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Investigation of a Convergent Route to Purpuromycin: Benzofuran Formation vs Spiroketalization

Stephen P. Waters, Michael W. Fennie, and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

marisa@sas.upenn.edu

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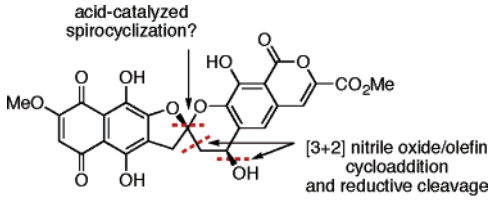
ABSTRACT



Purpuromycin, **1**

A mild and efficient [3+2] nitrile oxide/olefin cycloaddition allows coupling of the highly functionalized naphthalene and isocoumarin hemispheres of purpuromycin. A rationale of the inability of advanced keto alcohols to spirocyclize is presented based upon a systematic examination of the electronic factors present in these systems and suggests that the biosynthesis of purpuromycin does not proceed through open-chain intermediates.

Purpuromycin (**1**),[1] a member of the rubromycin family of natural products that also includes heliquinomycin and the griseorhodins,[2−4] is a polyketide consisting of highly functionalized naphthazarin and isocoumarin ring systems linked through a bisbenzannelated 5,6-spiroketal (above). Our particular interest in purpuromycin, isolated from the soil bacterium *A. ianthinogenes*, followed reports of its potent antimicrobial[5] and human telomerase inhibitory properties.[6] Moreover, its unique ability to bind with high affinity to all tRNAs, thereby inhibiting their acceptor capacity and disrupting further protein synthesis, represents a novel mode of action.[7]

While a formidable array of oxidation is present within the hexacyclic ring system, the most striking feature is the highly unusual 5,6-bisbenzannelated spiroketal core. Indeed, the only reported synthesis of a natural product featuring this moiety is that of heliquinomycin aglycon by Danishefsky and co-workers, which was realized through coupling of a lithiated naphthofuran with an arylacetaldehyde and Mitsunobu-like ring closure to form the spiroketal.[8] In addition, syntheses of simple 5,6-bisbenzannulated spiroketals have been disclosed by both de Koning,[9] and Brimble.[10]

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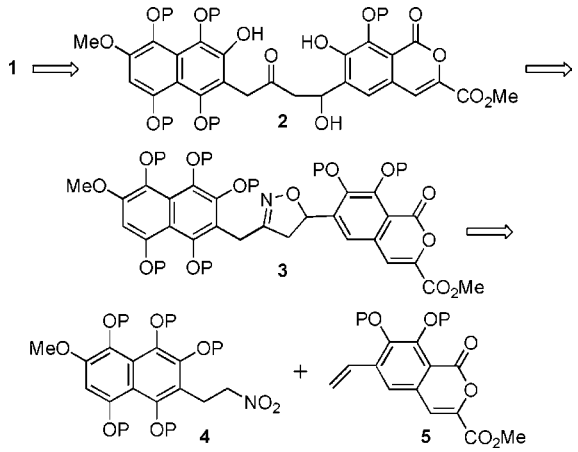
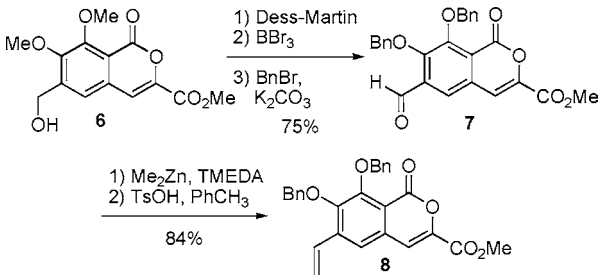
Our lab[11] has recently reported a convergent and mild coupling strategy involving the [3+2] cycloaddition of nitrile oxides and olefins to afford isoxazolines, which are converted to 5,6-bisbenzannulated spiroketals in three steps. Herein we report the application of that strategy to the requisite naphthalene and isocoumarin coupling partners (Scheme 1).

Scheme 1. Retrosynthesis of Purpuromycin



The isocoumarin coupling partner was synthesized as shown in Scheme 2. Oxidation of the primary alcohol in

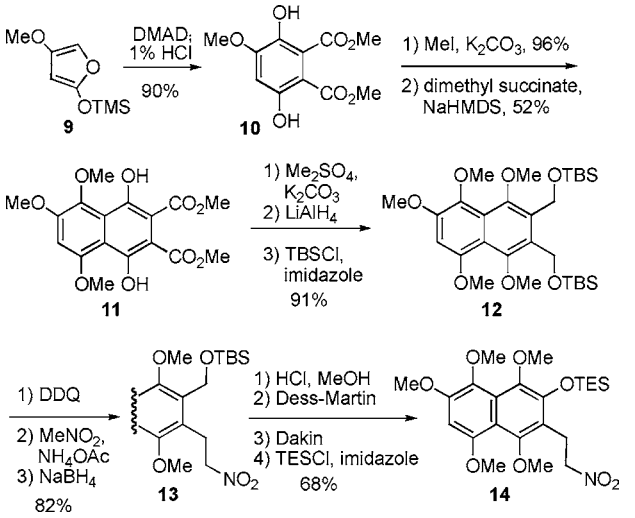
Scheme 2. Synthesis of Isocoumarin Fragment



previously reported **6**[12] with Dess−Martin periodinane, followed by protecting group interchange provided aldehyde **7**. Since attempts to homologate aldehyde **7** to styrene **8** failed with conventional Wittig reagents, a two-step protocol was implemented. Accordingly, dimethylzinc addition followed by TsOH mediated elimination afforded the desired alkene coupling partner.

For the naphthalene portion (Scheme 3), synthesis started with a [4+2] cycloaddition between furan **9** and dimethyl acetylene dicarboxylate (DMAD). Methylation and double Claisen condensation[13] with dimethyl succinate provided

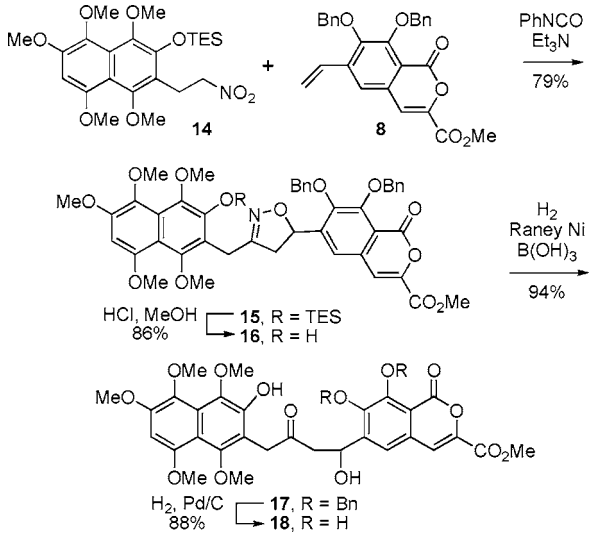
Scheme 3. Synthesis of Naphthalene Fragment



naphthalene **11**. Methylation, ester reduction, and silylation afforded naphthalene **12**. Selective oxidation with DDQ at the more electron-rich benzylic carbon[14] afforded an intermediate aldehyde, which was subjected to Henry condensation and reduction to provide nitroalkane **13**. Removal of the remaining silyl group, oxidation to the aldehyde, Dakin oxidation, and protection of the resulting phenol provided coupling partner **14**.

Attention turned to utilization of the [3+2] cycloaddition method for the complex fragment coupling. Fully functionalized isocoumarin **8** and naphthalene **14** underwent facile cycloaddition to afford isoxazoline **15** in good yield. Hydrolysis of the TES group in acidic methanol, reduction of the isoxazoline with Raney Ni, and hydrogenolysis of the benzyl ethers efficiently provided keto alcohol **18** in three steps (Scheme 4).

Scheme 4. Coupling of the Purpuromycin Fragments



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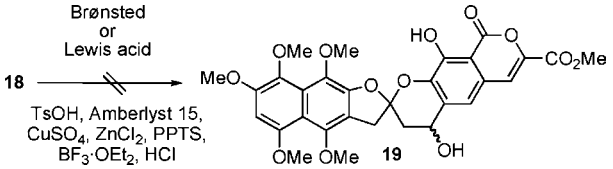
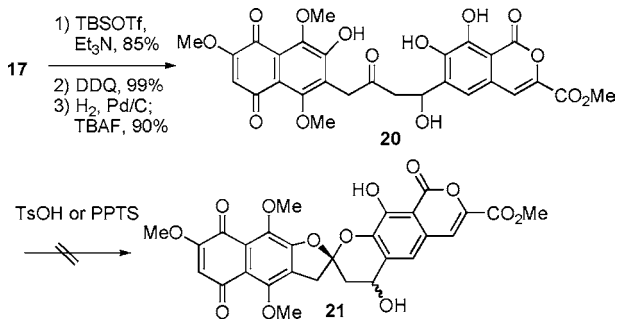
Despite an extensive body of precedent,[11,15] all attempts to effect acid-induced spirocyclization of **18** were unsuccessful (Scheme 5). Reasoning that undesirable transformations were occurring at the sensitive electron-rich naphthalene under the conditions required for spiroketalization, the corresponding naphthoquinone keto alcohol **20** was also synthesized from isoxazoline **17** (Scheme 6). Again, spiroketalization conditions gave rise to complex reaction mixtures.

Scheme 5. Attempted Spirocyclization of Naphthalene **18**

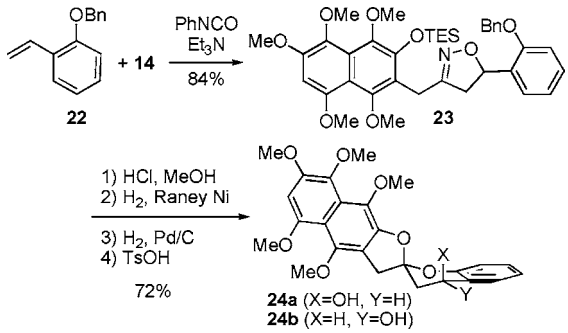


Scheme 6. Attempted Spirocyclization of Naphthoquinone

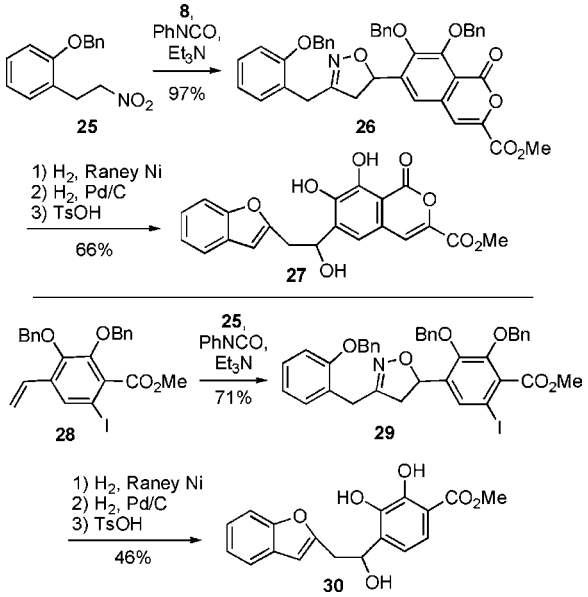


Clearly, a more precise understanding of the factors inhibiting spirocyclization was imperative. The [3+2] coupling strategy was ideal for this purpose as different left-hand and right-hand fragments could be examined in a combinatorial fashion (Schemes 7 and 8). Following the protocol outlined above, **14** and model styrene **22**[11] thus provided a keto alcohol which, upon treatment with catalytic acid, underwent smooth spirocyclization to **24a** and **24b** (1:1 mixture of diastereomers).

Scheme 7. Deconvoluting the Spirocyclization Factors

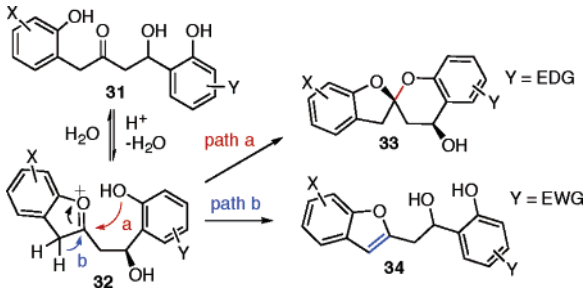


Scheme 8. Benzofuran vs Spirocyclization



However, the keto alcohol from isocoumarin fragment **8** and model nitroalkane **25**[11] did not form a spiroketal upon treatment with catalytic acid; instead, only the aromatic benzofuran **27** was obtained (Scheme 8). These findings suggest that the nucleophilicity of each phenolic participant is crucial. The inductive effects of the two carbonyl substituents in **8** diminish the nucleophilicity of the relevant phenol such that irreversible formation of the stable aromatic benzofuran becomes the dominant pathway (Scheme 9, path b vs path a).[16] With catechol ester **28** (Scheme 8), formation of a similar benzofuran **30** was observed.[17] From this result, even the presence of one electron-withdrawing group predisposes the system toward benzofuran formation (Scheme 9, path b).

Scheme 9. Spirocyclization and Elimination Pathways



Due to such facile formation, the conversion of benzofurans into the corresponding spiroketals is appealing.

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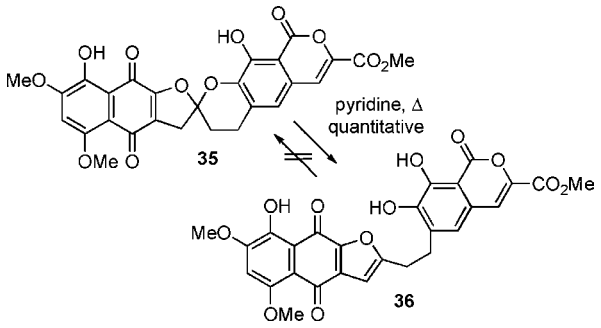
(16) For a discussion, see: Liptak, M. D.; Gross, K. C.; Seybold, P. G.; Feldgus, S.; Shields, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6421.
(17) Raney Ni also removed the iodide.

Degradation studies of β-rubromycin (**35**) have shown that furan **36** is obtained from refluxing pyridine (Scheme 10).[1b]

Scheme 10. Degradation of β-Rubromycin



However, we found that this electron-deficient furan fails to spirocyclize to the natural product under a variety of conditions. These results complement the finding of Danishefsky and co-workers that an electron-rich naphthofuran intermediate in the heliquinomycin aglycon synthesis was unreactive.[8]

Recent studies by Piel, who mapped the gene cluster for griseorhodin biosynthesis and found no less than 11 distinct redox-tailoring events along the pathway, suggest that the spiroketal cores are the product of a series of oxidative bond fragmentations from a common all-carbon precursor (**37**−**40**, Scheme 11).[18] From our studies, however, it appears that any electron-withdrawing group on the eastern hemisphere complicates conventional spirocyclization. This suggests that spirocyclization from an open-chain ketone precursor (**18**, **20**) may not play any direct role in the biosynthesis of purpuromycin. On the whole, these findings point to an as yet undefined biogenic pathway.

We have demonstrated that the [3+2] cycloaddition is a mild and effective means for rapid, convergent assembly of

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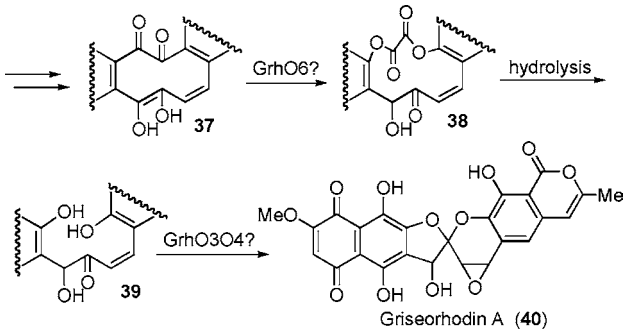
Scheme 11. Previously Proposed Biosynthesis Involving Spirocyclization from an Open Chain Intermediate



multiple bisbenzannulated spiroketal precursors in the presence of nucleophile and electrophile sensitive functionality. This approach permits the generation of multiple analogues to explore the bioactivity of the 5,6-bisbenzannulated spiroketals. The electronic factors required for spirocyclization of the rubromycins were identified through a systematic analysis of the individual fragments. These results have important implications to any synthesis of this class of compounds.[19] Further synthetic efforts toward this family of natural products and exploration of alternative biomimetic sequences are underway.

Acknowledgment. Support for this work was provided by the American Cancer Society (RSG-02-137-01-CDD). We thank Dr. Rakeshwar Bandichhor for the synthesis of precursors. β-Rubromycin was from Galileaus.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061112J

(19) For example, see the following recent report: Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2365.