hydrolyze nitrile **13** with DOWEX-50 resin in water under microwave heating.[22] We later observed clean conversion of **13** to xanthone **14** using microwave heating with aqueous $ZnCl_2$.[23] A ground state model of nitrile **13** (Figure 3) shows that the benzophenone exists substantially in a bisected conformation with hydrogen bonding maintained between the C-6 and C-10 phenols and the C-8 ketone. However, internal hydrogen-bonding of the phenols may be disrupted in water such that rotation can occur prior to cyclization to form xanthone **14**. Xanthone **14** was finally subjected to acidic methanolysis conditions (3 M H_2SO_4, MeOH, 60 °C) which afforded sydowinin B (**5**) in 50% yield (two steps).

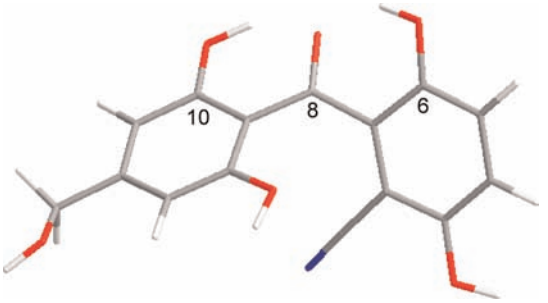
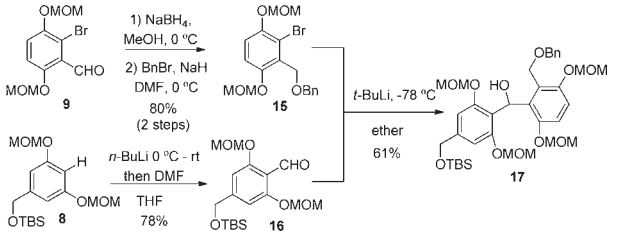


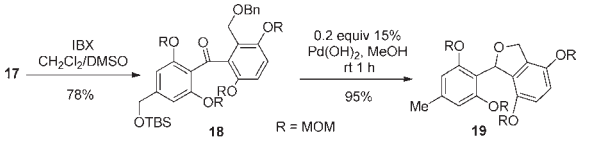
Figure 3. DFT minimized model of nitrile **13**.

Scheme 3. Alternative Route to Graphisin A



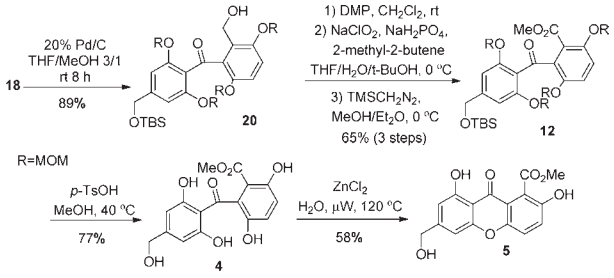
To enable installation of the requisite methyl ester and access graphisin A (**4**) without dehydrative cyclization, we implemented the alternative route shown in Scheme 3. Bromoaldehyde[24] **9** was reduced and benzyl-protected to afford aryl bromide **15** in 80% yield (two steps). Regioselective deprotonation of **8** and subsequent quenching with DMF provided benzaldehyde **16** (78%). Lithium–halogen exchange of aryl bromide **15** at −78 °C in ether with *t*-BuLi followed by a rapid quench with aldehyde **16** provided benzyl alcohol **17** (61%). Subsequent IBX oxidation afforded ketone **18** in 78% yield (Scheme 4). Initial attempted conditions for selective benzyl deprotection of **18** (H_2, $Pd(OH)_2$, MeOH) resulted in complete conversion to the over-reduced product **19**, analogous to a product[25] reported by Snider and co-workers for a similar substrate.[26] However, hydrogenolysis of **18** using Pd/C in THF/MeOH (3:1) led to the desired hydroxybenzophenone **20** (Scheme 5). It is apparent that sole use of a polar protic solvent activates **20** toward hemiketal formation which undergoes further hydrogenolysis to the corresponding dihydroisobenzofuran **19**.

Scheme 4. Dihydroisobenzofuran Formation



A three-step oxidation–methylation sequence was next conducted on the protected benzophenone **20** involving sequential Dess-Martin and Pinnick oxidations followed by treatment with excess $TMSCH_2N_2$ in 1:1 MeOH/Et_2O to provide methyl ester **12** in 65% yield over three steps (Scheme 5).[25] Compound **12** was fully deprotected with *p*-TsOH in MeOH to provide graphisin A (**4**) in 77% yield. Analytical data for **4** including ^1H and ^{13}C NMR spectra were in agreement with those reported for the natural product.[6] Graphisin A (**4**) could also be converted to sydowinin B (**5**) in 58% yield by dehydrative cyclization with aqueous $ZnCl_2$ under microwave conditions (120 °C).[23]

Scheme 5. Synthesis of Sydowinin B *via* Graphisin A



It has been proposed that the biosynthesis of various members of the blennolide/secalonic acid[27] family of natural products proceeds through oxidation/reduction of functionalized benzophenone intermediates resembling

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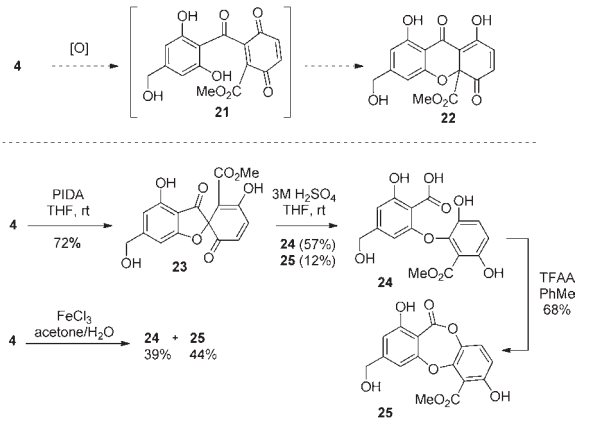
(24) Goddard, M. L.; Tabacchi, R. *Tetrahedron Lett.* **2006**, *47*, 909–911.
(25) Yu, M.; Snider, B. B. *Org. Lett.* **2011**, *13*, 4224–4227.
(26) We observed aryl and MOM ether peak broadening in the ^1H and ^{13}C NMR spectra for compound **19** similar to a 2,6-disubstituted aryl dihydroisobenzofuran reported in ref 25 (see Supporting Information for details).
(27) (a) Zhang, W.; Krohn, K.; Flörke, U.; Pescitelli, G.; Di Bari, L.; Antus, S.; Kurtan, T.; Rheinheimer, J.; Draeger, S.; Schulz, B. *Chem.—Eur. J.* **2008**, *14*, 4913–4923. (b) Gerard, E. M. C.; Bräse, S. *Chem.—Eur. J.* **2008**, *14*, 8086–8089. (c) Qin, T.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1714–1717.

Scheme 6. Oxidation of Graphisin A



graphisin A.[28] Accordingly, we conducted preliminary investigations as to whether graphisin A (**4**) could be converted to dienone **22** *via* oxidation to benzoquinone **21** followed by *oxa*-Michael addition (Scheme 6).[29] Treatment of graphisin A (**4**) with phenyliodine diacetate (PIDA) resulted in clean oxidative cyclization to spirodienone **23**.[30] Oxidations of hydroxybenzophenones to similar spiro-dienones are known[25,31]and are thought to occur *via* a phenoxide radical that is aligned to favor the five-membered ring due to a bisected conformation of the highly substituted benzophenone. Spirodienone **23** was treated under acidic conditions[25] to provide a mixture of rearranged acid **24** (57%) and depsidone **25** (12%). Acid **24** could be further cyclized to depsidone **25** by heating with TFAA in toluene (68%). In a similar fashion, oxidation of **4** with $FeCl_3$ provided a mixture of **24** (39%) and **25** (44%) as the sole products.

Following reported dehydrogenation conditions that likely proceed through quinone intermediates,[32] treatment of graphisin A (**4**) with Pd/C−O_2 also provided spirodienone **23** in 89% yield. This result supports the intermediacy of benzoquinone **21** enroute to **23**. While both 6-*endo*-*trig* and 5-*exo*-*trig* cyclization modes of **21** are possible,[33] the observed isomer **23** is likely favored due to the bisected conformation[34] of proposed intermediate **21** which places one *ortho*-phenol in favorable alignment with the π^*-orbital of the C-7 quinone carbon (Figure 4).

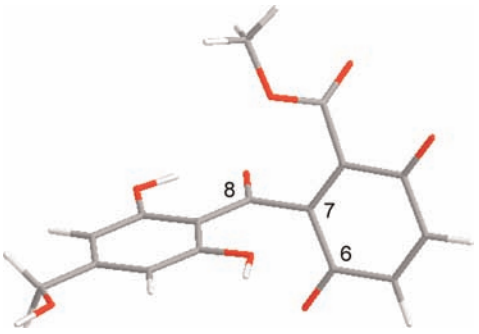


Figure 4. DFT minimized model of proposed benzoquinone intermediate **21**.

In conclusion, an efficient synthesis of graphisin A has been accomplished employing aryl anion addition to a benzaldehyde, followed by oxidation to a highly substituted benzophenone, subsequent methyl ester installation, and global deprotection. Graphisin A was further converted by dehydrative cyclization under microwave conditions to the xanthone sydowinin B. Oxidation of graphisin A led to formation of a spirodienone likely from a highly substituted and bisected benzoquinone intermediate. Further studies employing graphisin A and sydowinin B toward the synthesis of acremoxanthones and related natural products are currently in progress and will be reported in due course.

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Supporting Information Available. Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) For examples of cyclization of hindered 2-hydroxybenzoyl-*p*-quinones to xanthones, see: Nichols, A. L.; Zhang, P.; Martin, S. F. *Org. Lett*. **2011**, *13*, 4696–4699.

The authors declare no competing financial interest.