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Studies on a biomimetic oxidative dimerization approach to the hibarimicins

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Abstract

Nature utilizes dimerization as a method of producing structurally complex metabolites. The microbial metabolites known collectively as the hibarimicins are one example of complex natural products produced biosynthetically by dimerization of a phenolic aromatic polyketide. Described in this communication are model studies aimed at demonstrating regiocontrolled oxidative dimerization of phenolic ring systems related to the biosynthetic precursor of the hibarimicin family of natural products.

Keywords

Oxidative dimerization; Regioselectivity; Silicon tether; Quinone; Oxidation

The hibarimicins are among the most complex aromatic polyketide natural products identified to date, with over ten family members isolated from the soil bacterium *Microbispora rosea* subsp. *hibaria* TP-A0121.¹ The biosynthetic pathway leading to the hibarimicins proceeds by way of an initial oxidative dimerization of a tetracyclic monomer to provide HMP-Y1 followed by further oxidation to the aglycon hibarimicinone and glycosylation at peripheral hydroxyl groups (C10/C12 and C10'/C12', Figure 1).² Variation in the final glycosylation step leads to multiple glycosylated metabolites with structures of hibarimicins A, B, C, D and G assigned following extensive NMR analysis.³

To date, total syntheses of the aglycons hibarimicinone and HMP-Y1 have been achieved using a two-directional annulation approach starting from biaryl DE *o*-toluate esters and derivatives.⁴ Not previously described has been a biomimetic strategy using an oxidative dimerization of a tetracyclic precursor (cf. HMP-Y1 monomer to HMP-Y1, Figure 1). In the absence of an enzyme-mediated dimerization, such biomimetic homo couplings face several obstacles. First, oxidative dimerization needs to occur with high regio- and stereoselectivity.

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at do:XXXXX.

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In an earlier publication we addressed the latter employing a dynamic thermodynamic resolution where a copper(I)-sparteine reagent deracemized biaryl phenols to afford optically enriched atropisomers (80–93% ee).⁵ Herein we describe studies addressing the regioselectivity of the dimerization and provide insight into the emerging oxidation state of the dimeric product.

Enzymatic⁶ and chemical⁷ phenolic oxidative couplings have been described; with chemical methods frequently showing modest to undesired regiocontrol.⁸ We started our investigations by examining the oxidative dimerization of electron rich phenol **1**. In principal, three coupling products could be produced, C2–C2', C6–C6' and C2–C6' biaryls. Oxidation with vanadium oxychloride provided primarily quinone **2** and a low yield of C6–C6' bis-quinone **3**. The structural assignment of bis-quinone **3** was based on comparison with published spectral data.⁹ Oxidative coupling with copper(II) chloride-TMEDA or hypervalent iodine afforded primarily bis-quinone **3**, none of the intermediate bis-phenol were isolated under these reaction conditions. Sartoi¹⁰ reported on the use of aluminum chloride and ferric chloride to promote oxidative couplings by way of intermediate aluminum phenolates, when phenol **1** was subjected to these reaction conditions a 60% yield of bis-phenol **4** was observed, without any observed over oxidation to bis-quinone **3**. The C6–C6' connectivity of **4** was assigned based on an observed HMBC analysis and comparison to the C2–C2' biaryl described earlier (**9**, Scheme 3).⁵

Silicon tethers have been employed in directing oxidative coupling of homo and hetero bis-phenols. To evaluate this strategy, phenol **1** was treated with diisopropyldichlorosilane to give bis-silylether **5** in 76% yield.¹¹ Ferric chloride oxidation of **5** in nitromethane gave dibenzofuran **6** in 53% yield. Dibenzofuran **6** was produced from **5** by an initial coupling at C6 followed by a cation mediated cyclization and formal dehydration. The assignment of bond connectivity of **6** was based on an observed nOe between the C2 proton and neighboring methyl ether. Notably, as reported earlier aryl coupling could be directed to C2–C2' starting from alkyl ether derivatives of phenol **1**, such as benzyl ether **7**.⁵ To this end, directed ortho lithiation at C2 of **7**, followed by cuprate formation and oxidation gave biaryl **8** in 47% yield.¹² Removal of the benzyl groups then gave C2–C2' bis-phenol **9**.

We next turned our attention to examining an oxidative dimerization closely resembling the conversion of HMP-Y1 monomer to HMP-Y1 shown in Figure 1. To this end, we examined oxidative dimerization of tricyclic phenol **10** (Scheme 4). In this case, oxidation can lead to three isomeric dimeric products resulting from attachment at C2–C2', C2–C6' or C6–C6' positions. Direct oxidation of **10** proved unproductive yielding only quinone **11** when using the earlier described Sartoi reaction conditions.¹⁰ We therefore turned our attention to the silicon tethered substrate **12** produced from phenol **10** in 62% yield. Productive conditions for the intramolecular oxidative coupling employed ferric chloride in nitromethane to provide bis-quinone **13** in 41% yield. While attachment occurred at the desired C2–C2' sense, the reaction was accompanied by over oxidation to the quinone. However, this can be desirable as an entry into the hibarimicinone product manifold (cf. oxidation-cyclization, Figure 1).^{2,4b}

In conclusion, we have examined using model substrates a biomimetic oxidative dimerization directed toward the total synthesis of hibarimicin progenitors HMP-Y1 and hibarimicinone. These studies suggest a silicon tethering strategy to be most promising.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Hypothetical biosynthesis of hibarimicins.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.