

# Methodology for the synthesis of the core EFGH rings of diazonamide A

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Received 15 June 2006; accepted 18 June 2006

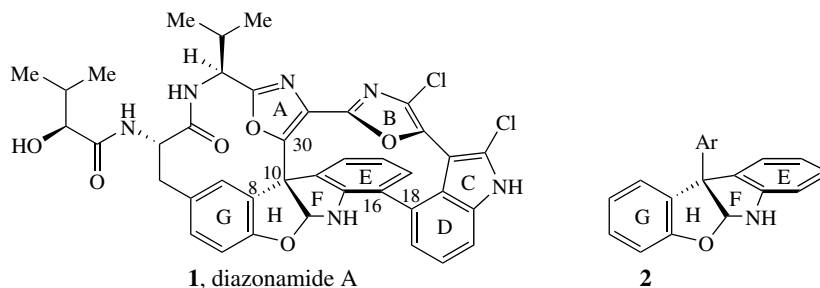
**Abstract**—Conversion of substituted 2-oxindoles into 2-thioindoles followed by Raney nickel desulfurization provides a mild method for synthesizing the core EFGH rings of diazonamide A.

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Diazonamide A was isolated from the colonial ascidian *Diazona chinensis*, collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines. It has potent *in vitro* activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cells ( $IC_{50} < 15$  ng/mL). The original structure, as reported in 1991 by Fenical and Clardy,<sup>1</sup> was corrected in 2001 to **1** by Harran, Scheme 1.<sup>2</sup> While there has been a large number of research groups involved in the total synthesis of diazonamide A,<sup>3</sup> only the Harran<sup>4</sup> and Nicolaou<sup>5</sup> groups have so far been successful.

As part of our efforts to synthesize diazonamide A, we required a mild method to construct the central hemiaminal functionality which contains the heteroatom connections of the core EFGH rings **2**. The published methods for the synthesis of the crucial hemiaminal

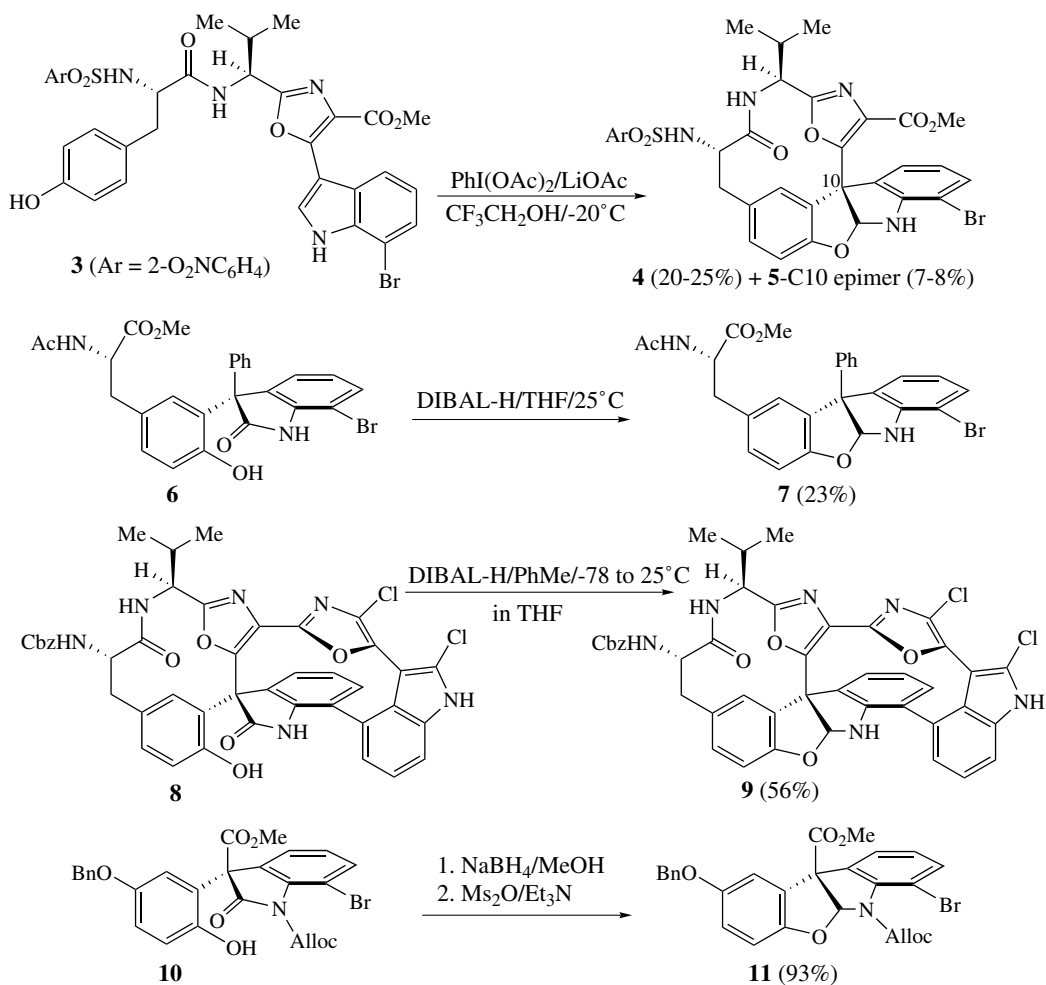
functionality are outlined in Scheme 2. Harran,<sup>4</sup> in his biomimetically inspired route to diazonamide, reported the hypervalent iodine mediated intramolecular oxidative coupling of **3** to give **4** and **5**. This elegant and direct strategy is not applicable to our route since we use a rearrangement of a 2-oxindole derivative to establish the C-10 quarternary carbon atom.<sup>6</sup> In a model study, as a prelude to the synthesis of diazonamide, Nicolaou et al.<sup>5</sup> reported the reduction of **6** to give **7**. Although this model study used a variety of reducing agents (Red-Al,  $LiBEt_3H$ ,  $BH_3 \cdot SME_2$ ,  $NaBH_4$ ,  $BH_3 \cdot THF$ , and  $TMSOTf/Et_3SiH$ ) only DIBAL-H in toluene (10 equiv, added portion wise) from  $-78$  to  $25$  °C accomplished the reduction of **8** to give **9**. Recently Vedejs and Zajac reported the reduction of the *N*-alloc activated 2-oxindole **10** with  $NaBH_4/MeOH$  followed by dehydration with  $Ms_2O/Et_3N$  to give **11** in excellent yield.<sup>7</sup>



Scheme 1.

**Keywords:** Diazonamide A; Hemiaminal; Thioamide; Raney nickel; Desulfurization.

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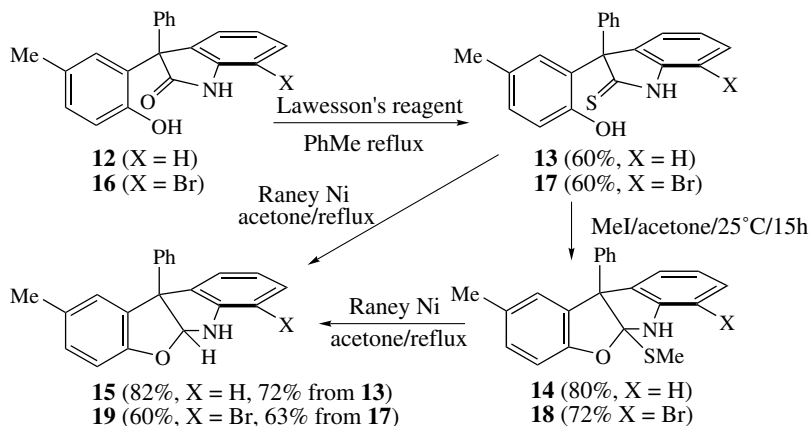
Scheme 2.

Attempted application of these reductions, and others, to some of the intermediate 2-oxindoles in our route was not successful because of over reduction to the 2H-indoline rather than the hemiaminal. As a consequence, we have developed a mild and selective procedure to accomplish this difficult reduction.

We conjectured that since thioamides are readily *S*-alkylated<sup>8</sup> and the resulting *S*-alkylthioimine can be

desulfurized by exposure to Raney nickel to give an imine, this reaction sequence could provide a mild method to convert compounds such as **12** into **15** (Scheme 3<sup>9</sup>).

Initially, we were concerned that the conversion of an amide into its thioamide derivative in the presence of a phenol, using thionating reagents such as Lawesson's reagent, might be problematic. The only report of this



Scheme 3.

type of conversion involved a hexa-substituted phenol,<sup>10</sup> and it is possible for a phenol with vacant *ortho*- and/or *para*-positions to undergo electrophilic aromatic substitution by the thiophosphoryl functionality in Lawesson's reagent. In the event this potential competing reaction did not occur, treatment of **12** and **16** with Lawesson's reagent in toluene heated at reflux (2–3 h) gave the thioamides **13** (60%) and **17** (60%) respectively, Scheme 3. As a control experiment, *p*-cresol was exposed to Lawesson's reagent in toluene heated at reflux, and only after approximately 20 h was some decomposition observed.

The thioamide **13** was treated with MeI/acetone at 25 °C for 15 h to give **14** (80%). Exposure of **14** to deactivated Raney nickel resulted in clean desulfurization to provide **15** (82%, structure by X-ray, see Fig. 1).<sup>11</sup> Similarly, the thioamide **17** was converted into **18** and desulfurized to give **19** (60%). In the course of investigating the –NMe

analogues (Scheme 4), we found that the thioamide could be converted into the hemiaminal using Raney nickel without the need for S-methylation. Applying this to **13** and **17** resulted in **15** (72%) and **19** (63%), respectively.

While we could convert **20** into its thioamide derivative **21** (69%), its S-methylation to give **22** (57%) was accompanied by hydrolysis to give **20** (12%) and recovered **21** (30%), Scheme 4. Moreover, attempted desulfurization of **22** with Raney nickel in dry acetone in the presence of 4 Å molecular sieves only gave **20** (69%). Consequently, we treated **21** directly with Raney nickel in acetone and isolated **23** in 86% yield.

The conversion of the amides **12**, **16**, and **20** into the hemiaminals **15**, **19**, and **23** requires two steps for each, and proceeds in an overall yield of 43%, 37%, and 59%, respectively (not optimized). The mild reaction

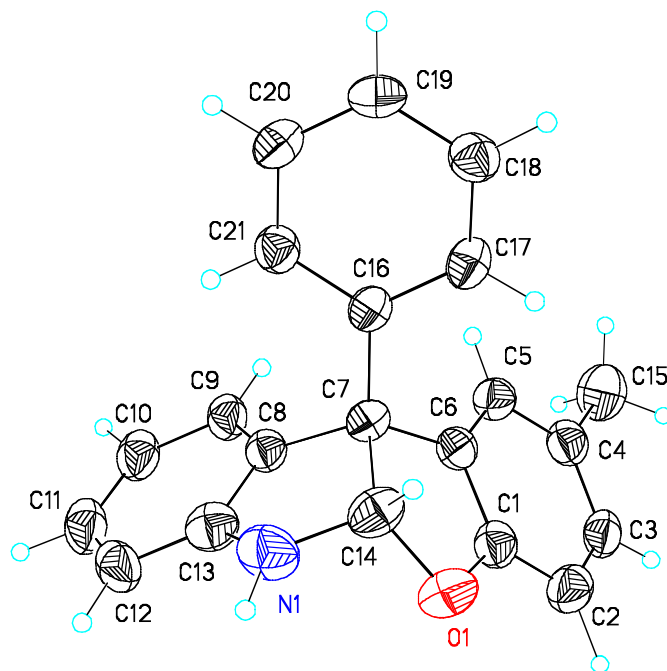
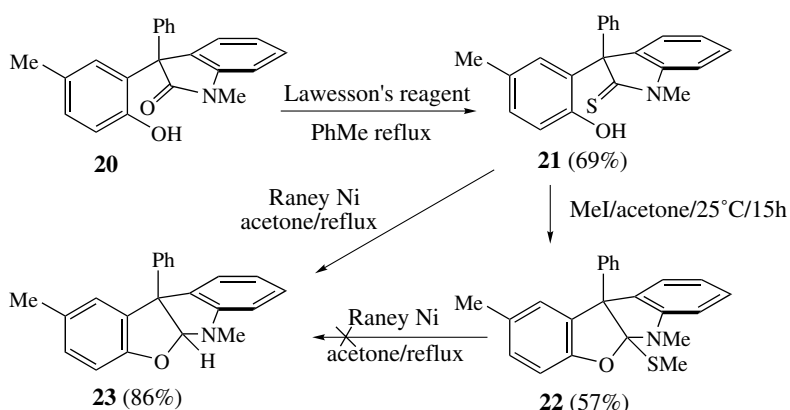


Figure 1. ORTEP of **15**.



Scheme 4.

conditions bode well for the success of this methodology on more complicated 2-oxindoles required for the total synthesis of diazonamide A.

### Acknowledgements

The NIH (CA RO1 50512) and the Welch Chair (F-0018) are thanked for their support of this research.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.06.123](https://doi.org/10.1016/j.tetlet.2006.06.123).

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11. Crystallographic data (excluding structure factors) for the compound **15** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 611305. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (0) 1223 336033 or e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)].