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Total Synthesis of Aurofusarin: Studies on the Atropisomeric Stability of Bis-Naphthoquinones

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Abstract

An efficient annulation involving pyrone addition to a quinone and Dieckmann condensation was developed for rapid assembly of a γ -naphthopyrone monomeric precursor to the bis-naphthoquinone natural product aurofusarin. Dimerization was achieved through Pd^{II}-catalyzed dehydrogenative coupling. Further studies employing asymmetric nucleophilic epoxidation indicate that the atropisomers of aurofusarin and derivatives are not configurationally stable at ambient temperature.

Keywords

annulation; axial chirality; epoxidation; dehydrogenative coupling; naphthoquinones

Naphthopyranone natural products^[1] are widely found in nature and typically possess the 1*H*-naphtho-[2,3-*c*]pyran-1-one core structure as present in the dimer xanthomegnin (**1**)^[2] (Figure 1). Aurofusarin (**2**)^[3] and the bis-epoxyquinol diaporine (**4**)^[4] an inhibitor of macrophage differentiation that induces conversion from the M2 (“repair-type”) to the M1 (“kill-type”) phenotype, are likely derived from the monomeric naphtho- γ -pyrone rubrofusarin (**3**).^[5] Such γ -naphthopyranone scaffolds are difficult to access and there are few reported syntheses to date. For example, rubrofusarin (**3**) was previously synthesized in 14 steps in low yield^[6] and a formal synthesis of **1** was achieved from a monomeric precursor (semi-vioxanthin).^[2]

Herein, we report a concise synthesis of the γ -naphthopyranone monomeric unit and its Pd-catalyzed dehydrogenative dimerization to a biaryl precursor for aurofusarin. Based on the work of Thomson and co-workers concerning bismurrayaquinoneA (**5**)^[7] and seminal work by Shair and coworkers on dimeric methoxyquinone-containing natural products,^[8d] we wondered whether the atropisomers of bisnaphthoquinones such as (**1**)^[2] and (**2**) are

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Conflict of interest

The authors declare no conflict of interest.

configurationally stable. Accordingly, we studied the axial chirality of **2** because it is crucial for the enantioselective synthesis of the congener diaporine (**4**).

Retrosynthetically, we envisioned that aurofusarin (**2**) may be accessed through oxidation of biaryl precursor **6** (Scheme 1). Construction of biaryl **6** requires highly selective conditions for oxidative dimerization, considering possible oxidation of **7** to a naphthoquinone. We proposed that monomer **7** may be obtained from aryl pyrone **8**, a compound derived from tandem Michael addition/Dieckmann condensation of methoxy benzoquinone **9**^[8] and dienol ether **10**. Compound **10** may be accessed from the commercially available dimethyl γ -pyrone **11**.

To prepare substituted pyrone **8**, we envisioned that treatment of **11** with trimethylsilyl triflate (TMSOTf) should afford a siloxypyrylium intermediate^[9] that may be deprotonated under basic conditions. Accordingly, **11** was consecutively treated with TMSOTf and 2,6-lutidine, followed by addition of quinone **9**.^[10] Acidic conditions for workup (aq. HCl) were found to be crucial for the formation of **8**, since a basic workup using tetra-*N*-butylammonium fluoride (TBAF) afforded an undesired benzofuran product^[11] (Scheme 2). To overcome difficulties encountered in the monomethylation of **8**, γ -pyrone **12** was synthesized through a double-methylation/selective demethylation sequence and was further converted into MOM ether **13**. We next evaluated Dieckmann cyclization of **13**. To our delight, use of lithium diisopropylamide (LDA) as base produced a 30% yield of the desired product **14**, which was further improved to 77% by using degassed solvent. Methylation of **14** with Cs₂CO₃/dimethyl sulfate (Me₂SO₄) in degassed acetone led to **15**, which was treated with trifluoroacetic acid (TFA) in CH₂Cl₂ to afford monomer **16** for dimerization studies.

Inspired by studies on the biosynthesis of aurofusarin, in which dimerization was shown to be catalyzed by *Gip1*, a copper-containing laccase enzyme,^[12] we wished to mimic this process by using metal-mediated oxidative conditions. Accordingly, we initiated dimerization studies using copper salts with diamine ligands,^[13a] which have been widely used in biaryl couplings. However, in general, conditions employing single-electron-oxidation metal catalysts such as NH₄VO₃, FeCl₃, SnCl₄, and AgOTFA only led to the production of a monomeric naphthoquinone product.^[11, 13]

We reasoned that the electron-rich substrate **16** may require milder oxidative coupling conditions, which prompted our investigation of palladium-mediated dehydrogenative coupling.^[14] After considerable experimentation, we found that treatment of **16** with Pd(OAc)₂ (10 mol%) in DMSO afforded dimer ($\pm$)-**17** (Table 1, entry 1). However, to achieve full conversion, a stoichiometric amount of Pd(OAc)₂ was required. Encouraged by these results, we evaluated a number of ligands to facilitate catalyst turnover. Yu and co-workers^[15] have demonstrated that monoprotected amino acids can be utilized as chiral ligands in asymmetric C–H bond activation. Accordingly, we evaluated the use of monoprotected amino acids with Pd(OAc)₂. Treatment of **16** with catalytic Pd(OAc)₂ and *N*-acetyl-L-leucine under aerobic conditions led to dimer ($\pm$)-**17** after heating at 70 °C for 4 h (entry 2). The structure of ($\pm$)-**17** was unambiguously confirmed by X-ray crystallographic analysis.^[16] Evaluation of solvents showed that anhydrous DMSO provided optimal results,

while non-coordinating solvents such as dichloroethane (DCE) (entry 3) led to lower reactivity. Other monoprotected amino acid ligands were found to be less effective for the transformation (entries 5–6). Among the chiral amino acid ligands evaluated, we unfortunately did not observe atropselectivity for the biaryl product **17**.^[17]

Attention was next turned to the synthesis of aurofusarin (**2**; Scheme 3). Treatment of ($\pm$)-**17** with ceric ammonium nitrate (CAN) led to formation of bis-naphthoquinone **18** (88% yield). Synthesis of aurofusarin (**2**) was achieved on a gram scale in 78% yield through selective demethylation of **18** using BBr₃. To study the atropisomeric stability of the bisnaphthoquinone moiety, a gram-scale synthesis of ($\pm$)-**17** (see Table 1) was achieved and the compound subjected to deracemization using Cu^I(+)-sparteine.^[18] Optimal conditions involved in situ generation of a stoichiometric copper- (II)/sparteine complex, which led to 71% mass recovery and (–)-**17** in 95% *ee* ($[\alpha]_D^{25} = -45^\circ$, $c = 0.1$, CH₂Cl₂; Scheme 4). Determination of the absolute configuration of (–)-**17** was attempted using X-ray crystallography, but only a chiral, racemic crystal of ($\pm$)-**17** was obtained. Presumably, photoracemization of (–)-**17** ($\lambda_{\max} = 405$ nm) may occur during crystallization through excited-state intramolecular proton transfer.^[11, 19]

To determine whether the atropisomers of bis-naphthoquinone **18** are configurationally stable, (–)-**17** was oxidized with CAN (Scheme 5a). Analytical chiral HPLC analysis of the resulting bis-quinone **18** did not reveal enantiomer separation, and additionally, no optical rotation was observed.^[11] Accordingly, further derivatization of **18** to epoxide **19** was performed. Epoxidation by NaOCl afforded bis-epoxide **19** as a single diastereomer. However, from chiral HPLC analysis, compound **19** derived from (–)-**17** was racemic, which further supports the idea that the atropisomers of **18** are likely rapidly interconverting. The relative stereochemistry of bis-epoxide **19** was further studied with the model reaction shown in Scheme 5b. Model bis-quinone **20**^[20] was treated with NaOCl in CH₃CN to afford epoxide **22** as a single diastereomer in 78% yield and the relative stereochemistry of **22** was determined by X-ray crystallographic analysis.^[16] From this model reaction, it appears that the *cis* relationship of the epoxides in **22** is derived from epoxidations *anti* to the methoxy groups in the bisected bis-quinone conformer **21**.

Based on the reactivity observed, we envisioned that asymmetric epoxidation of **18** derived from ($\pm$)-**17** could be utilized to further validate our hypothesis for atropisomeric instability of **18**.^[20] Asymmetric nucleophilic epoxidations of enones have been extensively studied^[21] but are generally conducted on simple monomeric quinones.^[22] Accordingly, a series of phase-transfer catalysts (PTCs) were examined, and the cinchonine-derived catalysts **23** and the corresponding dimeric cinchonine catalyst **24** provided up to 75% *ee*. We ultimately identified the Maruoka phase-transfer catalyst **25**^[23] (Scheme 6) as a suitable catalyst for asymmetric epoxidation, which afforded bis-epoxide (–)-**19** in 62% yield and 97% *ee* as a single diastereomer. The absolute configuration of (–)-**19** was determined by comparison of the experimental electronic circular dichroism (ECD) spectrum with calculated spectra.^[11] In this reaction, four stereocenters are formed with high selectivity.

A number of factors have been cited as contributing to atropisomeric stability of bis-quinones, including carbonyl bond lengths^[7] and out-of-plane-distortions.^[7] Shair and

coworkers have provided a rationale for the pH-dependent atropisomerism of the methoxyquinone-containing natural product hibarimicinone, which involves cross-conjugated resonance structures.^[8d] While related contributing zwitterionic structures and deviation of the quinone carbonyl group from planarity may be relevant for xanthomegnin **1** and aurofusarin methyl ether **18**,^[11] a comparison of the X-ray structures of **1** and **5** along with a DFT model of **18** (Figure 2) also shows shortening of the C–OCH₃ bond of **1** and **18** (1.342 Å and 1.345 Å) in comparison to the C–CH₃ bond length of **5** (1.479 Å). This bond shortening appears to be a factor in lowering the barrier for atropisomerization of **2**. The calculated barrier for **18** (24.6 kcal mol^{−1}, B3LYP/6-31G(d))^[11, 24] is also similar to the energy barrier for the interconversion of atropisomers (22.2 kcal mol^{−1}) suggested by Ki.^[25]

In summary, we have developed an efficient annulation involving pyrone addition to a quinone for rapid assembly of a γ -naphthopyrone monomer en route to the natural product aurofusarin. Dimerization of the γ -naphthopyrone was achieved through Pd^{II}-mediated dehydrogenative coupling wherein a simple mono-protected amino acid was found to be a suitable ligand for a catalytic process. In addition, asymmetric nucleophilic epoxidation of aurofusarin derivative **18** supports the hypothesis that the atropisomers of bismethoxy naphthoquinones such as aurofusarin are not configurationally stable. Extension of the method to access an enantioenriched bis-epoxide intermediate for the synthesis of diaporine is currently in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Aurofusarin (2) and related dimeric natural products.

Figure 2.
Bond-length analysis of the X-ray structures of **1** and **5** along with a DFT model of **2**.

Scheme 1.
Retrosynthetic analysis for aurofusarin.

Scheme 2.

Synthesis of a 9-hydroxy rubrofusarin derivative. MOM= methoxymethyl, TFA=trifluoroacetic acid.

Scheme 3.

Synthesis of aurofusarin from the protected dimer (±)-**18**. CAN=ceric ammonium nitrate.

Scheme 4.
Deracemization of biaryl **17**.

Scheme 5. Synthesis of bis-epoxide **22** and a model study for epoxidation.

Scheme 6.
Asymmetric nucleophilic epoxidation of **18**.

Dehydrogenative coupling of monomer **16**.

Table 1

Entry	Ligand	Solvent	T [° C]	t [h]	Yield[a] (conv.[b]) [%]
1	none	DMSO	70	20	23% (30%)
2	Ac- <i>L</i> -Leu-OH	DMSO	70	4	77% (100%)
3	Ac- <i>L</i> -Leu-OH	DCE	70	24	35% (47%)
4	Ac- <i>L</i> -Leu-OH	DMA	70	4	decomposition
5	Boc- <i>L</i> -Pro-OH	DMSO	70	14	28% (41%)
6	Boc- <i>L</i> -Val-OH	DMSO	70	12	48% (81%)

[a] Yield of purified ($\pm$)-**17**.

[b] Conversion as determined by ^1H NMR integration.

DMSO = dimethyl sulfoxide, DCE = 1,2-dichloroethane, DMA = *N,N*-dimethylacetamide.