Studies toward Diazonamide A: Development of a Hetero-Pinacol Macrocyclization Cascade for the Construction of the Bis-Macroyclic Framework of the Originally Proposed Structure

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Abstract: In this article, we describe further studies toward the originally proposed structure of diazonamide A (1). After confronting a number of failures in synthesizing the heterocyclic core of that structure, success was finally realized through the development of a novel hetero-pinacol-based macrocyclization cascade sequence. Subsequent elaboration led to an advanced compound bearing both of the 12-membered rings of the target molecule. In addition, preliminary biological studies with intermediates and simplified analogues obtained via the developed sequences are also described.

Introduction

In the preceding article in this issue,1 we delineated our first-generation approach to the originally proposed structure of diazonamide A (1, Scheme 1), one which proved capable of delivering the entire heteroaromatic core of the molecule in model systems but untenable in its late stages when applied to fully functionalized intermediates. Fortunately, such challenges often serve to extend the boundaries of established chemistry by forcing the practitioner to develop more creative solutions to unprecedented problems. As this article will detail, one such answer did eventually become apparent in the form of a designed and efficient cascade sequence using a hetero-pinacol-based macrocyclization to forge the final C-C bond needed to close the heterocyclic domain of 1 (see Scheme 1). This new approach not only accelerated our studies to access the remainder of the originally proposed structure of diazonamide A, work which culminated in the construction of both macrocyclic units of 1, but it also led to the invention of several new synthetic methods. Equally important, it fueled initial chemical biology studies that revealed a number of unexpected structure—activity relationships within the diazonamide class.

Results and Discussion

1. Studies toward Alternate Macrocyclization. Anytime that a strategy toward a complex molecule requires revision, one faces the difficult decision of either scrapping the original approach entirely, or retreating within the developed sequence to a point where some of the established chemistry can still be employed. In assessing which of these options to pursue, we felt that the first was far too extreme and instead anticipated that the viability of our original strategy to diazonamide A (1) could be resurrected by altering the manner in which we forged the C29—C30 bond to close the heteroaromatic core. Indeed, since the problem we had encountered with our first-generation approach was not the ring closure itself but obtaining subsequent functionalization, maybe that issue could be circumvented if the needed functional groups were installed directly during the cyclization step. For example, if an aldol-type ring closure of compounds of type 3 could be accomplished, with X representing a masked form of an amine such as a phthalimide, cyanide, nitro group, or azide, then hopefully it would be straightforward to form 2. From there, the A-ring oxazole could be built either through an oxidation followed by Robinson—Gabriel cyclodehydration, or oxazoline formation followed by aromatization.

Apart from its appeal as an idea that would be easy to test (since we would only need to construct different versions of 4), our failure to accomplish macrocyclic ring closures at other sites during our model studies enhanced our desire to devote time to its pursuit. For example, our attempts to form the 12-membered heteroaromatic ring through the C16—C18 biaryl axis both by intramolecular Ullmann-type2 and radical-based reactions of compound 9 (see Scheme 2) met with resistance, even though the test intermediate possessed an open F-ring to allow for maximal flexibility.


(2) Both classical, as well as milder, variants of this reaction were attempted. For leading references, see: Hennings, D. D.; Iwama, T.; Rawal, V. H. Org. Lett. 1999, 1, 1205−1208 and references therein.
Accordingly, our renewed efforts to accomplish C29–C30 macrocyclization via the plan delineated in Scheme 1 began by converting the alcohol within indole-oxazole 11 (Scheme 3) to a series of masked amines. Thus, treatment of 11 with phthalimide under Mitsunobu conditions led to the efficient formation of 12 in 87% yield after just 3 h of reaction time at 0 °C. Similar smoothness was observed in the formation of azide 13 upon reaction of 11 with the \( \text{pNO}_2 \) derivative of diphenylphosphoryl azide. Finally, cyanide 14 was obtained over two steps in 57% yield overall via initial halogen exchange followed by nucleophilic displacement with cyanide from KCN as promoted by 18-crown-6.

These three building blocks were then serially coupled to the previously synthesized EFG boronate fragment 5 (see Scheme 4) using Suzuki coupling conditions described earlier. Subsequent elaboration of these intermediates (i.e., 15, 16, and 17) to the desired test substrates (i.e., 18, 19, and 20) was then accomplished via HF-mediated silyl ether cleavage, reformation of the acetonide that broke apart in the previous reaction, and then oxidation (using Swern conditions to access 18 and 19 and Dess–Martin periodinane to generate 20). Unfortunately, despite the ease by which these three substrates were prepared with the established chemistry, effecting their macrocyclization proved impossible. Exposure of each to a variety of bases (NaH, KHMDS, LiHMDS, (3) Gilbert, A. M.; Antane, M. M.; Argentieri, T. M.; Butera, J. A.; Francisco, G. D.; Freedon, C.; Gundersen, E. G.; Graceffa, R. F.; Herbst, D.; Hirth, B. H.; Lennox, J. R.; McFarlane, G.; Norton, N. W.; Quagliato, D.; Sheldon, J. H.; Warga, D.; Wojdan, A.; Woods, M. J. Med. Chem. 2000, 43, 1203–1214.


Attempts to Accomplish Anion-Based Macrocyclizations

Reagents and conditions: (a) 5 (1.1 equiv), 12, 13, or 14 (1.0 equiv), Pd(dpdp)Cl₂ (0.2 equiv), K₂CO₃ (5.0 equiv), DME, 85 °C, 12 h; (b) aq HF (48%, excess), MeCN, 0 °C, 45 min; (c) 2,2-DMP, acetone, 25 °C, 5 min; (d) DMSO (10 equiv), (COCl)₂ (5.0 equiv), CH₂Cl₂, −78 °C, 45 min; Et₃N (20 equiv), CH₂Cl₂, −78 °C, 15 min or Dess–Martin periodinane (3.0 equiv), NaHCO₃ (10 equiv), CH₂Cl₂, 25 °C, 1 h, 51% overall for 18, 10% overall for 19, 40% overall for 20. dpdp = diphenylphosphinoferrocene; DME = ethylene glycol dimethyl ether; 2,2-DMP = 2,2-dimethoxypropane.

LDA, or KOr-Bu) universally failed to deliver anything resembling the desired product. Instead, we typically observed decomposition and, in some cases, recovered starting material.

Recognizing that the failures in these couplings could reflect the high proclivity for retro-aldol reactions, since nothing existed to prevent such an outcome in the same way that the loss of a phosphate irreversibly drove our previously successful Horner–Wadsworth–Emmons (HWE) macrocyclizations, we then turned to the synthesis of compound 24. Our expectation was that Dieckmann condensation would overcome this problem, especially since the Vedejs group had reported success in a related approach in their model studies toward 1. Unfortunately, this advanced intermediate similarly proved recalcitrant to macrocyclization under any conditions probed (including NaH, LiHDMST, KOr-Bu, and NaOMe).

2. Revised Retrosynthetic Analysis and Execution of the New Strategy. Although this litany of failures was certainly frustrating, it pushed us to think even more deeply about solving the problem of C29–C30 functionalization. Mindful of our previous use of the McMurry reaction (a pinacol coupling) to form a highly strained eight-membered ring in our total synthesis of Taxol, we hypothesized that perhaps we could enlist its hetero variant to fashion a fully functionalized C29–C30 bond for diazonamide A from a precursor aldehyde-oxime. This idea seemed encouraging since intramolecular hetero-pinacol couplings have been used on numerous occasions to fashion a diverse range of rings ever since the late 1970s when the Corey, Hart, and Bartlett groups independently demonstrated that oximes could serve as competent radical acceptors. For example, as shown in Part A of Scheme 5, the Naito group recently employed a hetero-pinacol cyclization initiated by SmI₂ to efficiently convert 25 into a seven-membered ring (26) appropriately functionalized to complete a total synthesis of balanol (27).

Despite this wealth of precedent, however, up to the end of the year 2000, no variant of the hetero-pinacol reaction had been successfully applied in a macrocyclization event to generate a ring size greater than seven, despite precedent for medium-size ring formation in related systems employing dialdehydes. In fact, a number of studies seeking to form such rings met only with failure. Nevertheless, we thought that the diazonamide...
framework might provide a particularly unique case of a 12-membered ring, as π-π stacking between the B- and E-rings could bring the aldehyde and oxime motifs quite close and significantly reduce their rotational freedom. Thus, the reaction might have at least some chance for success, although conventional wisdom seemed to point to a challenging proposition.

Since we would ultimately need an amide product, and not an N-O bond as that observed in the formation of compound 26 (see Scheme 5), following cyclization, we would have to break that linkage apart. As shown in Part B of Scheme 5, we were pleased to discover recent reports from the Keck group detailing that SmI₂ is particularly effective in this task. Thus, it appeared to us that it should be possible to accomplish both hetero-pinacol coupling and N-O cleavage in the same pot. Although a seemingly safe assumption, an extensive search of the literature revealed its success on only one occasion through a protocol which involved treating a substrate with 6.0 equiv of SmI₂ and then stirring for a prolonged period in deoxygenated H₂O. Our analysis of this unique result suggested that its success reflected the amount of SmI₂ employed, since if 4–5 equiv were required to accomplish just one of the reactions in Scheme 5, then at least 8–10 equiv would probably be required to effect both. Accordingly, our new plan for the synthesis of diazonamide A was to treat an intermediate such as 33 (see Scheme 6) with a gross excess of SmI₂, hoping that both cyclization and N-O cleavage could be accomplished concomitantly to afford a 1,2-amino alcohol product. Rather than isolate that likely polar intermediate, we would then try and couple that product directly with a protected form of L-tyrosine methyl ester to obtain 32. Thus, if this sequence could be realized, not only would it constitute the first example of a hetero-pinacol reaction leading to a medium- or large-sized ring, but it also would productively combine this transformation into a new reaction cascade that could potentially have wider applications.

Our explorations of this strategy began with the synthesis of a new EFG building block, as shown in Scheme 7, altered only from the fragment employed earlier (i.e., 5) by the use of a methyl ester as the methylene activating group in the 5-exo-tet cyclization leading to 36. Although the yield for this key conversion was lower (38%) than that achieved previously with cyanide due to a number of side-reactions initiated by the ester functionality, the presence of that motif provided a reactive handle easily convertible to a C-11 lactol and incapable of benzofuran fragmentation. As an added benefit, its incorporation also shortened the overall sequence from L-tyrosine methyl ester to the final boronate ester (37) by three steps.

Once this fragment was completed, it was coupled with the previously obtained indole-oxazole 38 through the standard Miyaura conditions for Suzuki coupling of boronate esters, leading to the assembly of 39 (see Scheme 8) in 83% yield. This new intermediate was then cleanly converted into aldehyde-oxime 33 through a tandem deprotection/oxidation sequence, followed by selective oxime capture of the more-activated


(16) The role of H₂O is either as a proton source, or, more likely, as a donor ligand which increases the reducing power of SmI₂. For leading references, see: (a) Hanessian, S.; Girard, C. Synlett 1994, 861–862. (b) Hasegawa, E.; Curran, D. P. J. Org. Chem. 1993, 58, 5008–5010.
aldehyde after just 10 min of reaction with MeONH₂·HCl in DMSO at 25 °C. Use of neat DMSO as solvent was critical for the success of this final operation leading to 33, as the same reaction in any alcoholic media was attended by a significant degree of acetonide cleavage (likely due to trace HCl derived from the oxime source). In any case, with an efficient synthesis of 33 achieved in 70% yield from 39, explorations into the key reaction of the proposed sequence could begin. Most gratifyingly, little reaction scouting was required. Following treatment of aldehyde-oxime 33 with a premixed complex of 9 equiv of freshly prepared SmI₂ and 36 equiv of HMPA in THF at 25 °C for 1 h, followed by an aqueous NaHCO₃ reaction quench, extraction, solvent removal, and subsequent peptide coupling using a DMF solution of Fmoc-protected L-valine (32), EDC, and HOBT, we obtained compound 32 as a mixture of stereoisomers in an isolated yield of 45%.

Mechanistically, we believe that the initial exposure of 33 to SmI₂/HMPA led to the generation of diradical intermediate 40, which then cyclized to provide 41. The presence of excess SmI₂ complexed with HMPA then effected N–O cleavage, leading to intermediate 42, which, upon workup, provided the desired amino alcohol that was later trapped through peptide formation. Consequently, each step in the sequence proceeded in an average yield of 75%. Although this picture differs from the more typical representation of this reaction where a ketyl radical attacks an intact oxime to account for the generation of 41, the isolation of noncyclized material with both the aldehyde and oxime reduced suggests that the existence of diradical 40 cannot be excluded. We also believe that our alternative takes into account the unique framework of diazonamide A (1), as our experience with compounds such as 33 suggests that the steric hindrance around that aldehyde would make it quite difficult to form a ketyl radical without touching the highly accessible oxime. As an alternative to either of these pictures, one could also invoke a samarium-bridged diradical such as 45 to account for the eventual formation of the bridged bond in 41.

Apart from these mechanistic considerations, it is worth noting that, in accordance with earlier reports exploring the hetero-pinacol coupling of aldehyde-oximes, the macrocyclization of 33 did not proceed in the absence of HMPA. Moreover, if the ratio of HMPA/SmI₂ was reduced from 4:1 to 2:1 (still using 9 equiv of SmI₂), 32 was observed, along with significant amounts of cyclized product, with the N–O linkage firmly intact, indicating that the presence of a suitable donor ligand in conjunction with excess SmI₂ is the combination required for reliable oxime cleavage following reductive cyclization. These results suggest that in cases where one would desire to effect only N–O cleavage, the addition of HMPA might greatly facilitate the transformation in circumstances that prove difficult or low-yielding with SmI₂ alone.

Having finally established a functionalized C29–C30 bridge after numerous failures, we could now investigate means by which to form the A-ring oxazole and complete the entire heteroaromatic core of 1. As mentioned earlier, two direct pathways were available to accomplish this goal from advanced intermediate 32: oxidation followed by Robinson–Gabriel dehydration, or oxazole formation and subsequent aromatization. While both might appear equally feasible on paper, our model studies suggested that the first was unlikely to succeed with 32 since only pTsOH in refluxing toluene proved effective in initiating the needed cyclodehydration on a substrate that lacked its numerous acid-labile functionalities. Accordingly, we elected to probe oxazole formation and found that the desired ring system (i.e., 46, Scheme 9) could indeed be formed in 24% yield over the course of 12 h using (diethylamino)sulfur trifluoride (DAST) in THF at −10 °C. The remaining material balance from this event was the enamide that resulted from simple dehydration of the C-30 alcohol. Although the yield for this operation was low, that outcome partially reflects the fact that only one of the two possible oxazole products (which we have tentatively assigned as drawn in Scheme 9) was formed in the event. Consequently, only the portion of starting material that possessed the proper C-29 and C-30 stereochemistry required to form this product could have participated productively in the cyclization. In truth, the efficiency of this reaction (or lack thereof) was ultimately of no consequence since we could never accomplish the subsequent oxidation leading to 31, despite nearly a dozen attempts.

With this approach reaching a roadblock, we turned to the second alternative for oxazole formation, and in line with our previous expectations, Robinson–Gabriel cyclodehydration proved impossible to achieve following the formation of 47 either with Dess–Martin periodinane on small scale or TPAP/

\( \text{(17) For example, see: Robertson, G. M. In Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 563–611.} \)

\( \text{(18) Similar findings were presented in another diazonamide study: Wipf, P.; Methot, J.-L. Org. Lett. 2001, 3, 1261–1264.} \)

\( \text{(19) Lafargue, P.; Guenot, P.; Lelouche, J.-P. Heterocycles 1995, 41, 947–958.} \)

\( \text{(20) This assignment is based, in part, on the fact that the alternate oxazole would suffer from severe steric interactions with the protons from the C-11 position in ring F. Such strain also renders the approach of DAST or any other reagent from that side of the molecule quite unlikely.} \)

\( \text{(21) Efforts to accomplish this conversion included several known oxidants for the process, including: MnO₃ in refluxing benzene or CH₂Cl₂, DQO in benzene at 25 °C, PdO/C in benzene at 25 °C, BrCCl₃ and DBU in MeCN at 25 °C, and NCS in CCl₄ at 25 °C and reflux.} \)
NMO (TPAP = tetra-n-propylammonium perruthenate, NMO = 4-methylmorpholine N-oxide) on larger scale. As shown in Table 1, no published oxazole formation protocol proved successful in converting 47 into 31, with some providing

\[ \text{Scheme 8. Successful Generation of the Fully Functionalized Heterocyclic Core (33) of the Originally Proposed Structure of Diazonamide A (1) Using Suzuki and Hetero-Pinacol Couplings}^a \]

\[ \text{Scheme 9. Formation of the A-ring Oxazole Subunit of the Proposed Structure of Diazonamide A (1) from Advanced Intermediate 32}^a \]
recovered starting material (entries 1–3) and others leading to complete decomposition (entries 4–6). Use of the same protocols with microwave activation\(^\text{23}\) instead of direct heat or efforts to minimize the steric bulk of the valine residue through alternate nitrogen protection (such as Boc or Alloc instead of Fmoc, as well as the use of N\(_3\) for the entire amine) provided no improvement either. Even probing the formation of a far simpler oxazole by using an acetate in lieu of the L-valine failed to afford any desired product. Our approach was seemingly at another dead end.

After examining the collected results more carefully, we wondered if a new opportunity for success might arise simply by modifying an existing procedure to accomplish Robinson–Gabriel cyclodehydration. More specifically, although POCl\(_3\) has proven to be quite effective at oxazole synthesis in a number of contexts,\(^\text{22a}\) perhaps when we attempted that reaction with 47, trace amounts of HCl from the reagent led its functionality to break apart before oxazole formation could occur. Thus, if we buffered that dehydrating reagent with a base such as pyridine to displace the POCl\(_3\) -activated alcohol. When this protocol was put to the test by adding a 2:1 mixture of pyridine/POCl\(_3\) to the reaction media basic could also accelerate the overall rate of the reaction by promoting the amide enolization required to form a ketone 47 and heating the resultant solution at 70 °C for 6 h, we were pleased to discover that oxazole 31 could be obtained in 45% yield with virtually all of the remaining material balance (33%) constituting recovered starting material (Table 1, entry 7). Nearly equal levels of success were observed with related substrates bearing alternate L-valine protection (entry 8).\(^\text{24}\)

Having finally overcome this major synthetic hurdle, we felt that the targeted structure (1) would soon be within reach.

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\(^{24}\) The scope of this new protocol is explored more fully in the final article in this series and has proven applicable to the formation of diverse oxazoles from ketoamides, thiazolines from thioamide-alcohols, thiazoles from ketothioamides, and furans from 1,4-dicarbonyls.

\(^{25}\) The same operation could also be accomplished in slightly lower yield using TBAF. For an application of this alternative protocol in total synthesis, see: Jiang, W.; Wanner, J.; Lee, R. J.; Bounard, P.-Y.; Boger, D. L. J. Am. Chem. Soc. 2002, 124, 5288–5290.
run at exceedingly low concentration). Although molecular models suggested that the reactive units should be quite close, the steric hindrance within the system and the entropic penalties associated with the formation of the highly strained 12-membered ring must have been the culprits that led to such difficulties. Indeed, the only smooth reaction which we ever observed in our first attempts occurred when 50 was exposed to diphenylphosphoryl azide (DPPA)\(^2^7\) in NaHCO\(_3\)-buffered CH\(_2\)Cl\(_2\), conditions which led to the formation of a product which we have assigned as the more flexible 13-membered cyclic urea \(\text{51})\) by the Harran group,\(^3^0\) leading us to abandon any further synthetic efforts toward the “oxygen analogue” of the real diazonamide A.

3. Analogue Synthesis and Chemical Biology Explorations. While we would not complete the synthesis of the originally proposed structure of diazonamide A (1), the developed sequences did allow us to make a few preliminary forays into the chemical biology of the diazonamide class. Such explorations were certainly of value, even though a key part of our intermediates did not exactly match the structure now proposed for the natural product, however, it is interesting to note here the decreased yield observed as part of our program to synthesize 1, but we also constructed and tested a series of simplified analogues. The preparation of these substances is shown in Schemes 11 and 12.\(^3^1\)

As revealed in Figure 2, with selected data for a few of the compounds examined, these studies unveiled a number of interesting structure–activity relationships. For instance, although analogues 60, 62, 63, and 64 are all several-hundred-


**Table 2.** Screening of Conditions To Accomplish Peptide Formation and Thereby Complete Both Macrocycles of Diazonamide A

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PyBroP, NaHCO(_3), DMF/CH(_2)Cl(_2) (1:1)(^a)</td>
<td>dimer/trimer</td>
</tr>
<tr>
<td>2</td>
<td>FDPP, NaHCO(_3), DMF/CH(_2)Cl(_2) (1:1)(^a)</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>EDC, HOBt, DMF/CH(_2)Cl(_2) (1:1)(^a)</td>
<td>dimer/trimer</td>
</tr>
<tr>
<td>4</td>
<td>DEPBT, i-Pr(_2)NEt, DMF/CH(_2)Cl(_2) (1:1)(^a)</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>DPPA, NaHCO(_3), DMF/CH(_2)Cl(_2) (1:1)(^a)</td>
<td>~60% of 52</td>
</tr>
<tr>
<td>6</td>
<td>HATU, collidine, DMF/CH(_2)Cl(_2) (1:1)(^b)</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>HATU, collidine, DMF/CH(_2)Cl(_2) (9:1)(^b)</td>
<td>5–10%</td>
</tr>
</tbody>
</table>

\(^{a}\) Concentration of 50 = 5.0 × 10\(^{-4}\) M. \(^{b}\) Concentration of 50 = 1.0 × 10\(^{-4}\) M. Range indicates maximum and minimum values obtained for several runs. PyBroP = bromotripyrrolidinophosphonium hexafluorophosphate; FDPP = pentafluorophenyl diphenylphosphinate; DEPBT = 3-di-ethyl phosphoryloxy)-1,2,3-benzotriazin-4(3H)-one; DPPA = diphenylphosphoryl azide.

**Figure 1.** Structural rearrangement of diazonamide A (1) to 53 based on the work of Harran and co-workers.\(^3^0\)
fold less cytotoxic than diazonamide A (53) against the 1A9 human ovarian carcinoma cell line, these four simple structural congeners indicate the importance of the two aryl chlorine residues (60 vs 63 and 62 vs 64) in conferring biological efficacy and that substitution of the indole nucleus (63 vs 64) can potentially lead to increased potency. Apart from these preliminary findings, however, we were unable to identify any intermediate or analogue possessing potency remotely commensurate to diazonamide A, even among compounds bearing both of the macrocyclic subunits of 1.

Conclusion

Despite the interruption of the sequence developed to access the originally proposed structure for diazonamide A (1), the campaign waged to reach advanced intermediate 51 was far from fruitless. Indeed, the adopted strategy inspired a novel extension of the hetero-pinacol reaction as part of a unique cascade sequence to construct complex macrocyclic systems. It also led to the discovery of a series of valuable synthetic methodologies, the most important in this article being the identification of a powerful method to accomplish Robinson–Gabriel cyclodehydration in hindered settings using POCl₃/pyridine. In addition, biological screening of analogues and intermediates synthesized as part of this program revealed several significant findings, particularly in terms of structure—activity relationships for the diazonamide class. Most important, as the remaining two articles in this series will detail, the developed chemistry proved directly translatable into a successful total synthesis of the revised structure of diazonamide A (53).

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

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