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Synthesis of the Tetracyclic Core of Exiguaquinol

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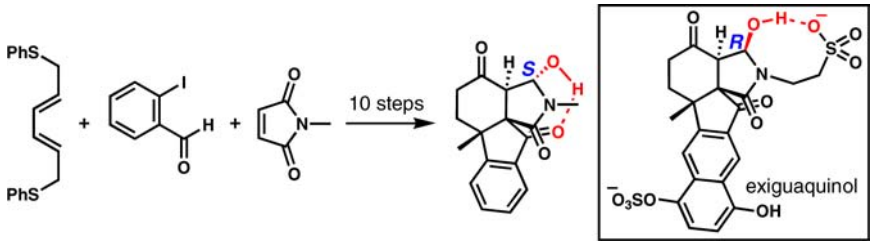
ABSTRACT



A Diels–Alder reaction, a desymmetrizing aldol reaction, and a reductive Heck cyclization are employed in a short synthesis of a tetracycle relevant to exiguaquinol, a potential antibiotic. Ground-state energies of this advanced model system and the natural product rationalize the incorrect hemiaminal configuration experimentally obtained and point to the importance of the sulfonate in dictating the relative configuration of the natural product.

The structurally novel pentacyclic compound exiguaquinol (**1**, Figure 1) was isolated by Quinn et al. from the Australian sponge *Neopetrosia exigua* and reported in 2008.[1] High-throughput screening of natural product extracts against the *Helicobacter pylori* MurI enzyme, a glutamate racemase enzyme that is essential for bacterial cell wall biosynthesis, led to the identification of **1** as the first natural product inhibitor of this enzyme. As a result, exiguaquinol might serve as an excellent lead compound for the development of more potent inhibitors of MurI and ultimately selective antibiotics against *H. pylori*.[1] With its complex and congested structure, the important link of *H. pylori*-induced gastritis to stomach cancer,[2] and the more general implications of MurI as a potential target for the development of new antibiotics, a research program aimed at the synthesis of this complex natural product was warranted on both chemical and biological grounds.

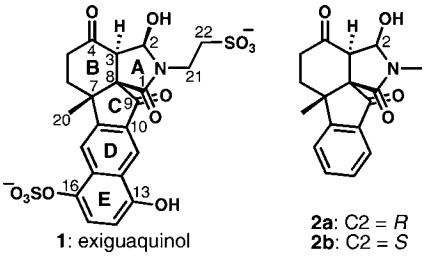


Figure 1. Exiguaquinol and tetracyclic model system hemiaminal diastereomers.

In addition to its biological activity, exiguaquinol (**1**) bears complex structural features that make it a worthwhile synthetic target. With five fused rings, four contiguous stereogenic centers (two vicinal quaternary), an aryl sulfate, and a pendant sulfonate, a laboratory synthesis of this compound presents significant difficulty. To address the stereochemical challenges, we aimed to develop a synthesis of the tetracyclic core (**2**) as a model system, with the stipulation that any such strategy be amenable to a

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(1) Almeida Leone, P.; Carroll, A. R.; Towerzey, L.; King, G.; McArdle, B. M.; Kern, G.; Fisher, S.; Hooper, N. A.; Quinn, R. J. *Org. Lett.* **2008**, *10*, 2585–2588.
(2) Polk, D. B.; Peek, R. M., Jr. *Nature Rev. Cancer* **2010**, *10*, 403–414.

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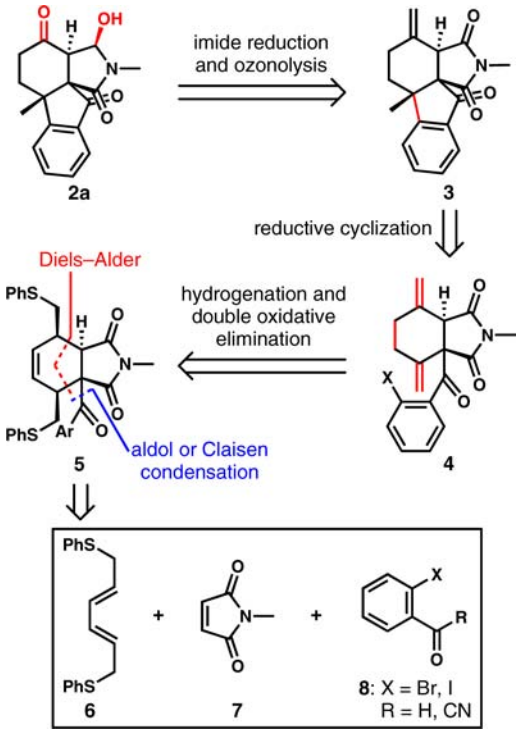
Scheme 1. Synthesis Plan To Access Tetracycle **2a** Bearing All of the Stereochemical Complexity of Exiguaquinol



synthesis of the natural product and structural analogues. Our retrosynthetic plan is illustrated in Scheme 1, wherein the exiguaquinol core (**2a**) is derived from tetracycle **3** via simple functional group manipulations. The C ring, with its vicinal quaternary stereogenic centers,[3] would be forged through a reductive 5-*exo* cyclization of aryl halide **4**. Key fused bicyclic intermediate **5** might be formed from three simple starting materials via a Diels–Alder reaction of **6** and **7** followed by an aldol addition or Claisen condensation, depending on the oxidation state of **8** used.

Diene **6** was synthesized on a multigram scale in two steps from divinyl glycol **9**, the commercially available pinacol coupling product of acrolein[4] (Scheme 2). Bromination of **9** with allylic transposition[5] afforded a dienyl dibromide intermediate, which underwent smooth nucleophilic displacement with sodium thiophenolate to afford **6**.[6] Thermal [4 + 2] cycloaddition between diene **6** and *N*-methylmaleimide afforded the Diels–Alder adduct in high yield and subsequent reduction with PtO_2 under H_2 pressure led to bicyclic compound **10**. Desymmetrizing aldol addition with *o*-iodobenzaldehyde led to a single diastereomer of the benzylic alcohol product, which was silylated to afford **11** in good yield. The inclusion of LiCl[7] during enolate formation was critical to reproducible reactions, especially on a multigram scale. Oxidation of the sulfides followed by thermal sulfoxide elimination generated desired diene **12** without complication.

The completion of the synthesis of the tetracyclic model system required a careful orchestration of the final steps. Selective monoreduction of succinimide **12** with $LiBH_4$ yielded hemiaminal **13** as a single diastereomer in high yield. X-ray crystal structure analysis indicated that the hemiaminal was epimeric to that found in the natural product. Reductive Heck cyclization[8] of **13** provided tetracyclic product **14** in good yield, demonstrating the power (and functional group compatibility) of this catalytic alternative to reductive, tin-based radical cyclizations in complex settings. Deprotection with TBAF and selective oxidation of the benzylic alcohol in the presence of the hemiaminal afforded indanone **15**. Ozonolysis delivered tetracyclic diketone **2b**, which remained epimeric at C2 as confirmed by X-ray crystal structure. Attempts to epimerize the hemiaminal to the "natural" *R*-configuration under acidic or basic conditions proved unsuccessful.[9]

Tetracycle **2b**, with its close structural relationship to exiguaquinol, does not offer any obvious rationale for the difference in configuration at a center that seemed certain to be under thermodynamic control. This quandary led us to consideration of a number of hypotheses, including the remote possibility of a misassignment of relative configuration in the natural product. However, the spectroscopic data were fully consistent with the proposed structure; therefore, we considered the possibility that the absence of the sulfonate in simplified system **2b** might lead it to adopt a different thermodynamic hemiaminal configuration. It seemed prudent to computationally model all of the different hydrogen-bonding options in both the model system and the natural product.

Gas-phase ground-state calculations on both epimeric forms of tetracycle **2** (Figure 2) revealed that the observed *S*-epimer of the core **2b** is thermodynamically more stable by 4.6 kcal/mol than that with the configuration corresponding to the natural product (**2a**). The lowest energy conformation of the experimentally observed *S*-configured epimer **2b** benefits from hydrogen bonding of the hemiaminal hydroxyl group with the C9 indanone carbonyl; a conformation wherein it is hydrogen bonded to the C4 ketone (not shown) is of significantly higher energy. The lowest energy conformation of *R*-configured epimer **2a** is also shown; in this configuration, the hemiaminal hydroxyl group is only able to hydrogen bond to the C4 ketone.

Not surprisingly, calculations of the exiguaquinol hemiaminal epimers suggest that the lowest energy conformation of the natural *R*-epimer (**1**) is thermodynamically preferred by 2.3 kcal/mol over the most stable conformer

(3) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. U.S.A.* **2004**, *101*, 11943–11948.

(4) For a modern procedure, see: Trost, B. M.; Aponick, A. *J. Am. Chem. Soc.* **2006**, *128*, 3931–3933.

(5) Schneider, G.; Horvath, T.; Sohár, P. *Carbohydr. Res.* **1977**, *56*, 43–52.

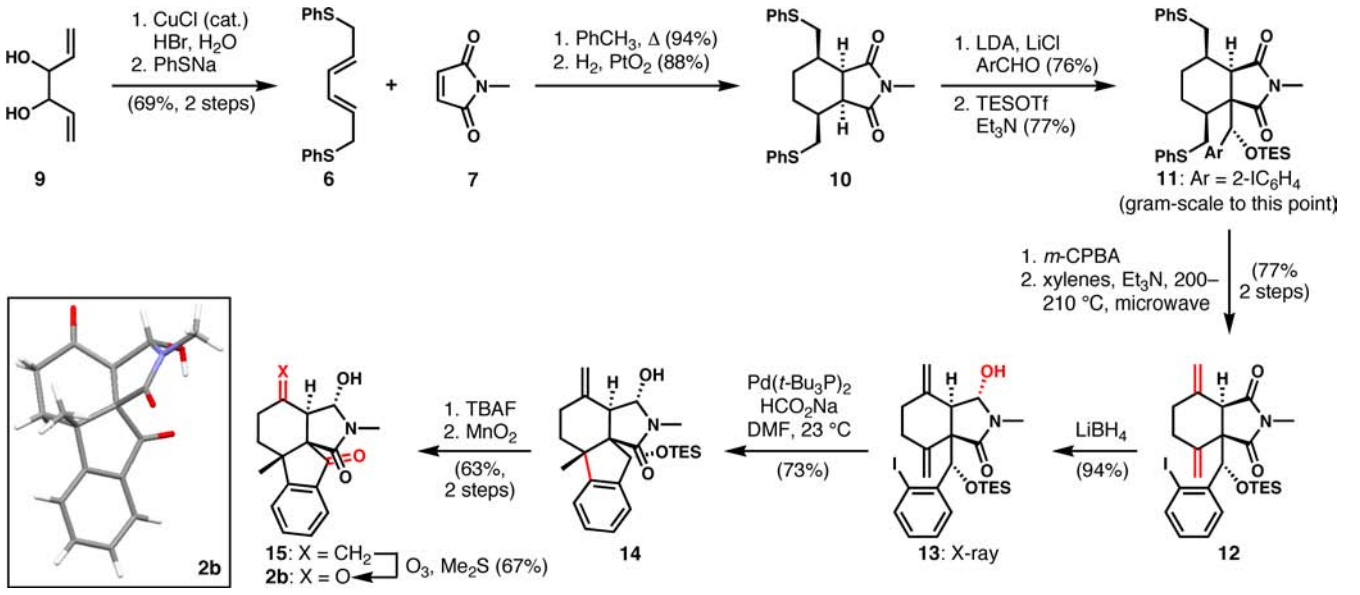
(6) Kauffmann, T.; Gaydoul, K.-R. *Tetrahedron Lett.* **1985**, *26*, 4067–4070.

(7) For a review on lithium enolate structure and reactivity, including discussions on the remarkable effects of additives such as LiCl, see: (a) Seebach, D. *Angew. Chem., Int. Ed.* **1988**, *27*, 1624–1654. See also: (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339–1347.

(8) Link, J. T. *Org. React.* **2002**, *60*, 157–534.

(9) *O*-Silylation of the hemiaminal in **2b** did not change the configuration at C2, in spite of the elimination of the proposed stabilizing hydrogen bond; however, silylation is likely to be kinetically controlled.

Scheme 2. Synthesis of the Tetracyclic "Core" of Exiguaquinol, Epimeric at C2



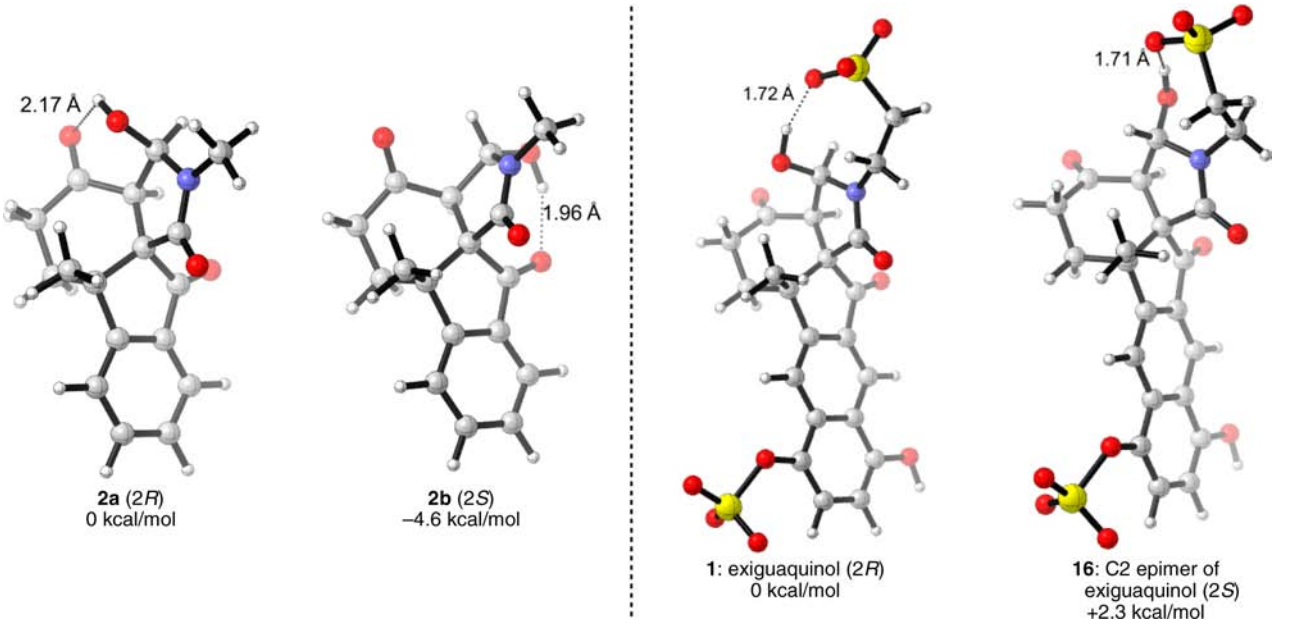


Figure 2. Computed relative free energies of the hemiaminal epimers of the tetracyclic "core" (**2a** and **2b**) and exiguaquinol (**1** and **16**). Calculations performed at the B3LYP/6-31G(d) level of theory in the gas phase.

of the *S*-isomer (**16**). As we had predicted, the sulfonate appears to be the root cause of the difference between **2** and exiguaquinol because it is apparently involved in hydrogen bonding with the hemiaminal in the lowest energy conformations of both epimers, with the natural configuration's conformation preferred by 2.3 kcal/mol. It is plausible that anomeric stabilization (good overlap of amide π system with C−O σ^* orbital) contributes to the preference for the natural configuration; this arrangement is not observed in **16**. For both epimers of exiguaquinol, the other hydrogen-bonded possibilities were also evaluated (for the *R*-epimer with the C4 carbonyl and for the *S*-epimer with both the C4 and C9 carbonyls); each of these was at least 7.5 kcal/mol higher in energy than the sulfonate–hemiaminal hydrogen-bonded conformer of the natural product.[10] That all of the calculations were

(10) See the Supporting Information for details.

performed in the gas phase does leave the possibility that solvation could lead to a different outcome; however, X-ray crystallography, solution NMR ($CDCl_3$), and computation all demonstrate that the *S*-configuration of the tetracyclic core is preferred, with the crystal structure revealing the same hydrogen bond to the indanone carbonyl. Also, in NMR studies of exiguaquinol performed in DMSO by the Quinn group, the *R*-configured hemiaminal was the only one observed.[1]

We did not anticipate the stability of conformations involving hydrogen bonding between the hemiaminal and the sulfonate via eight-membered rings, particularly relative to the six-membered arrangement involving the C4 ketone favored by **2b**. This phenomenon likely results from the ability of the hydrogen bond to partially offset some of the discrete charge of the sulfonate. Regardless of its physical basis, this bonding pattern might play a key role in determining the active configuration and conformation of exiguaquinol.

Via a short sequence of 13 steps, we have accessed a tetracycle bearing many of the features of exiguaquinol. In particular, this approach addresses the stereocontrolled introduction of three contiguous stereogenic centers, including two adjacent quaternary centers. The fourth asymmetric center, the hemiaminal C2, is generated with the unnatural *S*-configuration; however, computation strongly suggests that our synthesis plan will deliver the desired *R*-configured hemiaminal when applied to fully elaborated substrates. Interesting hydrogen-bonding effects between the two epimers in the model series as well as the natural product appear to define the thermodynamic preference at this center and point to the complexity of potential interactions of exiguaquinol's array of polar groups.

A triply convergent approach featuring a Diels–Alder cycloaddition and an aldol reaction, followed by a reductive Heck cyclization, rapidly assembles the tetracyclic core with high diastereocontrol, but in a racemic manner. This modular strategy will allow for the convenient introduction of the extended aromatic and taurine (2-aminoethylsulfonic acid) moieties of the natural product, and chiral base technology[11,12] will facilitate access to optically active material by enantioselective desymmetrizing aldol additions. Efforts to apply this route to enantioenriched exiguaquinol and analogues are underway to permit identification of a more potent inhibitor of the *H. pylori* MurI enzyme.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds; X-ray crystal structure for **13** and CIF data for both **2b** and **13**; computed structures of other hydrogen-bonded conformations of exiguaquinol and its epimer. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For a particularly relevant desymmetrization employing chiral amide bases, see: Simpkins, N. S.; Gill, C. D. *Org. Lett.* **2003**, 5, 535–537.

The authors declare no competing financial interest.