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Biomimetic Total Synthesis of (±)-Griffipavixanthone via a Cationic Cycloaddition–Cyclization Cascade

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Abstract

We report the concise, biomimetic total synthesis of the dimeric, Diels–Alder natural product griffipavixanthone from a readily accessible prenylated xanthone monomer. The key step utilizes a novel intermolecular [4+2] cycloaddition–cyclization cascade between a vinyl *p*-quinone methide and an *in situ* generated isomeric diene promoted by either Lewis or Brønsted acids. Experimental and computational studies of the reaction pathway suggest that a stepwise, cationic Diels–Alder cycloaddition is operative.

Dimeric xanthenes are a class of natural products with a wide range of structural diversity and biological activity, which underscores these compounds as attractive synthetic targets.¹ Among these compounds, griffipavixanthone (**1**) possesses a unique structure wherein the monomeric tetrahydroxanthone units are linked via an apparent Diels–Alder-derived bicyclic framework rather than the commonly encountered aryl–aryl or C–O bond (Figure 1).² Several related dimeric Diels–Alder xanthenes, namely garciobioxanthone (**2**),³ bigarcinenone B,⁴ and garcilivins A and C (not shown),⁵ wherein the monomeric xanthone units are linked by a single cyclohexene ring, have also been isolated and characterized.

Although biological activities of these dimeric xanthenes have not been extensively reported, **1** is reported to possess antioxidant properties,⁶ highlighted by *in vitro* inhibition observed against xanthine oxidase.⁷ In addition, **1** is active against several cancer cell

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09265.

Experimental details, computational data, and characterization data for new compounds (PDF)

X-ray crystallographic data for **11a** (CIF)

The authors declare no competing financial interest.

lines,^{2,8,9} and has recently been shown to downregulate the RAF pathway in esophageal cancer cells.¹⁰ Herein, we report the first chemical synthesis of **1** utilizing a biomimetic [4+2] cycloaddition–cyclization cascade between a monomeric, vinyl *p*-quinone methide (*p*-QM) dienophile and an *in situ* generated, isomeric diene promoted by either zinc(II) iodide (ZnI₂) or trifluoroacetic acid (TFA).

Biosynthetically, the cyclohexene core of **1** is likely formed via Diels–Alder cycloaddition between a prenylated tetrahydroxyxanthone and a related, formally dehydrogenated 1,3-butadiene,² both of which may be derived in nature from the monomer garcinexanthone C.¹¹ With our continuing interest in biomimetic syntheses of Diels–Alder natural products, this insight inspired us to consider development of a novel reaction cascade wherein both diene and dienophile could be generated from a single prenylated monomer.¹² Retrosynthetically, we envisioned that **1** may be accessed via intramolecular arylation between the *p*-QM and xanthone moieties of cycloadduct **3** (Scheme 1).^{13,14} *p*-QM **3** may be derived from oxidation of monomer **6** and subsequent [4+2] cycloaddition of the resulting vinyl *p*-QM **4** with the corresponding isomeric diene **5** generated *in situ* (*vide infra*).¹⁵

To test our biomimetic proposal, we first prepared the requisite prenylated xanthone monomer (Scheme 2). Condensation of 1,3,5-trimethoxybenzene with 2,3-dihydroxy-4-methoxybenzoic acid in the presence of Eaton's reagent at elevated temperature readily provided the desired xanthone as a mixture of 5-hydroxy- and 5-mesyloxyxanthones.¹⁶ Treatment of this crude mixture with methanolic potassium hydroxide allowed for smooth demesylation and isolation of the xanthone as the corresponding potassium salt, which was subsequently *O*-alkylated with prenyl bromide to afford prenyloxyxanthone **7** (53% yield, 3 steps) on a decagram scale. Thermal rearrangement of **7** in refluxing *N,N*-dimethylaniline (DMA) provided the prenylxanthone monomer **8** in 47% yield.¹⁷

Our preliminary efforts toward assessing oxidation and isomerization of the key monomeric vinyl *p*-QM intermediate first focused on trimethoxyxanthone substrate **8** in order to eliminate potential side reactions resulting from multiple unprotected phenols. We found that silver(I) oxide (Ag₂O) cleanly oxidized **8** to the desired *p*-QM **9** at ambient temperature in CH₂Cl₂ as solvent (Scheme 3).¹⁸ While treatment of **9** with silica gel, conditions known to isomerize prenylated *o*-quinones to *p*-QMs,¹⁹ typically led to complex product mixtures, exposure of **9** to catalytic amounts of *N,N*-diisopropylethylamine (DIPEA) promoted smooth conversion to 1,3-butadiene **10**.²⁰ To the best of our knowledge, this represents the first example of isomerization of a vinyl *p*-QM to the corresponding diene; however, analogous formal dehydrogenation of prenylated derivatives to 1,3-butenes has previously been reported.²¹

The isomerization of **9** to **10** permitted exploration of the proposed [4+2] cycloaddition. During isomerization experiments, only trace cycloaddition products were observed, even at elevated temperatures. Furthermore, conversion of **9** to **10** did not appear to be reversible under the isomerization conditions. These observations led us to conclude that activation of **9** was necessary for cycloaddition and the rate of cycloaddition must be faster than the conversion of **9** to **10**.

To address these requirements, Lewis²² or Brønsted²³ acid promoters appeared to be required, as they have been shown to activate *p*-QMs toward subsequent reactivity. Indeed, exposure of **9** to catalytic amounts of a number of Lewis acids led to complete consumption of starting material (CH₂Cl₂ as solvent) as determined by ¹H NMR analysis.²⁴ Although conversion of **9** led to numerous reaction products under many of these conditions, the unequal formation of two products with doublets at δ 8.74 and 8.46 ppm (¹H NMR) suggested formation of *p*-QM-containing cycloadducts with varying levels of diastereoselectivity.²⁴ Full spectroscopic characterization revealed that these species were indeed the desired [4+2] cycloadducts. After screening both Lewis acid and solvent, we were able to generate isolable quantities of each cycloadduct (Scheme 4). For example, use of lanthanum(III) triflate (La(OTf)₃) as catalyst in a 2:1 mixture of CH₂Cl₂ and hexafluoroisopropanol (HFIP) with DIPEA as additive at 30 °C selectively provided cycloadduct **11a** possessing an *anti* stereochemical relationship of the aromatic ring systems in 25% yield. The structure of **11a** was confirmed via single-crystal X-ray analysis (Figure 2) and reveals a significant deviation from planarity (21.3°) between the exocyclic alkene of the *p*-QM and the neighboring carbonyl. Use of ZnI₂ resulted in the highest selectivity and yield for the diastereomeric *syn*-cycloadduct **11b** (crude ratio **11b**:**11a** = 1.0:0.96) providing **11b** and **11a** in 17 and 18% yields, respectively. Furthermore, cycloadduct **11a** was found to be unreactive to treatment with ZnI₂, with no evidence of cycloadduct reversibility or epimerization, suggesting metal-ion-dependent stereoselectivity to access **11a/b** from **9**.²⁴

While numerous Lewis acids generated **11b** to varying degrees, subsequent arylation to yield the griffipavixanthone core was not readily observed beyond trace quantities. We therefore aimed to improve the Zn(II)-catalyzed conditions which provided the highest observed selectivity for **11b**, and develop a one-pot cycloaddition–cyclization cascade. After examining numerous conditions, we determined **9** to be a poor substrate for the desired transformation, which required 30 mol% of ZnI₂ and elevated (50 °C) temperature in 1,2-dichloroethane (DCE) to provide griffipavixanthone hexamethyl ether **12** in 4% yield (Scheme 5). We considered that the low yields may in part be due to intermolecular arylation of the electron-rich ring of **9** and the quinone methide moiety of a second molecule of **9**, as intermolecular arylations of *p*-QMs with electron-rich aromatics in the presence of Lewis acids have been reported.^{25,26} Indeed, reaction of **9** with excess 1,3,5-trimethoxybenzene in the presence of ZnI₂ cleanly afforded 1,6-arylation product **13** in 68% yield (eq 1).

(1)

To address this issue, we hypothesized that demethylation of **9** *ortho* to the xanthone carbonyl would remove electron density from the phloroglucinol-type ring through hydrogen bonding, thereby reducing this decomposition pathway. Indeed, we found that the di-*O*-methyl-protected vinyl *p*-QM **14**²⁴ was superior to **9**, requiring only 15 mol% of ZnI₂ at 40 °C for 16 h in DCE (0.05 M) to provide griffipavixanthone tetramethyl ether **15** in 15%

isolated yield. With increased amounts of precursor **15** in hand, full demethylation to ($\pm$)-**1** was achieved in 32% yield using a modified potassium carbonate/*p*-thiocresol protocol in *N,N*-dimethylacetamide (*N,N*-DMA) as solvent (Scheme 5).²⁷ Spectral data for synthetic ($\pm$)-**1** were in agreement with data previously reported for the natural product.²

In an effort to understand the direct conversion of **14** to **15**, experiments designed to interrogate the reactivity of cycloadduct intermediates leading to **15** were performed. We found that treatment of monomer **14** with 15 mol% of LaCl₃·2LiCl provided cycloadducts **16a/b** in 32% combined yield (crude ratio of **16a**:**16b** = 1.5:1.0) with minimal conversion to **15** observed. Spectral characterization and comparison with **11a/b** revealed that *anti*-cycloadduct **16a** was the major product formed upon reaction of **14** with both LaCl₃·2LiCl and ZnI₂, in contrast with that of **9**. Furthermore, cycloadducts **16a/b** were found to be substantially more reactive than **11a/b**, as treatment of both **16a** and **16b** with 30 mol% ZnI₂ led to **15** in 73% (brsm) and 80% isolated yield, respectively (Scheme 6). Similar results were also observed in the presence of 30 mol % of TFA, as both **16a** and **16b** yielded **15** in 78% and 82% yield, respectively.²⁸ In light of these results, we anticipated that **14** may also yield **15** under similar conditions. Indeed, treatment of **14** with 30 mol% of TFA at 35 °C for 18 h provided **15** in an improved 21% isolated yield, demonstrating that both Lewis and Brønsted acids are capable of promoting the observed cycloaddition–cyclization cascade to yield the griffipavixanthone core from monomer **14**.

The formation of griffipavixanthone precursor **15** from either **14** or a **16a/b** mixture (cf. Scheme 6) supports an ionic Diels–Alder reaction cascade in which six-membered ring formation is reversible.^{29,30} Figure 3 outlines a plausible mechanism which is supported by DFT computations.^{24,31,32} After acid-catalyzed isomerization of **14** to **10a**, the intermediate cation **17** may combine with **10a** to afford allylic cations, represented as **18a–c**. Cation **18a** was the lowest energy structure located; this should interconvert with an energetically favorable xanthonium ion **19** which arises from capture of the benzyl cation by the nucleophilic carbonyl of the pendant xanthone. Isomeric allyl cations **18b** and **18c** were found to possess the correct stereochemistry and conformation required to reversibly progress to stereoisomeric benzyl cation intermediates **20** and **21** with barriers of 9.2 and 17.5 kcal/mol, respectively. The cascade is completed by intramolecular arylation to yield arenium ions **22** or **23** through **TS4** or **TS5**, respectively. Selective formation of griffipavixanthone precursor **22** vs epimer **23** is consistent with the lower predicted barrier (16.5 vs 21.0 kcal/mol) for the irreversible arylation step. This difference is ascribed in part to the lower strain energy required to yield the *cis*- vs *trans*-fused polycyclic ring systems of **22** and **23**. We note that while these computational results are in agreement with our experimental findings, we cannot at this time rule out alternative stereochemical interconversion of **16a** and **16b** via elimination followed by regioselective protonation or 1,2-hydride shift³³ pathways of intermediates **20** and **21**.

In summary, we have developed the first synthesis of the Diels–Alder natural product griffipavixanthone (**1**) in racemic form. The unique polycyclic core of **1** was prepared under mild Lewis or Brønsted acidic activation via a multistep, one-pot [4+2] cycloaddition–cyclization cascade involving (1) isomerization of an isolable vinyl *p*-QM monomer to the

corresponding 1,3-butadiene *in situ*; (2) stepwise, reversible cationic [4+2] cycloaddition between the vinyl *p*-QM monomer and newly generated 1,3-butadiene; and (3) intramolecular arylation of a *p*-QM-containing cycloadduct. Experimental and computational investigations of the reaction mechanism support the proposed cationic reaction cascade. Further studies related to the asymmetric synthesis of griffipavixanthone are under investigation and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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griffipavixanthone (1)

garciobioxanthone (2)

Figure 1.
Structures of dimeric xanthones.

Figure 2.
X-ray crystal structure of cycloadduct **11a**.

Figure 3. Computational modeling (B3LYP/6-31G(d)) for Brønsted acid-catalyzed reactions. All free energies in kcal/mol relative to **18a**. See Supporting Information for full reaction coordinate diagram.

Scheme 1. Retrosynthetic Analysis for Griffipavixanthone

Scheme 2. Synthesis of Xanthone Monomer **8^a**

^aReagents and conditions: (a) Eaton's reagent, 110 °C, 5.5 h; (b) KOH (8.0 equiv), MeOH , rt, 15 h; (c) prenyl bromide (1.6 equiv), K_2CO_3 (0.21 equiv), DMF , 50 °C, 4 h; (d) DMA , 194 °C, 2 h.

Scheme 3. Synthesis and Isomerization of *p*-QM 9^a

^aReagents and conditions: (a) Ag_2O (1.20 equiv), CH_2Cl_2 , rt, 16 h; (b) DIPEA (0.15 equiv), CH_2Cl_2 , rt, 48 h.

Scheme 4. Lewis Acid-Controlled Dimerization of 8 to Cycloadducts 11a and 11b

Scheme 5. One-Pot Dimerization–Cyclization Cascade and Demethylation of 15 to ($\pm$)-1^a

^aReagents and conditions: (a) ZnI₂ (30 mol%), DCE, 50 °C, 24 h; (b) ZnI₂ (15 mol%), DCE, 40 °C, 16 h; (c) *p*-MeC₆H₄SH (10.0 equiv), K₂CO₃ (1.0 equiv), *N,N*-DMA, 166 °C, 1.5 h.

Scheme 6. Conversion of Cycloadducts 16a and 16b and 14 to 15 with Lewis and Brønsted Acids

^aReagents and conditions: (a) ZnI_2 (30 mol%), CH_2Cl_2 , 35 °C, 7 h (73% yield brsm from **16a**, 80% from **16b**); (b) TFA (30 mol%), CH_2Cl_2 , rt, 7 h (78% yield from **16a**, 82% from **16b**); (c) TFA (30 mol%), CH_2Cl_2 , 35 °C, 18 h (21% yield).