Article

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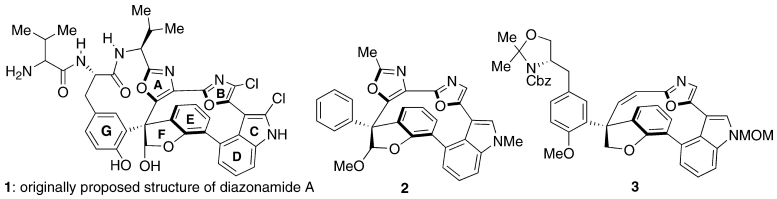
J. Am. Chem. Soc., **2004**, 126 (32), 10162-10173• DOI: 10.1021/ja040090y • Publication Date (Web): 27 July 2004



1: originally proposed structure of diazonamide A

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Studies toward Diazonamide A: Initial Synthetic Forays Directed toward the Originally Proposed Structure

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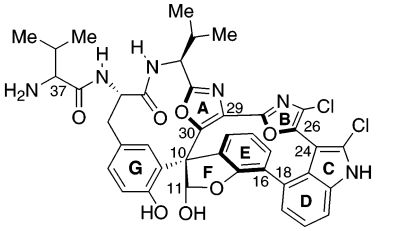
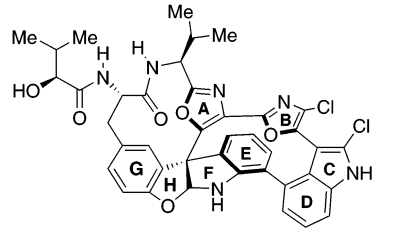
Abstract: A brief introduction into the chemistry of diazonamide A (**1**) is followed by first-generation sequences to access the originally proposed structure for this unusual marine natural product. These explorations identified a route capable of delivering a model compound possessing the complete heteroaromatic core of the natural product, highlighting in the process several unanticipated synthetic challenges which led both to new methodology as well as an improved synthetic plan that was successfully applied to fully functionalized intermediates.

Introduction

In 1991, Fenical and Clardy disclosed the structure of diazonamide A (**1**, Figure 1), a secondary metabolite isolated from the colonial ascidian *Diazona angulata* whose unprecedented molecular architecture included a cyclic polypeptide backbone, a strained halogenated heteroaromatic core trapped as a single atropisomer, and a lone quaternary center at the epicenter of its two major macrocyclic subunits.[1] Due to the unique challenges posed by this amazing molecular framework, in concert with impressive in vitro cytotoxicity (nanomolar activity against human colon carcinoma and B-16 murine melanoma cell lines)[2] and an inability to harvest additional material from the original source, this molecule beckoned to synthetic chemists worldwide. After nearly a decade of prodigious effort from a number of research teams,[3−11] including our own,[12] the synthetic gauntlet issued by these motifs was finally met with the first successful synthesis of the proposed structure of diazonamide A by the Harran group at the Southwestern Medical Center in Dallas, Texas.[13]



1: originally proposed structure of diazonamide A



2: revised structure of diazonamide A

Figure 1. The originally proposed structure of diazonamide A (**1**) and the revised assignment (**2**).

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10.1021/ja040090y CCC: $27.50

This accomplishment, though, would not constitute the final chapter in the intriguing story of diazonamide A, as fully synthetic **1** did not match natural diazonamide A, revealing that the original structural assignment based on NMR, X-ray crystallographic, and mass spectral data was in error. Their suggested revision (**2**, Figure 1), one which included alteration of the terminal amino acid, exchange of the heteroatom in ring F, and the addition of a tenth ring (ring H) to the natural product's architecture, launched a series of new synthetic campaigns worldwide.[14] Just six months later, in August of 2002, the first of these research programs reached fruition in our laboratory, unequivocally proving the correct molecular connectivities for diazonamide A as **2**.[15] A few months thereafter, our group completed a second total synthesis of this intriguing natural product through an entirely different synthetic approach,[16] one that shared with the first a reliance upon carefully tailored strategies, cascade reactions, and methodologies to handle its most difficult motifs.[17,18]

In this and the following article in this issue,[19a] as well as in two articles soon to be published,[19b,c] we present a complete chronicle of our five-year campaign to synthesize the original (**1**) as well as the revised structure (**2**) of diazonamide A and concurrently explore this natural product's intriguing chemical biology using the developed sequences. We begin in this article with our first-generation strategy to address the structural complexity posed by **1**. While this approach would ultimately prove unsuccessful, its prosecution identified and solved a number of key synthetic challenges posed by the diazonamide framework and resulted in several new synthetic methods and tactics which would prove to have much utility in our later drive to complete the total synthesis of **2**.

Results and Discussion

1. Retrosynthetic Analysis. Although several of the most forbidding structural elements possessed by the originally proposed structure of diazonamide A (**1**) are quite clear in a two-dimensional representation, no paper-based drawing can adequately convey its overall rigidity and compactness, especially as imposed by its two 12-membered macrocyclic rings. An appreciation for this fact is of critical importance, not only as an explanation for why the C16−C18 and C24−C26 biaryl axes are trapped as single atropisomers, but also as a clue that forming these ring systems in the laboratory is likely to be quite difficult. Consequently, we tailored virtually all of our retrosynthetic decisions simply around the questions of how and in what order to form these two formidable rings, rather than focus heavily on any other specific motif within **1**.

Scheme 1 provides our proposed solution to the original diazonamide problem, starting with two relatively minor modifications: excision of the L-valine side chain appended to the C-2 amine and removal of the two aryl chlorines. The first of these simplifications was implemented because the C-37 stereocenter of **1** remained unassigned,[1] thus enabling late-stage incorporation of both the L and D forms of **3** to verify the stereochemistry of that position, while the second reflected concerns about long-term stability to diverse reaction conditions.[3a,12b] With these operations leading to **4**, we then unlocked what we regarded to be the simpler of the two macrocycles to construct in the forward sense, the 12-membered AG-ring system, at the most obvious site: its central amide bond.[20] This operation revealed intermediate **5**, a new goal structure in which the oxidation state of the carboxylic acid needed for macrolactamization has been adjusted to a protected alcohol.

Having elected to pursue these initial retrosynthetic simplifications, we next turned our attention to the task of disassembling the heteroaromatic core of **5**. Although a number of possible points for ring dissection were conceivable, some possessing inherently far more forward synthetic risk than others, a particularly flexible and practical approach became evident when the A-ring oxazole was opened through a Robinson−Gabriel cyclodehydration transform to reveal a ketoamide in reduced form as **6**. Indeed, if the functionality needed for oxazole formation could be built from an alkene precursor such as **7**, then perhaps macrocyclization could be effected at C29−C30 through either ring-closing olefin metathesis[21] between the two terminal alkenes in **8** or, more classically, via an intramolecular Horner−Wadsworth−Emmons (HWE) reaction[22] using **9**. In both cases, we expected that these macrocyclization events would be atropselective as a consequence of the C-10 stereochemistry and π-stacking between the A-ring oxazole and the E-ring, achievable only if the rings are oriented in the desired fashion. Equally enticing from a more general strategic standpoint, these two potential macrocyclization precursors could be retrosynthetically traced to the same two generic building blocks, indole-oxazole **10** and EFG building block **11**, simply by severing their C16−C18 biaryl linkage through a biaryl coupling transform.

As such, the synthetic challenges posed by diazonamide A (**1**) have been reduced to the construction of two fragments of

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(16) Nicolaou, K. C.; Bheema Rao, P.; Hao, J.; Reddy, M. V.; Rassias, G.; Huang, X.; Chen, D. Y.-K.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1753−1758.

(17) A third total synthesis of diazonamide A, proceeding in a longest linear sequence of 19 steps, was recently accomplished: Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961−4966.

(18) For highlights of synthetic studies towards the diazonamides, see: (a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003; Ch. 20, pp 550−588. (b) Wittmann, V. *Nachr. Chem.* **2002**, *50*, 477−482. (c) Ritter, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2489−2495.

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(20) Examples of such challenging macrolactamizations can be found in: Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J.-H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862−1871.

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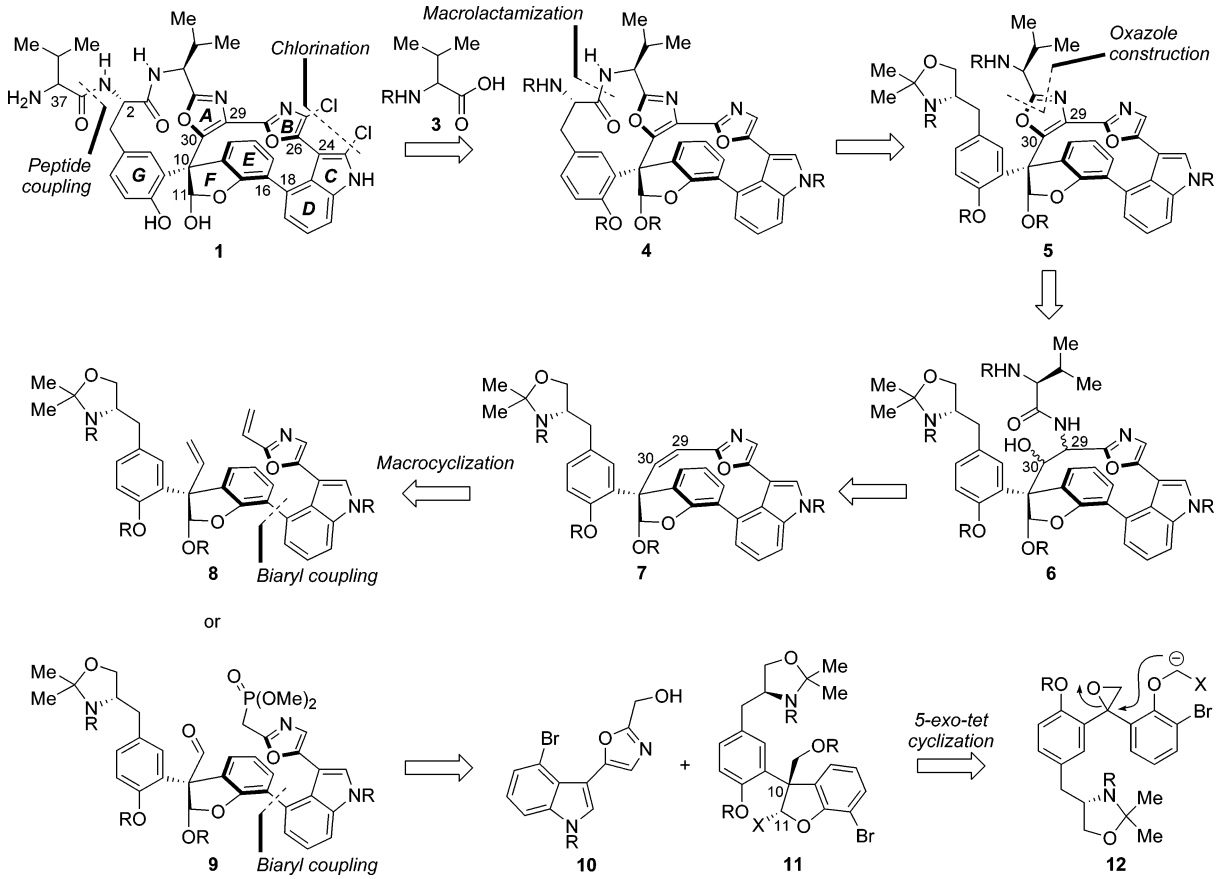
Scheme 1. Retrosynthetic Analysis of the Originally Proposed Structure of Diazonamide A (**1**)



relatively equal complexity and size in what is overall a convergent synthetic blueprint. With the synthesis of compounds of type **10** expected to pose few difficulties, the only major concern that remained was how to construct the C-10 quaternary center of **11** stereoselectively, a problem that published studies toward **1** (ca. 1999)[3c,5b,6d,9d,e,10,11] had failed to solve with resounding success. Our analysis suggested that if a biaryl precursor of general structure **12** could be coaxed to form the indicated anion (using a judiciously chosen substituent X to adjust the pK_a of that site), and then a subsequent 5-*exo*-tet cyclization could provide the structure of the desired intermediate in a single operation.[23] If true, then absolute stereocontrol could result from this key reaction if the epoxide within **12** was formed stereoselectively, assuming, of course, that the distal stereocenter was an innocent bystander during the event.

2. Studies Directed toward the EFG Fragment. Armed with this plan, we immediately sought to explore the feasibility of its key steps by constructing a series of model compounds that differed from what we would consider to be the fully functionalized intermediates of Scheme 1, simply with the replacement of an unadorned phenyl group for ring G. Thus, the first critical task was to deduce whether 5-*exo*-tet cyclization of compounds of type **12** (see Scheme 1) was actually possible, since the success or failure of this strategy would dictate our ability to construct any appropriately decorated EFG fragment. With this in mind, we prepared a variety of biaryl epoxides bearing different alkoxymethylene units (**16**, **17**, **18**, **20**, and **21**, see Scheme 2) over the course of a few self-explanatory operations from aldehyde **13**[24] and exposed each to LDA in THF and KO*t*-Bu in DMF at a variety of temperatures. Table 1 summarizes the key results from these studies.

Under no circumstance tested could we induce epoxides bearing either a SPh (**16**) or a TMS-activated methylene (**20**) to cyclize. However, if the sulfur atom of **16** was oxidized to its sulfoxide counterpart (**17**), then the action of LDA in THF at −78 °C for 5 min, followed by a quench with 1 M aqueous HCl at that temperature, delivered the desired 5-*exo*-tet product (**A**) in 56% yield (entry 2). Similar levels of success were achieved with cyanide **21** using KO*t*-Bu in DMF at −57 °C (entry 8). Intriguingly, in both cases, the remainder of the material balance was accounted for not through decomposition or recovered starting material, but instead by the formation of a singular byproduct: 3-phenylbenzofuran **22**.

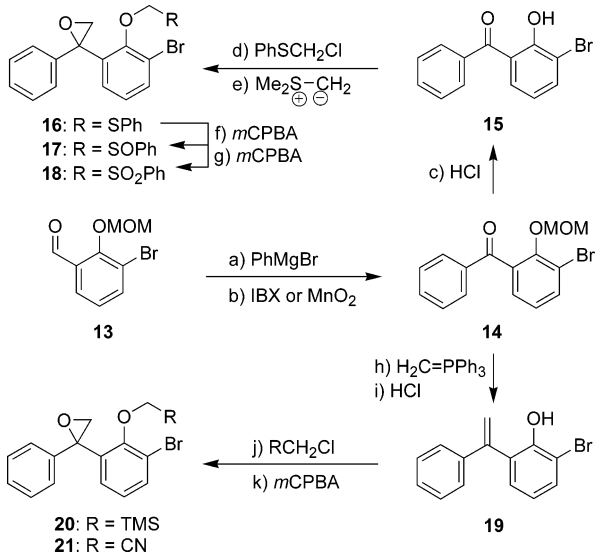
Scheme 3 provides one possible mechanistic explanation for this outcome, using compound **21** for illustration purposes. Simply put, 3-phenylbenzofuran **22** could result if a portion of alkoxide intermediate **24** underwent a Grob-like fragmentation,[25] expelling both formaldehyde and cyanide anion prior to being quenched with HCl. Such a side-reaction would appear quite

(23) In general, Lewis acid catalysts are required to direct the attack of nucleophiles toward the more substituted carbon of an epoxide (see: Mordini, A.; Bindi, S.; Pecchi, S.; Capperucci, A.; Degl'Innocenti, A.; Reginato, G. *J. Org. Chem.* **1996**, *61*, 4466−4468). However, on the basis of Baldwin's rules and biaryl activation of the epoxide, we felt that the greater preference of 5-*exo*-tet cyclization compared to the competing 6-*endo*-tet reaction would afford the desired product in this case.

(24) Mizuno, T.; Takeuchi, M.; Shinkai, S. *Tetrahedron* **1999**, *55*, 9455−9468.

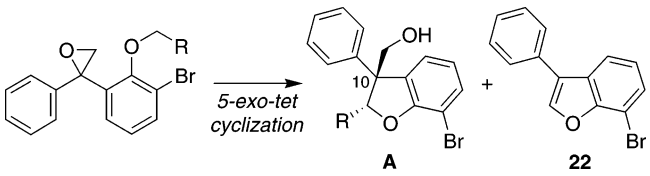
(25) For the original discovery of this process, see: (a) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594−610. For a review of its use in chemical synthesis, see: (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535−546.

Scheme 2. Synthesis of Various Biaryl Epoxides To Evaluate the Potential for a 5-*exo*-tet Cyclization To Establish the C-10 Quaternary Center of Diazonamide A[a]



[a] Reagents and conditions: (a) PhMgBr (1.0 M in THF, 1.3 equiv), THF, −78 → 25 °C, 2 h, 100%; (b) IBX (2.0 equiv), THF/DMSO (1:1), 25 °C, 1 h, 93%, or MnO_2 (10 equiv), CH_2Cl_2, 25 °C, 12 h, 95%; (c) concentrated HCl, MeOH/CH_2Cl_2 (1:1), 25 °C, 12 h, 97%; (d) $PhSCH_2Cl$ (2.0 equiv), K_2CO_3 (1.5 equiv), DMF, 25 °C, 12 h, 93%; (e) trimethylsulfonium iodide (1.5 equiv), KO*t*Bu (1.0 M in THF, 1.4 equiv), DMSO, 0 °C, 10 min, 96%; (f) *m*CPBA (1.1 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, −10 °C, 30 min, 86%; (g) *m*CPBA (2.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 91%; (h) methylene triphenylphosphonium bromide (1.4 equiv), *n*BuLi (1.6 M in hexanes, 1.2 equiv), THF, 0 °C, 12 h, 86%; (i) concentrated HCl, MeOH/CH_2Cl_2 (1:1), 25 °C, 12 h; (j) $ClCH_2CN$ (3.0 equiv) or $ClCH_2TMS$ (3.0 equiv), K_2CO_3 (2.0 equiv), acetone, 56 °C, 12 h; (k) *m*CPBA (3.0 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 6 h, 68% over two steps for **20**, 71% over two steps for **21**. IBX = *o*-iodoxybenzoic acid; DMF = *N*,*N*-dimethylformamide; *m*CPBA = *meta*-chloroperoxybenzoic acid; TMS = trimethylsilyl.

Table 1. Exploration of the 5-*exo*-tet Cyclization To Establish the C-10 Quaternary Center of Diazonamide A

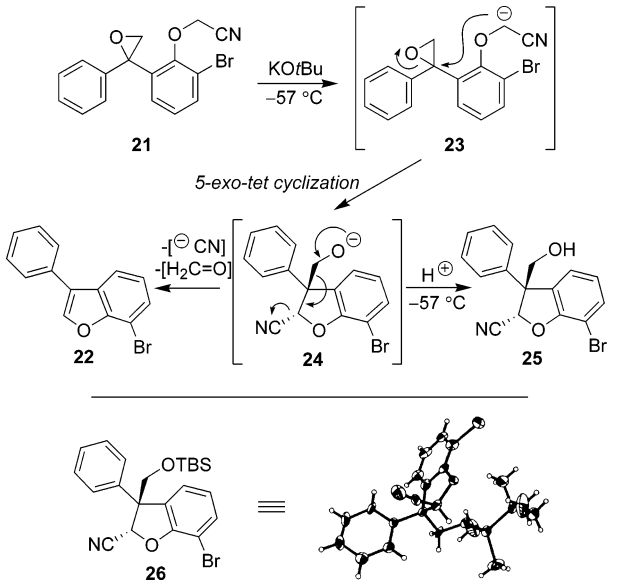


entry	compound	conditions (5 min reaction; then HCl quench)	yield (%) 5-*exo*-tet product (**A**)	yield (%) **22**
1	**16**: R = SPh	LDA[a], THF, −78 °C	recovered s.m.	
2	**17**: R = SOPh	LDA, THF, −78 °C	56	28
3	**17**: R = SOPh	KO*t*Bu, DMF, −57 °C	0	93
4	**18**: R = SO_2Ph	KO*t*Bu, DMF, −57 °C	0	91
5	**20**: R = TMS	LDA, THF, −78 → 25 °C	recovered s.m.	
6	**21**: R = CN	LDA, THF, −78 °C	decomposition	
7	**21**: R = CN	KO*t*Bu, DMF, 0 °C	0	95
8	**21**: R = CN	KO*t*Bu, DMF, −57 °C	45	52
9	**21**: R = CN	KO*t*Bu, THF/DMF (1:1), −78 °C	76	12

[a] LDA = lithium diisopropylamide.

reasonable on the basis of first principles, as the process creates three fragments from one molecule of starting material and the final product (**22**) gains enthalpically from aromatic stabilization. This picture is also consistent with experimental findings such as the exclusive formation of **22** when the reaction was conducted at higher temperature (entry 7, Table 1) and the improved yield of **25** when the temperature was lowered to −78 °C (entry 9, Table 1). It is further supported by a crystal structure of compound **26**, proving the exclusive *trans*-disposition of the hydroxymethylene and cyanide groups (see ORTEP drawing, Scheme 3).

Scheme 3. Proposed Mechanism To Account for the Formation of **22** and/or **25** Following the Treatment of Epoxide **21** with Base

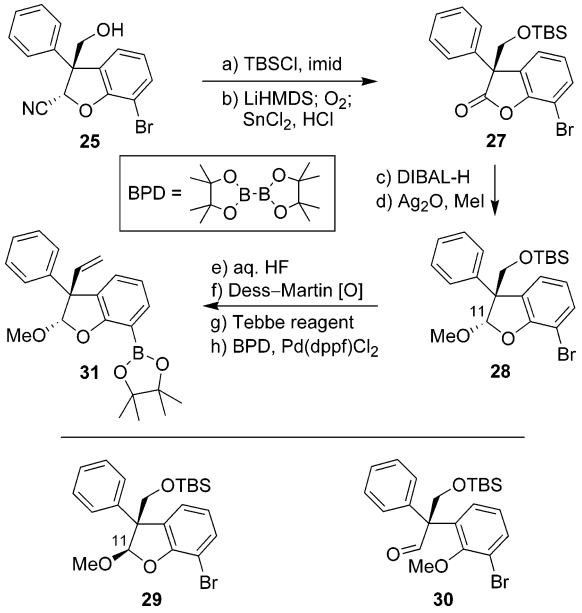


Needless to say, this initial series of results was quite exciting on many fronts. First, because the 5-*exo*-tet cyclization reaction could be driven cleanly to form 3-phenylbenzofuran products, an important pharmacophore found in a number of natural products and drug leads,[26] we were quite content that we had uncovered a new approach for their synthesis, one which ultimately proved amenable to both parallel solution and solid-phase platforms.[27] Second, since the X-ray crystal structure of compound **26** revealed that we had only formed one group of diastereomers from the cyclization, we knew that if the epoxide in compounds such as **17** or **21** could be accessed in enantiopure form, then this approach would deliver the C-11 quaternary center of **1** enantioselectively. Finally, because more than one methylene activating group had succeeded in our 5-*exo*-tet studies, we had several options in C-11 functionalization to achieve the synthesis of a complete EFG fragment.

Pressing forward, we elected to use intermediate **26** (the TBS-protected variant of **25**) to explore the next critical stage of our general synthetic approach: forming the heteroaromatic core of diazonamide A through ring-closing olefin metathesis. Our goal was to convert this intermediate into a suitable partner for a metal-mediated union of the Suzuki or Stille type, and, as shown in Scheme 4, that objective was accomplished over several steps. First, cognizant of the ability of LiHMDS and oxygen to convert secondary nitriles into ketones,[28] we thought the same reaction conditions might be sufficient to transform compound **26** into its corresponding lactone. Pleasingly, this

(26) (a) Cagniant, P.; Cagniant, D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; Vol. 18, pp 337−482. (b) Mustafa, A. In *Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1974; Vol. 29, pp 1−514.
(27) Nicolaou, K. C.; Snyder, S. A.; Bigot, A.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1093−1096.
(28) Freerksen, R. W.; Selikson, S. J.; Wroble, R. R.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 4087−4096.

Scheme 4. Conversion of Advanced Model Compound **25** into the Complete EFG System (**31**)[a]

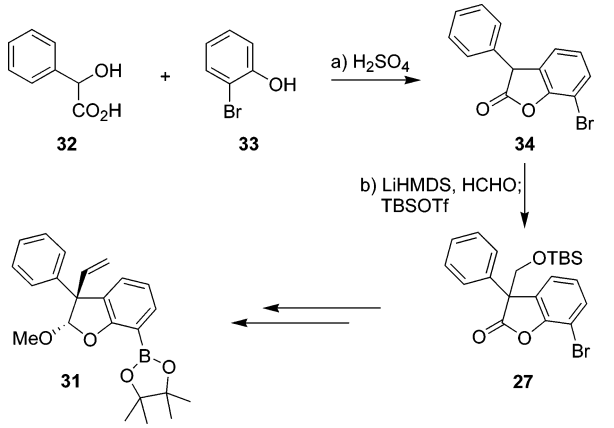


[a] Reagents and conditions: (a) TBSCl (1.5 equiv), imidazole (2.0 equiv), DMF, 25 °C, 12 h, 92%; (b) LiHMDS (1.0 M in THF, 2.0 equiv), THF, −78 °C, 15 min; O_2, 15 min, −78 °C; 1 M $SnCl_2$ in 10% aq HCl, −78 → 0 °C, 30 min, 94%; (c) DIBAL-H (1.0 M in toluene, 1.5 equiv), toluene, −78 °C, 1 h, 92%; (d) Ag_2O, MeI (5.0 equiv), CH_2Cl_2, 25 °C, 2.5 h, 72%; (e) aq HF (48%, excess), MeCN, 0 °C, 1 h, 99%; (f) Dess−Martin periodinane (1.2 equiv), CH_2Cl_2, 0 → 25 °C, 2 h, 96%; (g) Tebbe reagent (0.5 M in toluene, 1.5 equiv), THF, 0 °C, 10 min, 74%; (h) bis(pinacolato)diboron (1.2 equiv), Pd(dppf)Cl_2 (0.15 equiv), KOAc, DMSO, 90 °C, 6 h, 42%. TBS = *tert*-butyldimethylsilyl; LiHMDS = lithium bis(trimethylsilyl)amide; DIBAL-H = diisobutylaluminum hydride, BDP = bis(pinacolato)diboron; dppf = diphenylphosphinoferrocene.

conjecture proved to be true, as we observed the smooth formation of intermediate **27** in 94% yield following a $SnCl_2$ workup to break apart the initially formed peroxide intermediate. With this new reactive handle unveiled, partial reduction to the lactol, as effected with DIBAL-H in toluene at −78 °C, followed by methylation with Ag_2O and MeI in CH_2Cl_2 at 25 °C, served to provide a protected variant of the diazonamide F-ring (**28**) in 66% yield over two steps. In addition to **28**, these conditions also gave rise to the chromatographically separable C-11 epimer **29** and aldehyde **30**, each of which were obtained in 12% yield. Several other methylation procedures were probed at this stage in hopes of improving the yield of **28**, and while most could suppress the formation of **30** (such as NaH, MeI, THF, 0 °C), none provided a better relative ratio of **28**:**29**. As such, we utilized the Ag_2O-based protocol to process material. Although one might question our concern over commanding the C-11 stereochemistry at this stage in the synthesis, as the correct disposition of the F-ring lactol in diazonamide A (**1**) is likely to be the product of thermodynamic control, it stemmed from fears that the bulk at C-11 could impact later attempts at macrocyclization. Specifically, we felt that our chances for success in these likely difficult ring closures would best be enhanced by using material in which groups attached to C-11 were pointed as far away as possible from the reactive centers needed for cyclization (vide infra).

With ample amounts of intermediate **28** in hand, the installation of the alkene needed for metathesis was achieved over three steps in 70% yield by cleaving the TBS ether with aqueous HF in MeCN, oxidizing the resultant alcohol with Dess−Martin periodinane and then olefinating with the Tebbe reagent. The model EFG fragment (**31**) was then completed in 42% yield by exchanging the aryl bromide for a boronate ester using Miyaura's conditions [Pd(dppf)Cl_2·CH_2Cl_2, bis(pinacolato)-diboron, and KOAc] in DME at 90 °C.[29]

Scheme 5. Alternate Racemic Synthesis of Advanced EFG Fragment **31**[a]



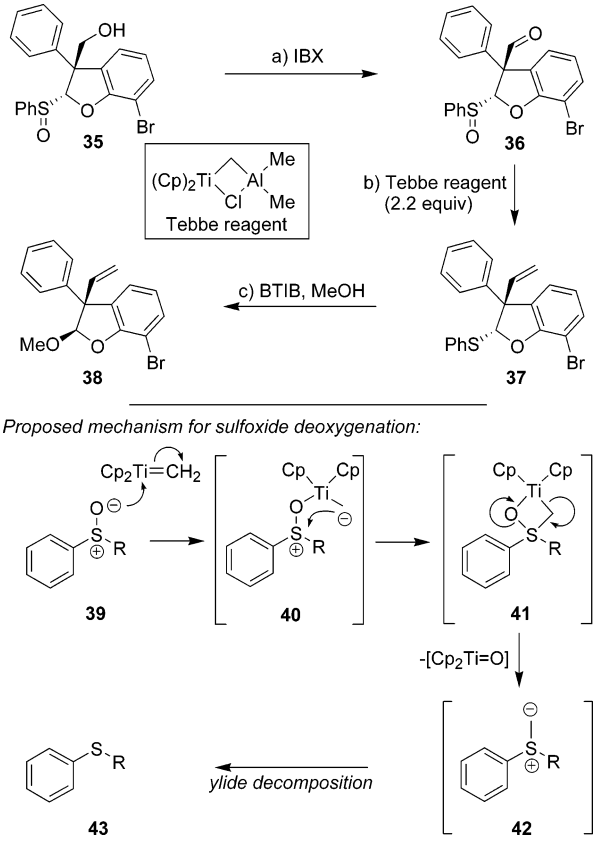
[a] Reagents and conditions: (a) **32** (1.0 equiv), **33** (1.0 equiv), H_2SO_4 (70% aq), 0 → 70 °C, 2 h, 42% (95% based on recovered **33**); (b) LiHMDS (1.0 M in THF, 1.5 equiv), HCHO (3.0 equiv), THF, 0 → 25 °C, 1 h; then TBSOTf (2.0 equiv), Et_3N (2.0 equiv), 10 min, 75%.

Before we describe efforts to synthesize this compound's coupling partner, there are several observations related to these final reactions that are worth mentioning. First, the use of any basic fluoride source (such as TBAF) to remove the silyl group from **28** led to exclusive formation of 3-phenylbenzofuran **22**. The same outcome also occurred when attempts were made to olefinate the intermediate aldehyde under Wittig conditions, presumably due to the existence of a betaine intermediate unobserved in the reaction with Tebbe reagent based on the higher oxophilicity of titanium. Taken in conjunction with the earlier studies in the context of Table 1, these two findings reveal the impressive fragility of functionalized systems such as **25** under basic conditions and highlight an issue that will reappear in later steps of the sequence. Second, attempts to improve the yield of boronation through more "standard" protocols, such as lithiation followed by a quench with $B(OMe)_3$, failed numerous attempts, leading in all cases to reduced material (i.e., dehalogenation). Third, while the overall sequence to **31** was quite efficient for its length (15 steps), supplies of this key intermediate could be enriched through the two-step synthesis of lactone **27** shown in Scheme 5.[30] Of course, while this alternate approach was effective for forming racemic **31** in just 8 steps for our model studies, we did not expect that it could prove useful in applications to access fully functionalized diazonamide intermediates, both for its failure to offer any means to control the C-11 stereochemistry and for its overall harshness (which would likely be incompatible with an elaborated G-ring).

(29) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510.

(30) The opening operation was patterned after that reported by: Padwa, A.; Dehm, D.; Oine, T.; Lee, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 1837−1845. The addition of HCHO was achieved using the protocol reported by: Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590−3596. For a related example, see: Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021−9032.

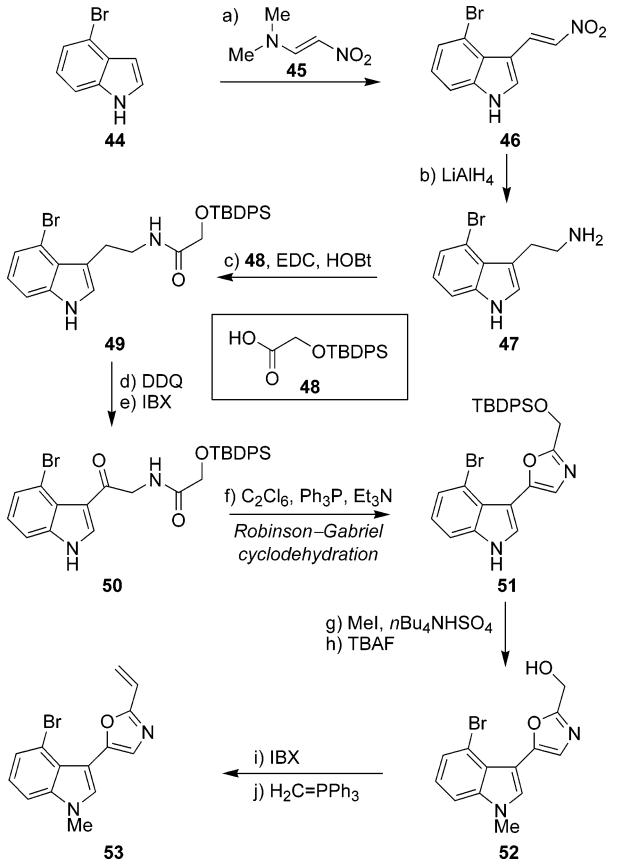
Scheme 6. Conversion of Advanced Model Compound **35** into an Alternate EFG System (**38**)[a]



[a] Reagents and conditions: (a) IBX (1.3 equiv), THF/DMSO (1:1), 25 °C, 1 h, 83%; (b) Tebbe reagent (0.5 M in toluene, 2.2 equiv), THF, −20 → 0 °C, 1 h, 78%; (c) [bis(trifluoroacetoxy)iodo]benzene (1.5 equiv), MeOH, 25 °C, 3 h, 83%. BTIB = [bis(trifluoroacetoxy)iodo]benzene.

As a final aside, significant effort was also expended to advance 5-*exo*-tet product **35** to the same EFG model system (**31**). As revealed in Scheme 6, these forays began by oxidizing **35** to aldehyde **36** using *o*-iodoxybenzoic acid (IBX).[31] This intermediate was then treated with excess Tebbe reagent (2.2 equiv) in toluene at 0 °C for 1 h in hopes of forming the requisite alkene needed to probe eventual olefin metathesis. While this transformation would proceed smoothly, these conditions also led to the reduction of the sulfoxide to the corresponding sulfide, presumably through the indicated mechanism proceeding by way of intermediates **39**−**42**, to provide **37** in 78% yield. Although unexpected, this outcome was quite fortuitous because it allowed immediate probes aimed at replacing the phenylsulfide in **37** with methoxide using bis(trifluoroacetoxy)iodobenezene in methanol.[32] Sadly, any initial excitement was soon dashed because this exchange only provided material with the stereochemical disposition of **38**, as verified by nOe comparisons to similar compounds obtained from intermediates **28** and **29**. As such, we viewed this product (**38**), and the overall sequence from **35**, as useless for further studies toward diazonamide A on the basis of the considerations mentioned above. On the positive side, however, these explorations did induce us to explore the sulfoxide deoxygenation process (**36** → **37**) in more detail, ultimately leading to a new, general, and mild synthetic method for the reduction of diverse and heavily functionalized sulfoxides, selenoxides, and *N*-oxides using titanocene methylidenes.[33]

Scheme 7. Preparation of Indole-oxazole Fragment **53**[a]



[a] Reagents and conditions: (a) dimethylamino-2-nitroethylene (1.1 equiv), TFA, 25 °C, 30 min; (b) $LiAlH_4$ (1.0 M in THF, 6.0 equiv), THF, 25 → 65 °C, 4 h, 87% over two steps; (c) **48** (1.0 equiv), EDC (1.0 equiv), HOBt (1.0 equiv), CH_2Cl_2, 25 °C, 2 h, 79%; (d) DDQ (3.0 equiv), THF/H_2O (9:1), 0 °C, 3 h; (e) IBX (3.0 equiv), THF/DMSO (1:1), 25 °C, 3 h, 90% over two steps; (f) Cl_3CCCl_3 (2.0 equiv), Ph_3P (2.0 equiv), Et_3N (4.0 equiv), 25 °C, 15 min; (g) MeI (4.0 equiv), nBu_4NHSO_4 (1.1 equiv), C_6H_6, 10% aq NaOH, 25 °C, 20 min, 88% over two steps; (h) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 15 min, 92%; (i) IBX (3.0 equiv), THF/DMSO (1:1), 25 °C, 3 h, 90%; (j) methylene triphenylphosphonium bromide (1.5 equiv), *n*BuLi (1.6 M in hexanes, 1.3 equiv), THF, 0 °C, 15 min, 89%. TFA = trifluoroacetic acid; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; TBDPS = *tert*-butyldiphenylsilyl; HOBt = 1-hydroxybenzotriazole trihydrate; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBAF = tetra *n*-butylammoniumfluoride.

3. Synthesis of the BCD Indole-Oxazole Fragment. Despite the problems encountered within the context of Scheme 6, since we had an efficient sequence available to prepare the desired EFG fragment, effort was immediately directed at preparing an appropriate coupling partner, namely BCD indole-oxazole **53**. As shown in Scheme 7, explorations to access this fragment began from the known 4-bromoindole (**44**),[34] a starting material that already contained the C- and D-rings of the needed compound. As such, only an oxazole had to be appended to

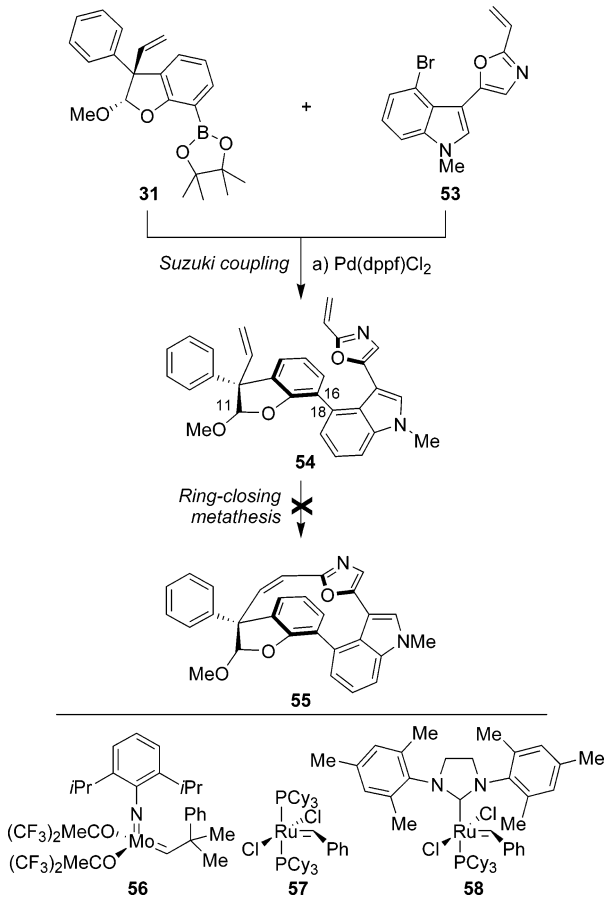
(31) IBX is readily and safely prepared from 2-iodobenzoic acid and OXONE following the method of: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.
(32) Moriarty, R. M.; Kosmeder, J. W. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 6, pp 3982−3984.
(33) Nicolaou, K. C.; Koumbis, A. E.; Snyder, S. A.; Simonsen, K. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 2529−2533. For an earlier report of one of the reactions disclosed in this communication, the conversion of pyridine *N*-oxides to 2-methylpyridines, using a tantalum methylidene, see: Mullins, S. M.; Bergman, R. G.; Arnold, J. *Organometallics* **1999**, *18*, 4465−4467.
(34) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657−2662.

complete the target. Anticipating that a Robinson−Gabriel cyclodehydration reaction could be called upon to accomplish this task, the opening operations sought to install the functionality needed to create the ketoamide precursor required for that event (i.e., compound **50**). Thus, TFA-promoted condensation with dimethylaminonitroethylene (**45**),[35] followed by $LiAlH_4$-mediated reduction in refluxing THF, served to convert **44** into 4-bromotryptamine (**47**) in 87% overall yield. Subsequent peptide coupling with TBDPS-protected glycolic acid (**48**),[36] mediated by EDC and HOBt, then led to the smooth preparation of **49** in 79% yield, a compound separated from the desired ketoamide substrate (**50**) only by the absence of a carbonyl group. This deficiency was rectified over the course of two steps in 80% yield through the initial installation of a hydroxyl group, as accomplished by the action of DDQ in aqueous THF at 0 °C, followed by oxidation of the newly installed functionality with IBX. Interestingly, although DDQ in aqueous media is known to convert materials such as **49** directly into compounds such as **50**,[11,37] the second oxidation step could never be induced with this particular substrate. As revealed by several additional studies, the bromine substituent was the likely culprit, as application of the same conditions to the debrominated variant of **50** led directly to a ketone.

With these operations accomplished, the synthesis of **53** was then completed in five additional steps: 1) formation of the oxazole ring using Wipf's variant of the Robinson−Gabriel cyclodehydration reaction;[38] 2) *N*-methyl protection of the indole nucleus under phase transfer conditions (88% yield over two steps);[39] 3) TBAF-mediated cleavage of the terminal TBDPS group (92% yield); 4) oxidation of the resultant hydroxyl group with IBX (90% yield); and 5) generation of the desired alkene upon Wittig reaction with $Ph_3P{=}CH_2$ (89% yield).

4. Efforts To Accomplish Macrocyclization. With our having synthesized both boronate ester **31** and indole-oxazole **53**, the stage was now set to attempt biaryl coupling of the two fragments, and subsequently, the key olefin metathesis-based macrocyclization. Pleasingly, as shown in Scheme 8, the first of these critical operations proceeded quite smoothly as Suzuki coupling was readily effected in 62% yield over the course of 6 h using catalytic amounts of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ and excess K_2CO_3 in DME at 85 °C.[40] Our excitement at reaching this advanced stage, however, was quickly dashed as attempted ring-closing olefin metatheses in the presence of catalyst **56**,[41] **57**,[42] or **58**[43] (toluene, 70 °C, several days or CH_2Cl_2, 40 °C, several hours) failed to result in macrocycle **55**. Instead, we only recovered starting material (**54**) or observed complete polymerization/decomposition. Due to the proximity of the more accessible alkene to a Lewis basic nitrogen atom within the oxazole ring, it is possible that their failure stemmed from nonproductive chelation following catalyst insertion; steric hindrance close to the other olefin could also have been a deciding factor.[44]

Scheme 8. Attempted Ring-closing Metatheses To Create Macrocyclic Alkene **55**[a]

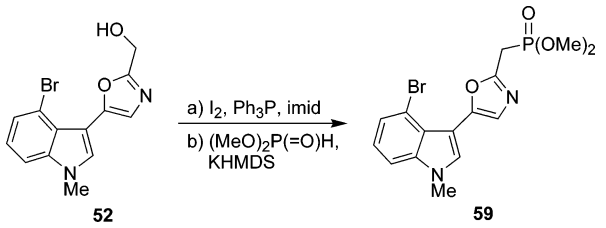


[a] Reagents and conditions: (a) **31** (1.0 equiv), **53** (1.0 equiv), $Pd(dppf)Cl_2$ (0.2 equiv), K_2CO_3 (3.0 equiv), DME, 85 °C, 6 h, 62%. Cy = cyclohexyl.

In any case, with this reaction defining a limitation for the power of ring-closing olefin metathesis in complex molecule synthesis, we needed to alter our strategy. So, as discussed earlier, we turned to the prospect of an intramolecular HWE reaction for macrocyclization, an extremely powerful and mild C−C bond forming process which has been widely employed in chemical synthesis, especially on highly functionalized substrates.[22] Although that precedent was encouraging, the pursuit of this plan did have us concerned, not because we thought that it would be difficult to access the needed fragments but because of the proclivity of a number of our benzofuranone intermediates to undergo cyclofragmentation to 3-arylbenzofuran products. More specifically, since the aldehyde derived from compound **28** (see Scheme 4) aromatized under standard Wittig reaction conditions, we thought that the same outcome would occur from an HWE macrocyclization reaction, especially since it could relieve the strain that would be imparted with the formation of a 12-membered ring.

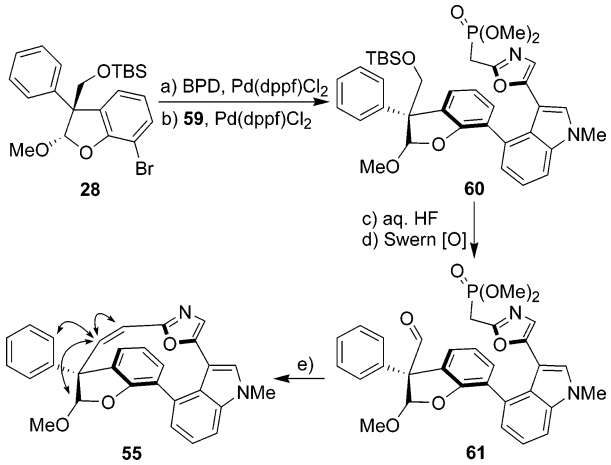
(35) Severia, T.; Bohme, H.-J. *Chem. Ber.* **1968**, *101*, 2925−2930.
(36) Roth, G. A.; McClymont, E. L. *Synth. Commun.* **1992**, *22*, 411−420.
(37) Oikawa, Y.; Toshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457−1462.
(38) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.
(39) For other phase-transfer catalysts which can effect the same operation using milder bases, see: Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915−13928.
(40) It is important to note that attempts to accomplish C16−C18 biaryl bond formation through Stille coupling met with failure despite several attempts (though the requisite Me_3Sn group could be attached to both reactive partners).
(41) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.
(42) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.
(43) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(44) For pertinent discussion on the roles of sterics in metathesis reactions, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Grubbs, R. H.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. For recent reviews on metathesis, see: (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

Scheme 9. Synthesis of Indole-oxazole **59**[a]



[a] Reagents and conditions: (a) Ph_3P (1.7 equiv), imidazole (2.0 equiv), I_2 (1.5 equiv), CH_2Cl_2, 0 °C, 10 min, 94%; (b) $(MeO)_2P(=O)H$ (2.0 equiv), KHMDS (0.5 M in toluene, 1.5 equiv), THF, 0 °C, 10 min, 86%. KHMDS = potassium bis(trimethylsilyl)amide; imid = imidazole.

Scheme 10. Successful Execution of an HWE Approach To Accomplish the Synthesis of Heterocyclic Macrocycle **55**[a]



[a] Reagents and conditions: (a) BPD (1.2 equiv), $Pd(dppf)Cl_2$ (0.15 equiv), KOAc (3.0 equiv), DMSO, 90 °C, 4 h, 50%; (b) **59** (1.0 equiv), $Pd(dppf)Cl_2$ (0.30 equiv), K_2CO_3 (3.0 equiv), DME, 85 °C, 8 h, 67%; (c) aq HF, MeCN, 0 °C, 45 min; (d) DMSO (10 equiv), $(COCl)_2$ (5.0 equiv), CH_2Cl_2, −78 °C, 15 min, then substrate, CH_2Cl_2, −78 °C, 30 min, then Et_3N (20 equiv), −78 → 25 °C, 30 min, 85% over two steps; (e) LiHMDS (1.0 M in THF, 5.0 equiv), THF, 0 °C, 2 h, 25%. DME = ethylene glycol dimethyl ether. Selected nOe's shown for **55** confirm the indicated stereochemistry.

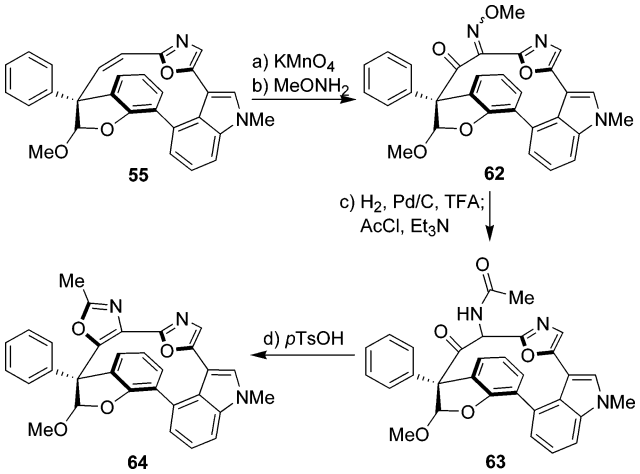
Nevertheless, we felt that we should still try the idea since it would be easy to test. We began by converting indole-oxazole intermediate **52** (Scheme 9) into an appropriate phosphonate by exchanging the oxazylic alcohol for an iodine under typical conditions (I_2, Ph_3P, imidazole, CH_2Cl_2, 0 °C) and then displacing this new leaving group with the anion derived from dimethyl phosphite (81% overall). Standard Arbuzov conditions [$P(OMe)_3$, Δ, 12 h] delivered **59** in only mediocre yield (<20%) in this final reaction, while the use of NaH or HMDS bases other than KHMDS to generate the needed anion provided significant amounts of reduced material in addition to **59**. With this fragment suitably outfitted, the previously obtained benzofuranone intermediate, **28**, was then transformed into an aryl boronate using the same conditions as before (see Scheme 10). This piece was then directly coupled to phosphonate **59** in 67% yield utilizing the previously described Suzuki reaction protocol; to the best of our knowledge, this reaction represents the first example of a readily enolizable phosphonate being successfully employed in a Suzuki-type coupling reaction. While certainly not a discovery of great magnitude, had this transformation failed, the HWE strategy could not have been explored, as any attempt to install the same phosphonate post-Suzuki reaction met with failure.

Having reached **60**, we were now in a position to access the key aldehyde-phosphonate HWE precursor (**61**). This objective was accomplished in 85% yield over the course of two steps by first cleaving the TBS ether in **60** under acidic conditions with aqueous HF and then oxidizing the resultant alcohol with a standard Swern protocol. The stage was now set for the most important reaction up to this point in the sequence. Most gratifyingly, exposure of this new intermediate to the action of LiHMDS in THF at 0 °C for 2 h under high dilution conditions (1.0×10^{-5} M) did initiate the desired ring-closing reaction, leading to macrocycle **55** in 25% yield. Only a small amount of material (<5%) participated in the previously feared cyclofragmentation reaction, with the remainder accounted for by phosphonate decomposition prior to cyclization. While the yield of **55** might seem unduly low for this process, it partially reflects the fact that at 0 °C compound **61** exists as two noninterconvertable atropisomers along the C16−C18 biaryl axis (as verified by ^1H NMR analysis), so the maximum possible yield for the process under these conditions was 50%. At 25 °C, the two atropsiomers of **61** exchange on the NMR time scale to reflect signals corresponding to one compound, but any attempt to accomplish macrocyclization at this temperature led to near-exclusive benzofuran formation instead of alkene **55**. No other base explored at 0 °C, whether NaH, KHMDS, or NaHMDS, provided a better yield of **55**, though all worked with varying levels of success (5−20%). Finally, in line with expectations, compound **55** was formed as a single atropisomer, and any attempt to employ material bearing the opposite C-11 stereochemistry of **61** failed to provide any product from HWE macrocyclization.[12a]

5. Completion of Model Studies. Having finally found a way to construct the final C−C bond of the heterocyclic-based macrocycle of diazonamide A, we wanted to conduct one more model study before moving on to fully functionalized intermediates: identifying a sequence capable of fashioning the final A-ring ozazole from the C29−C30 olefinic residue. Our initial efforts along these lines were directed at forming a diketone moiety from the alkene in **55** (see Scheme 11), expecting that the resultant carbonyl group near the B-ring oxazole could be readily converted into an amine over the course of a few steps. As such, we attempted to dihydroxylate that olefin under standard conditions (OsO_4, acetone/H_2O, quinuclidine, 25 °C). What occurred was something we should have expected. The reaction proceeded smoothly in solution, but any attempt to isolate the diol product led to significant amounts of ring scission through the same cyclofragmentation pathway encountered on several occasions up to this point. Thus, with this approach shut down due to a diol yield of less than 5%, we sought diketone formation through less conventional means, and after considerable experimentation, found that conditions developed by Sharpless using $KMnO_4$ and $Cu(OAc)_2 \cdot H_2O$ in neat acetic anhydride rose to the occasion,[45] providing direct access to the needed diketone in 35% yield. Key to obtaining a consistent yield of this product was the portionwise addition of $KMnO_4$ over a 45 min period, using the monohydrate salt of $Cu(OAc)_2$, and a total reaction time no greater than 1.5 h. Otherwise, the only major product observed was the ring-opened dicarboxylic acid.

(45) Sharpless, K. B.; Lauer, R. F.; Repic, O.; Teranishi, A. Y.; Williams, D. R. *J. Am. Chem. Soc.* **1971**, *93*, 3303−3304.

Scheme 11. Completion of Model Studies Leading to the Complete Heteroaromatic Skeleton (**64**) of the Originally Proposed Structure of Diazonamide A (**1**)[a]



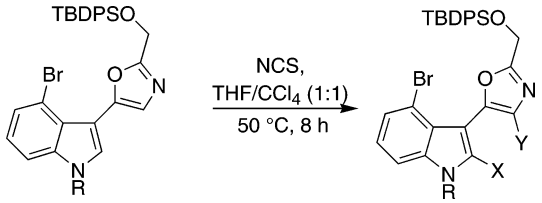
[a] Reagents and conditions: (a) $KMnO_4$ (6.0 equiv), Ac_2O, 0 °C, 2 h, 35%; (b) $MeONH_2$·HCl (20.0 equiv), EtOH, 25 °C, 12 h, 95%; (c) Pd/C (10%, 2.0 equiv), H_2 (3.0 atm), TFA/MeOH (1:20), 25 °C, 12 h, then AcCl (3.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 25 °C, 30 min, 80%; (d) *p*TsOH, benzene, 80 °C, 20 h, 50%. *p*TsOH = *p*-toluenesulfonic acid.

With oxidation achieved, the more activated and less sterically hindered carbonyl group was then converted into its corresponding methoxime derivative (**62**, Scheme 11) in 95% yield over the course of 12 h using excess $MeONH_2$·HCl in EtOH, enabling subsequent hydrogenolysis in acidified methanol to generate an amine at that site. Acetylation of this new function using AcCl then furnished acetamide **63** in 80% yield from **62**. Now, only oxazole formation remained to complete this model study, and fortunately, the needed Robinson−Gabriel dehydration could be initiated by *p*TsOH in refluxing benzene, giving rise to **64** in 50% yield.[5b,12b,46] By reaching this point, not only had we verified all of the opening elements of our synthetic plan as outlined in Scheme 1 but we also had accomplished the first synthesis of any material resembling the complete heteroaromatic core of diazonamide A (**1**).

At the same time, we had to concede that the relatively modest yields observed for HWE closure to generate **55** and subsequent diketone formation suggested that it would be challenging to process sufficient material to reach diazonamide A (**1**) in the context of a fully elaborated G-ring. Accordingly, we recognized that the functionalization of the C-11 position in "real" system compounds would have to be better tailored to prevent benzofuran formation. If we could achieve that objective, then it would be quite reasonable to expect dramatic yield improvements, especially in the HWE macrocyclization step since we could likely employ a higher reaction temperature to equilibrate the C16−C18 biaryl atropisomers and, thereby, drive the potential yield above 50%.

Apart from this key concern, we also knew that we would have to address the issue of indole protection in any future studies with fully functionalized intermediates, a matter of contention that we had side-stepped by placing the convenient, but noncleavable, methyl group onto all of our compounds up to this point. We also needed to determine how we would accomplish chlorination of the B- and C-rings. Both of these questions were answered through the studies summarized in Table 2. We began by attempting to chlorinate indole-oxazole **51** (entry 8) using NCS as an electrophilic source of chlorine in THF/CCl_4 (1:1) at 70 °C. While successful in furnishing the desired chlorines, this reaction also led to complete *N*-chlorination, a side-reaction that proved difficult to counter or subsequently ameliorate through dechlorination. Accordingly, indole protection was obviously required during the chlorination step, and as indicated by the exposure of compounds **67**, **69**, **71**, **73**, and **75** to the same conditions, as long as that indole protecting group was electron-donating or electron-neutral, both the B- and C-rings could still be smoothly chlorinated (entries 1−4). On the basis of these results, only three options for indole protection were available other than engagement by a methyl group, and in light of the diverse reaction conditions used in our model studies to reach **64**, only two of these (a benzyl group or a methoxymethyl ether) would likely prove resilient enough to complete a drive toward **1**. Neither, though, was an ideal candidate, as benzyl protecting groups on indoles are typically cleaved under substrate-dependent hydrogenation conditions which often require significant screening to identify (and could initiate dechlorination), while MOM ethers are deprotected only through the use of strong Lewis acids.[47] However, since a number of reports[48] indicated that benzylic groups on indoles could be stubbornly resilient to cleavage, we elected to press forward with MOM protection on our indole intermediates.

Table 2. Model Studies Exploring Chlorination via Electrophilic Aromatic Substitution; the Role of Indole Protection



entry	compound	product	yield (%)
1	**65**: R = Me	**66**: X = Cl, Y = Cl	84
2	**67**: R = Bn	**68**: X = Cl, Y = Cl	68
3	**69**: R = MOM[a]	**70**: X = Cl, Y = Cl	72
4	**71**: R = TBS	**72**: X = Cl, Y = Cl	75
5	**73**: R = Boc	**74**: X = H, Y = Cl	81
6	**75**: R = Ts[b]	**76**: X = H, Y = Cl	79
7	**51**: R = H	**77**: R = Cl, X = Cl, Y = Cl	56

[a] MOM = methoxymethyl. [b] Ts = *p*-toluenesulfonyl.

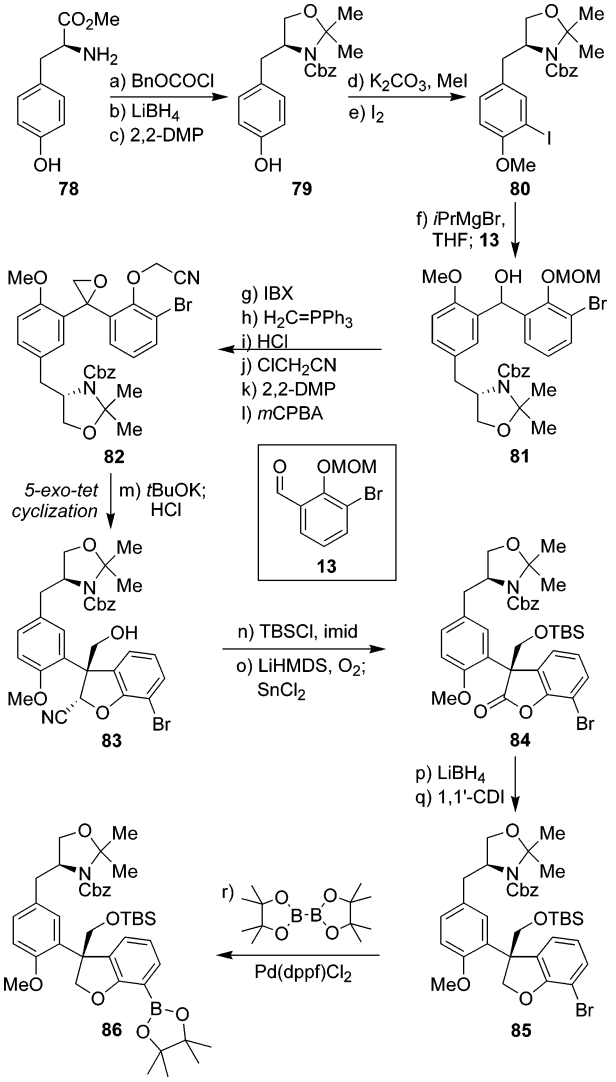
6. Application of the Developed Strategy to Fully Functionalized Intermediates. With these extensive model studies completed, we began our drive to apply the same strategy toward fully functionalized intermediates, starting with work toward the EFG fragment using the commercially available L-tyrosine methyl ester (**78**) as our new G-ring. As shown in Scheme 12, its conversion into **79** was accomplished in 90% overall yield via initial Cbz-protection of the free amine followed by $LiBH_4$ reduction of the ester group and acetonide capture (*p*TsOH, 2,2-

(46) Parsons, R. L.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 4733−4734. It is important to note that no other oxazole-forming protocols attempted [such as Martin's sulfurane or the previously used conditions from the Wipf group (ref 38)] succeeded on this substrate. This issue would prove problematic throughout the course of our diazonamide program.

(47) Meyers, A. I.; Highsmith, T. K.; Buonara, P. T. *J. Org. Chem.* **1991**, *56*, 2960−2964.

(48) For some discussion on this topic, see: (a) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994; pp 220−227. (b) Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1152−1156.

Scheme 12. Synthesis of Advanced EFG Fragment **86**[a]

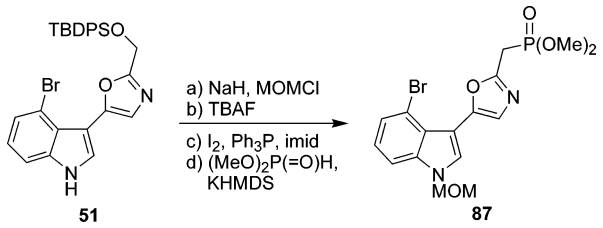


[a] Reagents and conditions: (a) BnOCOCl (1.0 equiv), $CHCl_3$, 25 °C, 3 h, 94%; (b) $LiBH_4$ (2.0 M in THF, 3.0 equiv), 0 → 25 °C, THF, 2 h, 99%; (c) 2,2-dimethoxypropane (10 equiv), *p*TsOH (0.1 equiv), acetone, 25 °C, 30 min, 97%; (d) MeI (5.0 equiv), K_2CO_3 (10 equiv), DMF, 25 °C, 10 h, 92%; (e) I_2 (1.1 equiv), $Ag(OCOCF_3)_2$ (1.5 equiv), $CHCl_3$, 25 °C, 4 h, 77%; (f) *i*PrMgBr (1.0 M in THF, 1.5 equiv), THF, −20 °C, 15 min; then **13** (1.0 equiv), THF, −78 °C, 15 min, 69%; (g) IBX (1.2 equiv), DMSO/THF (1:1), 25 °C, 4 h, 98%; (h) methylene triphenylphosphonium bromide (2.0 equiv), *t*BuOK (1.0 M in THF, 1.5 equiv), THF, 0 → 25 °C, 6 h, 86%; (i) concentrated HCl, MeOH/CH_2Cl_2 (1:1), 25 °C, 12 h, 98%; (j) $ClCH_2CN$ (1.5 equiv), K_2CO_3 (1.5 equiv), acetone, 56 °C, 3 h, 95%; (k) 2,2-dimethoxypropane (10 equiv), *p*TsOH (0.1 equiv), acetone, 25 °C, 30 min, 96%; (l) *m*CPBA (77%, 2.0 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 0 °C, 8 h, 84%; (m) *t*BuOK (1.0 M in THF, 1.5 equiv), THF/DMF (1:1), −78 °C, 5 min, then 10% aq HCl, −78 °C, 5 min, 52%; (n) TBSCl (3.0 equiv), imidazole (6.0 equiv), DMF, 25 °C, 6 h, 88%; (o) LiHMDS (1.0 M in THF, 2.0 equiv), THF, −78 °C, 15 min; O_2, 15 min, −78 °C; 1.0 M $SnCl_2$ in 10% aq HCl, −78 → 0 °C, 30 min, 73%; (p) $LiBH_4$ (2.0 M in THF, 2.0 equiv), Et_2O, 0 °C, 3 h, 88%; (q) 1,1′-carbonyldiimidazole (1.3 equiv), THF, 67 °C, 1 h, 90%; (r) bis(pinacolato)diboron (1.2 equiv), $Pd(dppf)Cl_2$ (0.2 equiv), KOAc (3.0 equiv), DMSO, 85 °C, 6 h, 76%. 2,2-DMP = 2,2-dimethoxypropane; 1,1′-CDI = 1,1′-carbonyldiimidazole.

dimethoxypropane, acetone, 25 °C). Subsequent methylation (MeI, K_2CO_3, DMF, 25 °C) and iodination[49] using molecular iodine and $Ag(OCOCF_3)_2$ then served to complete the assembly

(49) For an earlier example of this procedure, see: Carruthers, W.; Coggins, P.; Weston, J. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 611−616.

Scheme 13. Synthesis of MOM-Protected Indole-oxazole **87**[a]



[a] Reagents and conditions: (a) NaH (1.3 equiv), THF, 0 °C, 5 min, then MOMCl (1.2 equiv), 0 °C, 5 min, 95%; (b) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 15 min, 92%; (c) Ph_3P (1.7 equiv), imidazole (2.0 equiv), I_2 (1.5 equiv), CH_2Cl_2, 0 °C, 10 min, 94%; (d) $(MeO)_2P(=O)H$ (2.0 equiv), NaH (1.5 equiv), THF, 0 °C, 10 min, 86%.

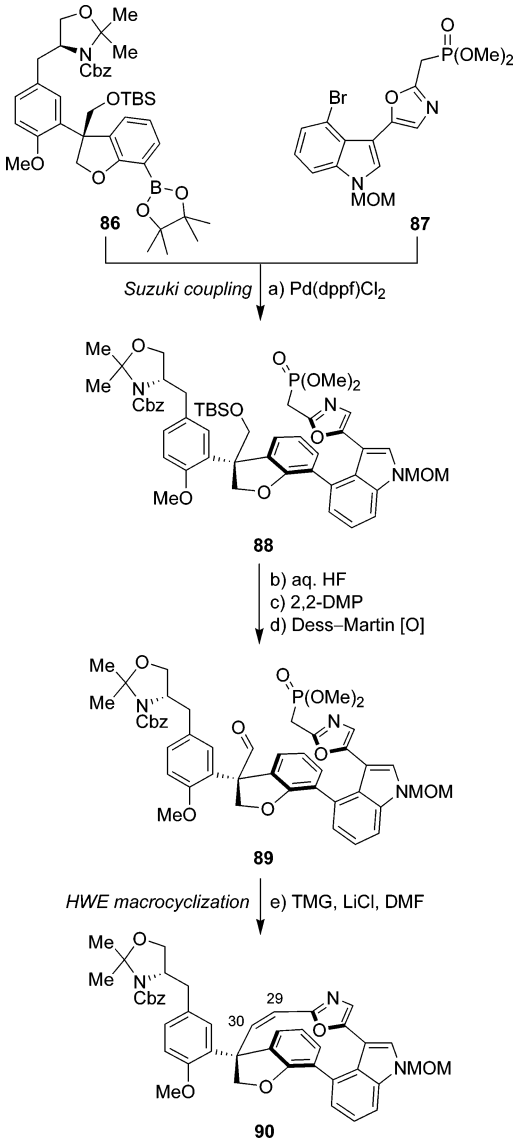
of **80**, ready for subsequent metal−halogen exchange with *i*-PrMgBr to accomplish the synthesis of **81** through a standard Grignard reaction with aldehyde **13**. From this advanced intermediate, application of the same general sequence employed earlier served to advance this compound to lactone **84** in yields that were commensurate to our model studies. The smooth nature of these operations requires little commentary beyond that already presented, except to note that, while 14 distinct steps were required to reach **84** from **78**, most of these operations proceeded without byproduct formation, such that column chromatography was typically performed only six times during the entire sequence. As such, it was quite easy to bring material to this advanced stage. It is also important to note that we could not form the epoxide within **82** diastereoselectively irrespective of epoxidation protocol employed (including attempts with Jacobsen's salen catalysts[50] and Shi's L-fructose-derived chiral dioxirane,[51] among a number of others). While clearly a major concern, we left further study of this problem for later, electing instead to press forward with our C-10 epimeric material in order to evaluate the remainder of the strategy.

With **84** in hand, we next reduced its lactone ring fully to the corresponding diol in 99% yield over the course of 2 h with $LiBH_4$ in THF at 25 °C. The thought behind this operation being that if we could engage the new diol in an appropriate protecting device, such as a cyclic carbonate, then we could solve the issue of C-11 functionalization and prevent future cyclofragmentations leading to benzofuran products. However, when that intermediate was exposed to 1,1′-carbonyldiimidazole in refluxing acetone in the hope of accomplishing that objective, only the five-membered ring corresponding to **85** was formed, a result with some precedent under harsher reaction conditions.[52] While unexpected, this outcome was still acceptable since its functionalization would certainly prevent benzofuran formation. Accordingly, we completed the synthesis of aryl boronate **86** in 76% yield from **85** using the same conditions that had succeeded earlier.

With a suitably functionalized EFG segment in hand, its indole-oxazole coupling partner was then prepared exactly as before, as shown in Scheme 13, with the only alteration being MOM protection of the indole nucleus. With these four steps proceeding in a combined yield of 71% from **51**, probes at the rest of the strategy could now begin. As indicated in Scheme

(50) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063−7064.
(51) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806−9807. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224−11235.
(52) Stafford, J. A.; Valvano, N. L. *J. Org. Chem.* **1994**, *59*, 4346−4349.

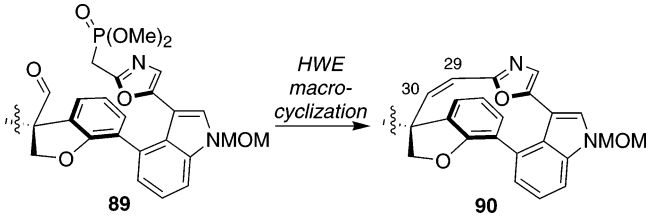
Scheme 14. Suzuki Coupling and HWE Condensation To Generate One of the 12-Membered Macrocycles of the Originally Proposed Structure of Diazonamide A (**1**)[a]



[a] Reagents and conditions: (a) **86** (1.05 equiv), **87** (1.0 equiv), $Pd(dppf)Cl_2$ (0.2 equiv), K_2CO_3 (5.0 equiv), DME, 85 °C, 12 h, 83%; (b) aq HF (48%, 3.0 equiv), MeCN, 0 °C, 45 min; (c) 2,2-DMP, acetone, 25 °C, 5 min; (d) Dess−Martin periodinane (3.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 70% over three steps; (e) TMG (5.0 equiv), LiCl (5.0 equiv), DMF, 70 °C, 12 h, 55−60%. TMG = 1,1,3,3-tetramethylguanidine.

14, initial Suzuki coupling proceeded in an excellent yield of 83% over the course of 12 h in refluxing DME as catalyzed by $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ in the presence of K_2CO_3. Aldehyde formation (**89**) was then accomplished over three steps in 70% overall yield, enabling probes of HWE macrocyclization to commence. At first, these studies were disappointing, as the use of LiHMDS in THF provided only a modest and highly variable yield of macrocycle **90** irrespective of temperature (see Table 3). However, better yields (35%) were obtained if we switched to Masamune−Roush conditions (LiCl, DBU, MeCN, 25 °C),[53] and when we changed the base to the bulkier 1,1,3,3-tetramethyguanidine (TMG),[54] used DMF as solvent, and

Table 3. Exploration of Conditions To Accomplish the HWE Macrocyclization Leading to **90**



entry	conditions	yield (%)
1	LiHMDS, THF, 0 °C	0−25[a]
2	DBU, CH_3CN, 25 °C	decomposition
3	DBU, LiCl, CH_3CN, 25 °C	35
4	TMG, LiCl, CH_3CN, 25 °C	decomposition
5	TMG, LiCl, DMSO, 25 °C	55
6	TMG, LiCl, hexane, 25 °C	no reaction
7	TMG, LiCl, toluene, 25 °C	decomposition
8	TMG, LiCl, CH_2Cl_2, 25 °C	no reaction
9	TMG, LiCl, DMF, 25 °C	23
10	TMG, LiCl, DMF, 70 °C	55−60[a]

[a] Range indicates maximum and minimum values obtained for several runs.

elevated the temperature to 70 °C, the formation of **90** could be effected in 55−60% yield. Similar yields were also realized at ambient temperature using DMSO as solvent (entry 5). As such, simply by altering C-11 functionalization, we had developed a sequence that could reliably deliver macrocycle **90** in yields sufficiently acceptable to provide enough material supplies to study the completion of the heterocyclic core of diazonamide A (**1**).

Unfortunately, despite our ability to prepare over a hundred milligrams of **90** with ease, the olefin within **90** proved resilient to oxidation of any kind. Use of any dihydroxylation protocol with all published amine accelerants and, in some instances, stoichiometric OsO_4, only led to recovered starting material.[55] Efforts to enlist $KMnO_4$ to form a diketone similarly provided recovered starting material along with small amounts of open dicarboxylic acid products. Hydroboration with a variety of hydride sources also failed to convert **90** into anything useful to explore the sequence further. Thus, for some reason that is not distinctly clear at present, the mere addition of a few atoms to ring G provided enough steric bulk to completely shut down reactive pathways that proceeded in all of our slightly simpler model systems. We now had to identify a new way to create the heterocyclic core of **1**.

Conclusion

As often occurs during efforts directed toward the synthesis of complex molecules, the presence of a singular functional group or motif can instigate a number of unanticipated challenges that can complicate, and sometimes even thwart, a well-conceived synthetic plan. This article has detailed a number of such findings, some of which served a useful purpose in leading to new synthetic methodology (including the facile synthesis

(53) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *21*, 2183−2186.

(54) Our use of this base was inspired by the elegant studies of Allen, J. R.; Harris, C. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1890−1897.

(55) For a review summarizing many of the procedures we attempted, see: (a) Kolb, H. C.; VanNieuwenhze, M.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. Other conditions probed included those reported in: (b) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771−6772. (c) Corey, E. J.; Sarshar, S.; Azimioara, M. D.; Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851−7852.

of 3-arylbenzofurans, a way to make benzofuranones using 5-*exo*-tet cyclizations, and a means to deoxygenate sulfoxides), while others could not be circumvented. Nevertheless, as the following articles will detail,[19] the chemistry described in this first-generation approach toward the original structure of diazonamide A (**1**) laid a solid foundation which would inform a new strategy that ultimately enabled the construction of both the macrocyclic rings within **1**. Equally important, this platform would help to shape both of our later drives to accomplish the total synthesis of the revised structure of diazonamide A (**2**).

Acknowledgment. We thank Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), predoctoral fellowships from the National Science Foundation, Pfizer, and Bristol-Myers Squibb (all to S.A.S.), postdoctoral fellowships from the Alfred Benzons Foundation (K.B.S) and The Skaggs Institute for Chemical Biology (X.H.), and a grant from American Biosciences.

Supporting Information Available: Experimental procedures and compound characterization (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA040090Y