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An Approach to the Bis-oxazole Macrocycle of Diazonamides

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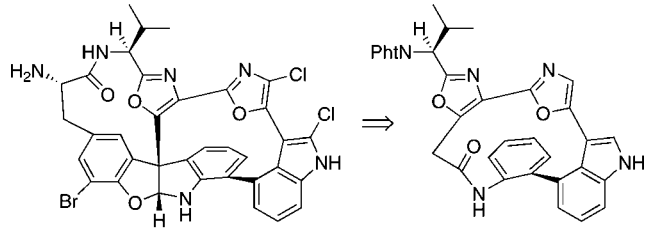
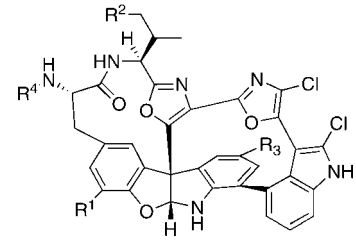
ABSTRACT



A convergent approach to a macrocyclic compound embodying the complete "eastern" quadrant of diazonamides is described. The opening sequence in this work relies on an oxazole-forming reaction devised earlier in this group, while a late step involves a Robinson−Gabriel cyclization of an amidoketone to form a second oxazole.

Few natural products have captured so much attention in the synthetic arena as the diazonamides, **1** (Scheme 1).[1] Indeed, intense activity aiming to conquer their delightfully intricate structure, initially engendered by the discovery of the first members of the family,[1] continues unabated to this day.[2] To wit, since the successful conclusion of the initial synthetic campaign[3] and relative background work,[4] two formal syntheses of **1a**[5] have appeared in the literature, as have about half[6] of the numerous synthetic studies published to date.[7] Noteworthy biological properties[8] add a significant dimension to such chemical pursuits, which, understandably, have largely focused on the creation of the problematic stereogenic quaternary center at the core of the molecules. Yet, the assembly of the bis-oxazole-containing macrocycle that constitutes the "eastern" portion of diazonamides also raises interesting chemical issues.[7] In that connection, a recent report from the Moody group[9] describes the remarkable

Scheme 1. Structures of Diazonamides A−E



1a diazonamide A $R^1 = R^2 = R^3 = H$; R^4 = (*S*)-2-hydroxy-3-methylbutanoyl
1b diazonamide B R^1 = Br, $R^2 = R^3 = R^4 = H$
1c diazonamide C $R^1 = R^2 = R^3 = H$; R^4 = (*S*)-2-amino-3-methylbutanoyl
1d diazonamide D $R^1 = R^4 = H$, R^2 = Me, R^3 = Cl
1e diazonamide E $R^1 = R^3 = R^4 = H$; R^2 = Me

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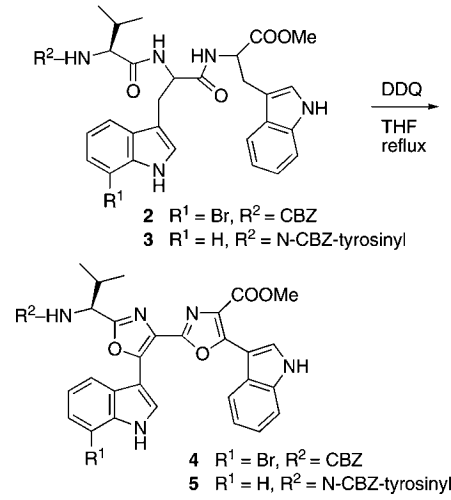
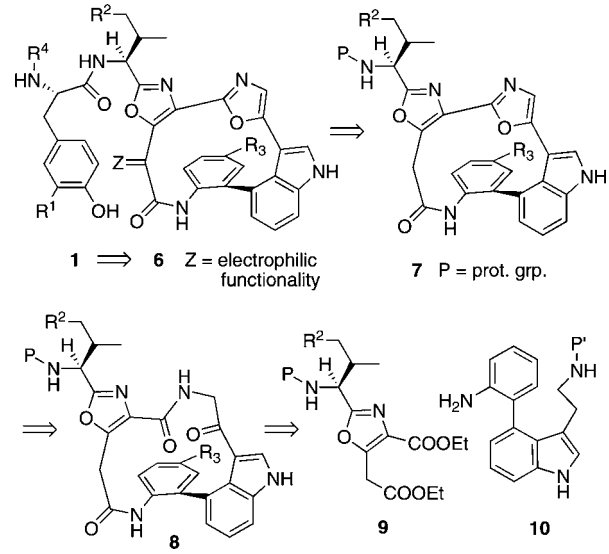
biomimetic conversion of **2**−**3** into **4**−**5**, respectively, under oxidative conditions (Scheme 2). Such a development prompts us to disclose results of our own efforts in this area. As outlined in Scheme 3, we have been interested in an approach that would advance synthetic intermediate **6** (Z = appropriate electrophilic functionality) to the natural products. In turn, compound **6** would be obtained from **8** via Robinson−Gabriel oxazole formation and further elaboration of the resultant macrolactam **7**. The synthesis of **8** could proceed through the union of oxazoles **9**, which should be available through an oxazole-forming reaction developed earlier in this group,[10] and 4-aryltryptamine **10**. Herein, we detail procedures for the implementation of such a plan.

The condensation of valine-derived chloroglycinate **11**[11] with the dimethylaluminum acetylide prepared from

Scheme 2. Moody Biomimetic Oxazole Formation



Scheme 3. Approach to Diazonamides



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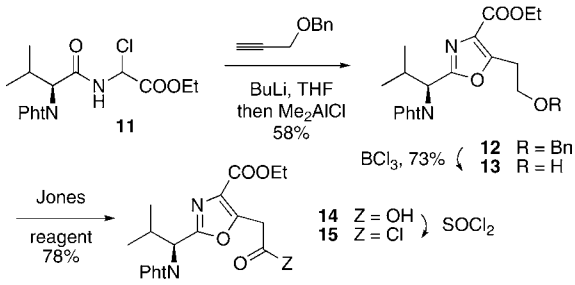
benzyl propargyl ether (Scheme 4; Pht = phthalimido) afforded enantiopure oxazole **12**. Without extensive

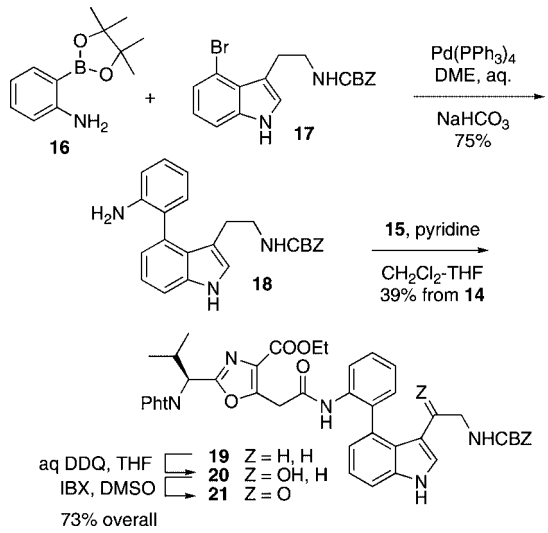
Scheme 4. Oxazole Formation from α-Chloroglycinates



purification, this material was debenzylated (BCl_3) to furnish alcohol **13**, a substance that proved to be quite sturdy, being best advanced to acid **14** by Jones oxidation. Acid chloride **15** emerged uneventfully upon treatment of **10** with $SOCl_2$.

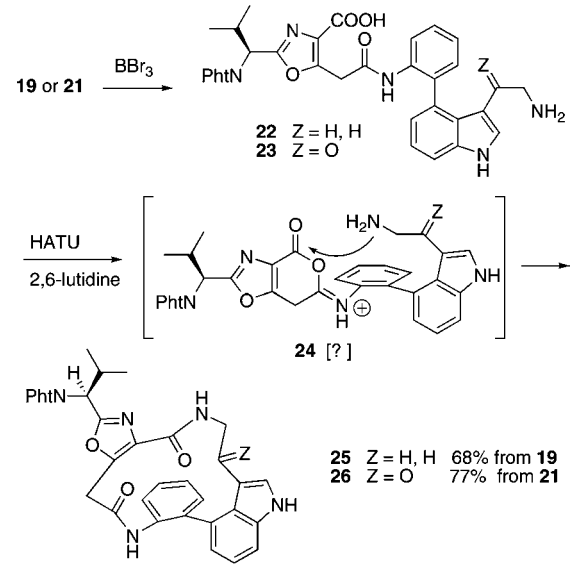
Parallel work yielded 4-arylindole **18**, prepared by Pd-mediated coupling of commercial boronic ester **16** with the known **17**[6g] (Scheme 5). Substance **18** is axially chiral,

Scheme 5. Coupling of **15** and **18** and Oxidation of Product **19**



but for the purpose of the present study it was employed as the racemate.[12] The condensation of **15** with **18** was difficult, presumably on account of the hindered nature of the amino group, and it proceeded to furnish **19** in a moderate 39% yield. This material, resulting through the union of enantiopure **15** with racemic **18**, was obtained as a 1:1 mixture of atrop-diastereomers, as were all subsequent synthetic intermediates derived from it. Conversion of **19** into **21**, as required for the ultimate formation of the second oxazole ring in a Robinson−Gabriel mode, was achieved in 73% yield by hydroxylation with DDQ, followed by IBX oxidation of the intermediate carbinol **20**.[6g] Both **19** and **21** underwent simultaneous cleavage of the CBZ and ethyl ester groups upon exposure to BBr_3 to afford the extremely polar amino acids **22** and **23**, respectively (Scheme 6). These were not thoroughly

Scheme 6. Preparation of Macrocyclic Compounds **25** and **26**



characterized. Instead, they were immediately cyclized (HATU)[13] to afford macrolactams **25** and **26** (68% and 77% overall yield, respectively). It is unclear at this time whether this transformation occurred by direct nucleophilic attack of the amino group onto the HATU-activated carboxyl group or through the intervention of an azlactone-type intermediate such as **24**. Regardless, it is worthy of note that, contrary to the case of **19**, the action of aqueous DDQ upon **25** failed to induce hydroxylation in an efficient manner, preventing a possible conversion into **26**. In this respect, the behavior of **25** differs from that of a related system described by Moody,[6g,14] which underwent the oxidation in question in 84% yield, underscoring the fact that the reactivity of such macrocycles is quite sensitive to structural details.

Finally, exposure of **26** to the action of TsOH in refluxing toluene triggered formation of bis-oxazole **27**, a 1:1 mixture

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(11) Ref 10 as well as: Zhang, J. *Tetrahedron Lett.* **2010**, *51*, 4699.

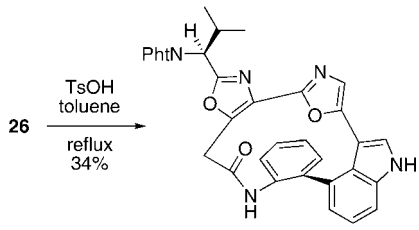
(12) No literature record of compound **18** appears to exist, but the corresponding 4-(3-aminophenyl) indole has been described in a recent patent application: Wells, J.; Renslo, A. R.; Wolan, D.; Zorn, J. PCT Int. Appl. (2009),WO 2009089508.

(13) Carpino, L. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

(14) The Moody substrate differs from **25** in that the oxazole ring and the benzene nucleus are bridged by a plain methylene group (i.e., the CO−NH linkage is missing), which furthermore connects to the *meta* position of the phenyl group.

of atrop-diastereomers, in 34% yield after purification (Scheme 7). This compound embodies a specific example of generic intermediate **7**. Its successful formation in the fashion just described validates the surmise of Scheme 3, it complements the Moody approach, and it delineates a heretofore unexplored route to the "eastern" segment of diazonamides. Research aiming to advance **27** to a totally synthetic diazonamide continues, and results in this area will be described in due course.

Scheme 7. Robinson−Gabriel Route to Macrocyclic Bis-oxazole **27**



27, Pht = phthaloyl

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Supporting Information Available: Experimental procedures and characterization data for new compounds, plus NMR (^{1}H and ^{13}C) spectra of several products. This material is available free of charge via the Internet at http://pubs.acs.org.

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