Macrocyclic Triarylethylenes via Heck Endocyclization: A System Relevant to Diazonamide Synthesis

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Diazonamide A (**1**, Figure 1) and its congeners[1] are impressive products of invertebrate secondary metabolism wherein at least three proteinogenic amino acids have been incorporated, perhaps by posttranslational modification of a short oligopeptide, into a heterocyclic network of considerable complexity. Notably, **1** has shown potent cytotoxicity in vitro toward a transformed human cell line (HCT-116),[1a] but a subsequent lack of natural material[1c] has prevented further study. To enable future mode-of-action studies and to access a range of related polycyclic structures, we outline here our approach to diazonamide synthesis and describe initial results demonstrating that Heck endocyclization can form highly functionalized lactam rings containing an imbedded 1,2-diaryl-1-(5′-oxazoyl)ethylene.

When considering possible routes to assemble the diazonamide skeleton,[2] it was evident that potentially complicating issues of atropisomerism could be avoided if the D−E biaryl linkage was designated as the final carbon−carbon bond to be formed (Figure 1). In the presence of a conformationally rigid, correctly configured A−F macrolactam, intramolecular biaryl formation at C16 in **2** necessitates that the relative rotational orientation of rings A−E adopt a desired atropisomeric relationship (as depicted in **2**) to bring C18 within bonding distance of C16. We currently envision that halogenation at C25 and C27 can occur late in the synthesis and that the D−E linkage can be established by intramolecular orthophenolic coupling. This implicates either serotonin or a derivative of 5-HT as the original source of carbons 18−27. Lactam **3** therefore contains all the stereochemical information needed to complete natural diazonamides. A protected derivative of this molecule, with the C11 hemiacetal in open tautomeric form, is seen as the ring-contracting pinacol rearrangement product of vicinal diol **4** or its functional equivalent. To the extent that C10 stereochemistry in **4** correlates to that sought in **3** through inversion of configuration at the migrating terminus, macrocyclic olefin **5** is a reasonable link to **3** through a sequence beginning with face-selective oxidation.

Functionalized lactams related to **5** were without precedent prior to this study,[3] although it was fairly obvious how two (A and F) of the three-component rings in this structure

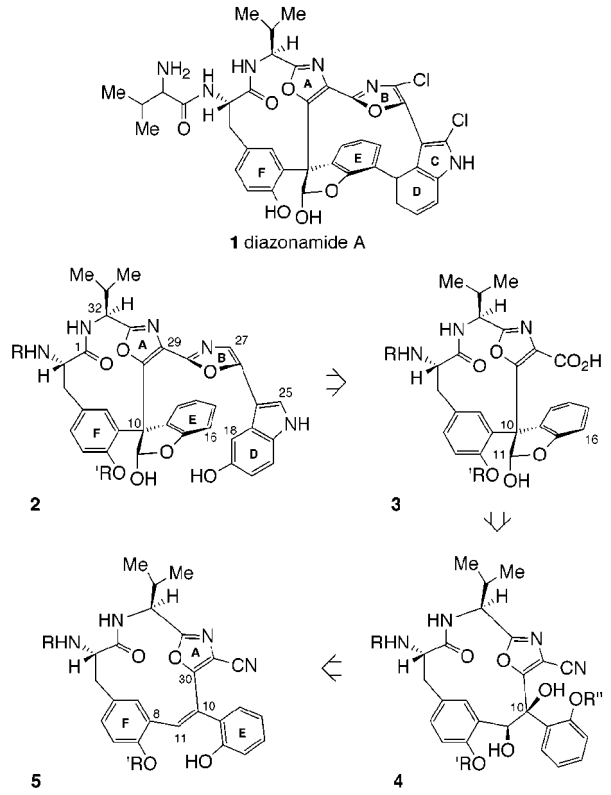

Figure 1.

were related to natural amino acids. The A ring (C29−C33) was synthesized in one step from commercial materials by treating *N*-Boc-L-Val-OH (**6**) with aminomalononitrile *p*-toluenesulfonate and EDC[4] in pyridine (Scheme 1). Following trituration of a concentrated residue with water, aminooxazole **7** was isolated by filtration (>95% purity) and converted directly to bromide **8** through in situ bromination of a derived nitrosamine.[5] This succinct preparation of a fully functionalized A-ring, combined with the availability of several halogenated tyrosine derivatives, led us to consider a third building block (E-ring) which would permit consecutive formation of the C8−C11 and C10−C30 bonds in **5** via metal-catalyzed cross-couplings. A trifluoroacetate salt derived from **8** was condensed independently (TBTU, DIPEA, CH_3CN) with 3,5-dibromo-*N*-Boc-L-Tyr-OH (**9**) and 3-iodo-*N*-Boc-L-Tyr-OH (**10**) to afford dipeptides **11a** and **11b**, respectively (Figure 2). Interestingly, when **11b** was treated with bis-stannyl styrene **13c** in the presence of 5 mol % $PdCl_2(CH_3CN)_2$, a single adduct assigned as α-styryl stannane **12b** was isolated in 30% yield. Intractables and starting material accounted for the remaining mass. Resubjecting **12b** to the reaction conditions did not induce a second, ring-closing Stille coupling. The same net results were observed in reactions between tribromide **11a** and **13c**. While synthetically unproductive, it was during these experiments that we observed a marked susceptibility to

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(2) For other approaches to diazonamide synthesis, see: (a) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223−2226. (b) Jamison, T. F. Ph.D. Thesis, Harvard University, Cambridge, MA, 1997. (c) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, *16*, 2413−2419. (d) Vedejs, E.; Wang, J. B. Abstracts of Papers, 212th National Meeting of the American Chemical Society, Orlando, FL; American Chemical Society: Washington, DC, 1996; ORGN 93. (e) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Véliz, E. A.; Yang, Z. C. *Synlett* **1996**, 609−611. (f) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, *66*, 2107−2110.

(3) Shortly after we began our studies Jamison and Schreiber reported the preparation of cyclic 3-aryl-2-(5′-oxazoyl)benzofurans related to lactams **5**. In this approach 3-iodo-*N*-Cbz-L-Tyr-OMe was acylated with 3-iodo-7-methoxybenzofuran-2-carboxylic acid and the C8−C11 bond was formed by internal coupling of the incipient diiodide with excess $Ni(PPh_3)_4$. The product coumarin was reduced to provide a C30 alcohol from which the A-ring oxazole was assembled. Lactamization subsequently closed the 13-membered ring. See ref 2b.

(4) This modified version of Freeman's oxazole synthesis simplifies product isolation and eliminates the need for a purification step. Confer: Freeman, F.; Chen, T.; van der Linden, J. B. *Synthesis* **1997**, 861−862.

(5) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2426−2430.

(6) (a) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (b) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447−471.

(7) Energy profiles for a simulated torsion about the C10−C30 bond in low-energy conformers of **16d** and **16f** were generated within the dihedral driver subroutine of Macromodel V6.0.

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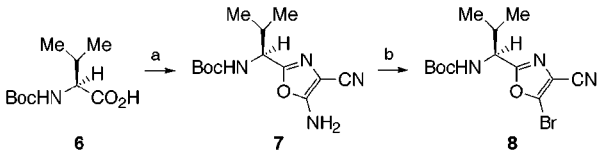
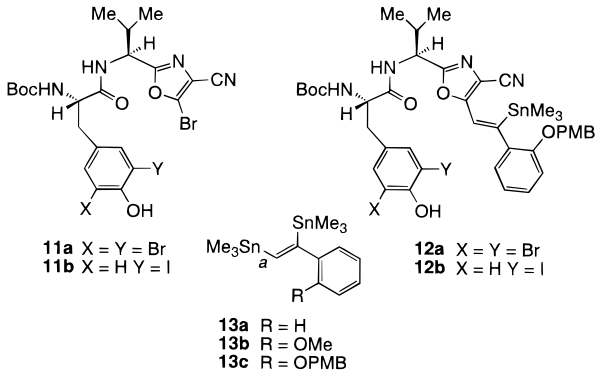
Scheme 1[a]



[a] a) aminomalononitrile *p*-toluenesulfonate, EDC, pyridine, rt (64%). b) *t*-BuONO, $CuBr_2$, CH_3CN, 0°C (50-55%).

selective protiodestannylation at the distal carbon−tin bond (*a*) in bis-stannane **13c**. Treatment of **13c** with silica gel impregnated with oxalic acid provided mono-stannane **14** (Scheme 2) as an air stable, amorphous solid in 87% yield. This result allowed us to exploit the initially troublesome preference for Stille coupling at the oxazoyl bromide in polyhalides **11a**/**b** (an undesired regiochemical result when metathesizing at bond *a* with **13c**). A mixture of **11a** or **11b** and **14** was stirred in the presence of 2 mol % $PdCl_2(CH_3CN)_2$ (DMF, rt), and the resultant mono adducts were etherified (DEAD, PPh_3, BnOH) to afford *seco* F-A-E systems **16f** and **16d** in 65% and 57% overall yields, respectively. To access ring system **5**, we attempted to initiate intramolecular carbometalation of the vinylogous acrylonitrile in **16d**/**16f** using a variety of Heck cyclization protocols.[6] These experiments uniformly met with failure, leading to recovered starting material, slow degradation or, in the case of iodide **16d** with phosphine additives, polar residue presumed to be phosphonium salt. It was unclear whether this was due to the substrate poisoning the catalyst or adopting preferentially a conformation which precluded coordination of the tethered C10−C11 olefin to an intermediate palladium(II) halide putatively formed at C8. Another explanation was that the region around C10 was simply too hindered. Modeling suggested that the E-ring in **16d**/**16f** would rotate out of a plane defined by the vinyl oxazole to minimize destabilizing nonbonded interactions.[7] As a result, the E-ring alkoxy group shields one face of the terminal olefin. To vary functionality at this position while continuing to differentiate the E- and F-ring phenols, the sequence of component assembly was reorganized.

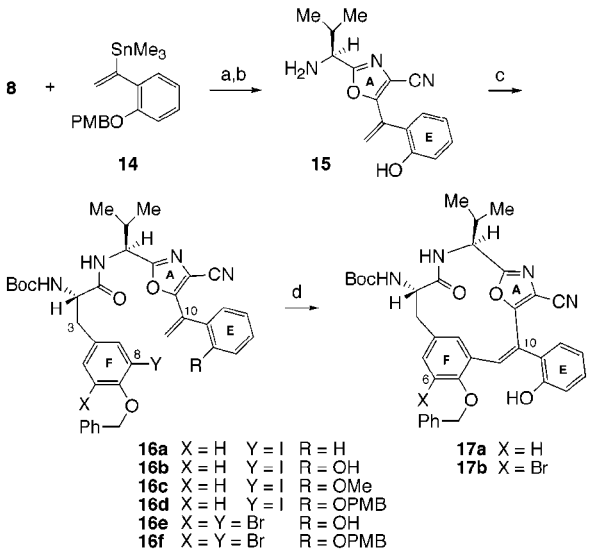
Cross-coupling of **14** with bromide **8** and treatment of the resulting adduct with excess BBr_3 gave amino phenol **15** in high yield (Scheme 2). Peptide coupling between **15** and the O-benzylated derivatives (**9b**/**10b**) of tyrosine halides **9**/**10**[8] then afforded free phenols **16e** and **16b**, respectively. The same sequence, employing vinyl stannanes **13a**/**13b**, was used to prepare unsubstituted analog **16a** and anisole **16c**. Heck cyclization attempts resumed, and, after much experimentation, exposure of **16c** to 10 mol % $Pd_2(dba)_3$ and Ag_3PO_4 (0.025 M in THF at 75 °C) was found to give an endocyclization product in only 2% yield. Likewise, **16a** gave 6% of a ring-closed material under identical conditions.[9] It was thus intriguing to find that free phenol **16b** gave macrocycle **17a** in 66% yield using this same procedure. Moreover, dibromide **16e** underwent a group selective Heck endocyclization to afford mono bromide **17b**,[10] albeit in lower yield. Taken together, these results de-emphasize the role of sterics at the E-ring ortho position and suggest instead that the system may need to be preorganized for internal carbopalladation of the 1,1-disubstituted ethylene to proceed at a useful rate. Preorganization might arise from the



11a X = Y = Br
11b X = H Y = I
12a X = Y = Br
12b X = H Y = I
13a R = H
13b R = OMe
13c R = OPMB

Figure 2.

Scheme 2[a]



16a X = H Y = I R = H
16b X = H Y = I R = OH
16c X = H Y = I R = OMe
16d X = H Y = I R = OPMB
16e X = Y = Br R = OH
16f X = Y = Br R = OPMB
17a X = H
17b X = Br

[a] a) 2 mol % $PdCl_2(CH_3CN)_2$, DMF, rt (94%). b) 2.5 eq. BBr_3, CH_2Cl_2 -78°C (91%). c) **9b** or **10b**, TBTU, DIPEA, CH_3CN, rt (89% for **16b**, 86% for **16e**). d) 10 mol % $Pd_2(dba)_3$, Ag_3PO_4, THF, reflux, 11h (66% for **17a**, 41% for **17b** based on recovered **16e**).

formation of an intermediate cyclic palladium(II) phenoxide via reaction of a C8 palladium(II) halide with the E-ring phenol or phenoxide. To our knowledge, there is no precedent for this type of substrate direction in intramolecular Heck cyclizations although Miura has recently invoked an intermediate palladium(II) phenoxide in the bimolecular arylation of naphthols with aryl halides catalyzed by Pd(0).[11] Mechanistic insight notwithstanding, the efficient conversion of **16b** to **17a** demonstrates that considerably more hindered macrocyclic olefins are available via Heck cyclization than had been reported previously.[12] Whether this protocol is restricted to our current substrate class or will prove more broadly applicable is the subject of ongoing experiments. Methods to convert lactams **5** to diazonamide fragments **3** and further efforts directed toward the total synthesis of these unique natural products will be reported shortly.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H NMR spectra for **7**, **8**, **13c**, **14**, **15**, **16b**/**e**, and **17a**/**b** (20 pages).

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(9) Yields based on analyzing crude HPLC traces and spectroscopic data, retrospectively, after **17a** had been fully characterized in latter experiments.

(10) C6 bromo derivatives provide access to the diazonamide B series. See refs 1a and 1b.

(11) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1742.

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