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Diazonamide Support Studies: Stereoselective Formation of the C10 Chiral Center in both the CDEFG and AEFG Fragments

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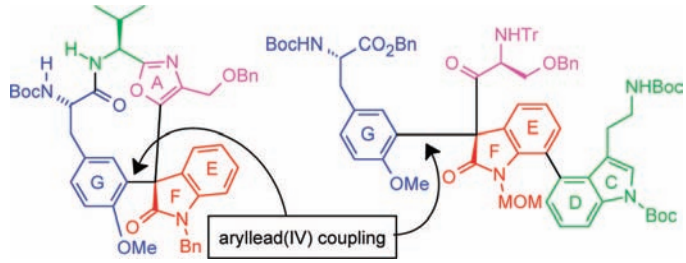
ABSTRACT



The synthesis of both the AEFG macrolactam and the CDEFG bis-indole/tyrosine units found in the marine natural product diazonamide A is presented. Key to the success of the synthesis is the highly stereoselective direct *C*-arylation of an oxindole by an aryllead(IV) reagent derived from tyrosine.

The combination of unusual molecular architecture and high biological activity found in the marine natural product diazonamide A (**1**, original structure, Figure 1)[1] has generated considerable interest from the synthetic organic chemistry community. Harran's synthesis of **1** uncloaked the true structure of diazonamide A as **2** and produced a highly active synthetic analogue (**3**).[2] To date, there have been three total syntheses[3,4] of this potent cytotoxic compound[5] together with a formal total synthesis and a wealth of synthetic[6] methodology development.[7] Herein, we disclose our synthetic work

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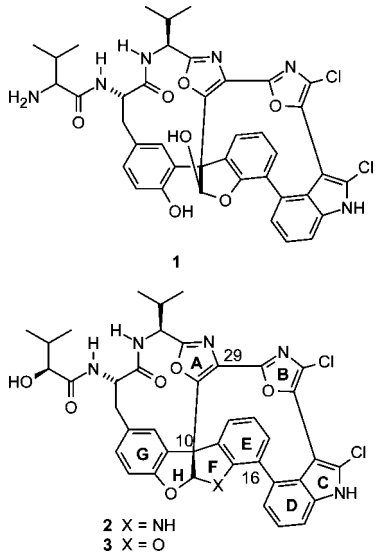
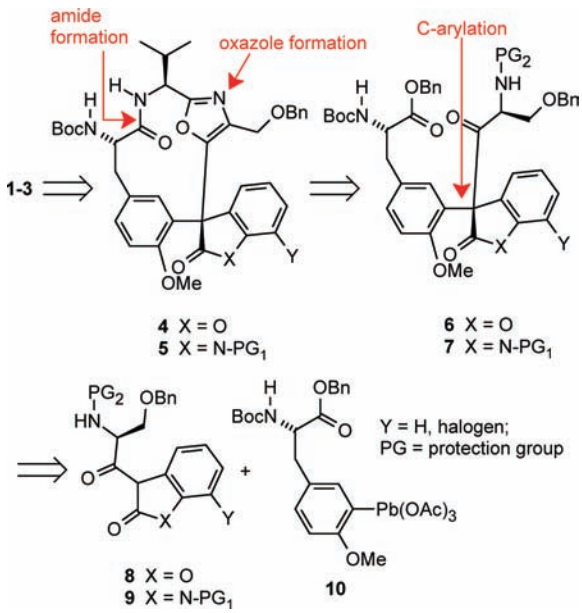


Figure 1. Nominal and true diazonamide A structures.

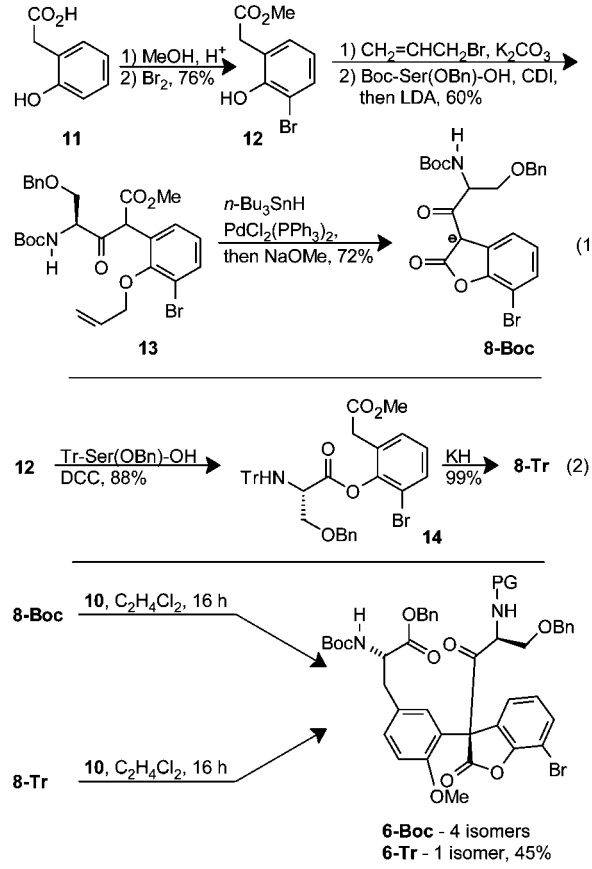
on both the nominal and true diazonamide structures. Our approach has been focused on the C10 center, both the literal and figurative core of compounds **1**−**3**, and the ability to form this quaternary carbon in a highly diastereoselective manner through the direct *C*-arylation of benzofuranone and oxindole adducts with an aryllead(IV) reagent derived from tyrosine.

Scheme 1. Retrosynthesis



Our analysis (Scheme 1) envisioned advanced AEFG lactone **4** (original structure) or lactam **5** (true structure) leading to the target compound through elaboration of the B, C, and D rings using the functionality at C29 and C16. Further simplification leads to **6**/**7**, in which the C10 center is established via the coupling of **8**/**9** to aryllead reagent **10**.[8] Earlier work had shown that the stereocenter of the tyrosine-derived reagent **10** was too remote from the reaction site to affect the stereochemical outcome of the coupling reaction.[9] However, there was optimism for two reasons. First, Lubell and Rapoport[10] had demonstrated (modest) stereoselectivity upon α-substitution of enantiomerically pure α′-amino ketones bearing sterically bulky protection on the amine. Since we had already documented high cyclic stereoselection in the aryllead coupling reaction in systems where the existing stereocenter is two bonds removed from the reaction site,[11] acyclic stereoselection seemed a distinct possibility. Second, the **8**/**9** stereochemistry would arise from the amino acid serine, which is readily available in either enantiomerically pure form. Since this stereocenter was slated for destruction in the formation of ring A (oxazole), our quest was for high diastereospecificity without initial regard to the absolute chirality at C10.

Scheme 2. Benzofuranone Approach



Initial work focused on **8** as the coupling partner for **10** toward nominal structure **1**. Esterification of commercially available hydroxyphenylacetic acid **11**, followed by selective ortho-bromination of the phenol,[12] yielded **12** (76%, Scheme 2, eq 1). Allyl protection of the phenol was followed by acylation via CDI activated Boc-Ser(OBn)-OH to give **13**

(60%). Allyl removal ($PdCl_2(PPh_3)_2/Bu_3SnH$) followed by treatment of sodium methoxide led to the benzofuranone salt **8-Boc**.

Reaction of **10** with **8-Boc** afforded none of the desired structure **6**; only small amounts of unidentifiable compounds were isolated (Scheme 2). This result inspired two changes in our synthetic design. The protection group on the serine residue was changed from -Boc to trityl in the hopes that the large $-CPh_3$ group would preclude both racemization[13] and general degradation. Moreover, an alternative approach to benzofuranone salt **8** was developed (Scheme 2, eq 2) to overcome the poor yield of the carbon acylation step in the production of **8-Boc**. Phenol **12** was coupled with Tr-Ser(OBn)-OH (DCC, 85%) to yield **14**, which was reacted with KH (1 equiv) to initiate a cascade reaction. Intramolecular acyl transfer and subsequent intramolecular lactonization precedes deprotonation of the resulting β-keto lactone by the liberated methoxy anion, resulting in formation of the desired benzofuranone potassium salt **8-Tr**. Reaction of **10** with **8-Tr** in 1,2-dichloroethane at 40 °C overnight afforded a single isomer of the desired coupling product **6** in 45% yield from **14**. However, our elation was shortlived due to the revision of the structure of diazonamide A to **2**. Hence, we abandoned this work and moved to a strategy employing oxindole **9**.

Lubell and Rapoport[10] reported α′-alkylation of α-amino ketones protected with the *N*-9-phenylfluorenyl (PhFl) group. Diastereomeric ratios originated from an equilibrium between two reactive conformations that, with our structures superimposed on the logic of our Berkeley colleagues, results in cyclic structure **A** as the major isomer (Figure 2). Reaction

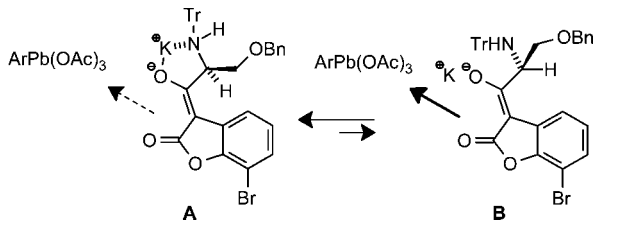


Figure 2. Mechanistic interpretation.

of this structure with **10** leads to the desired product. Experimentally, enolates **A/B** react with *tert*-butyl(chloro)diphenylsilane to afford the expected silyl enol ether (see the Supporting Information).

The synthesis of oxindoles of type **9** has been reported by our laboratory[14] and relies on the direct acylation of the requisite oxindole by the stable acid imidazolide formed from Tr-Ser(OBn)-OH and CDI. Treatment of **9-Bn** with NaH and tyrosine derivative **10** afforded two C10 isomers of desired compound **15** (**7**, PG_1 = Bn, PG_2 = Tr, X = H) *in 70% isolated yield as an approximate 8:1 separable mixture (major isomer: 62%, Scheme 3).*

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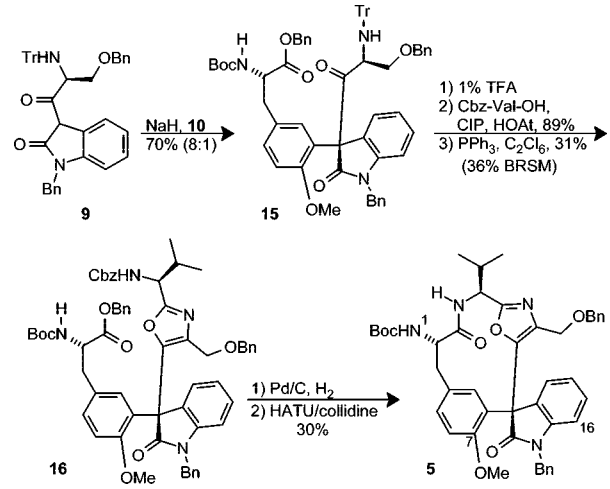
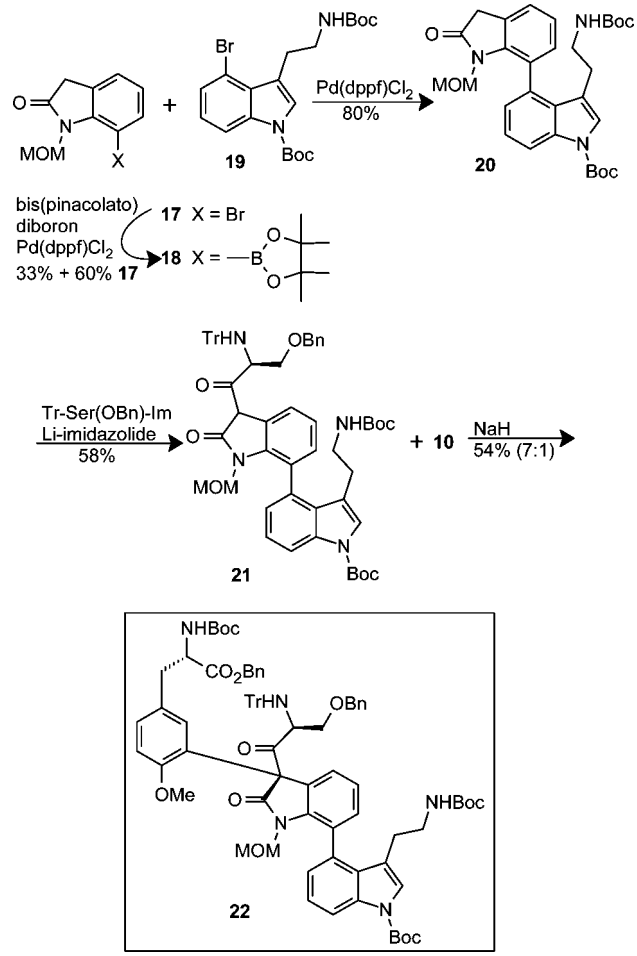
Scheme 3. Oxindole Approach



Trityl group removal (1% TFA in CH_2Cl_2) and direct coupling with Cbz-Val-OH (CIP/HOAt, 89%, 55% from **9**) preceded oxazole formation, which proved challenging. Best results occurred with PPh_3/C_2Cl_6[15] to give desired product

Scheme 4. CDEFG Fragment



16 (31% yield, 36% BRSM). Closure of the 12-membered lactam ring required reductive removal of the benzyl and -Cbz protection groups to liberate the amino and acid functionalities. Direct macrolactamization employing Nicolaou's procedure[3a] afforded the desired AEFG macrocycle in 30% yield for the two steps. Confidence in the C10 stereochemical assignment resulted from the similarity in yield between our result and that of Nicolaou (36%) for minimally different compounds (N1-Cbz vs -Boc, C7-OMOM vs OMe, C16-Br vs H) and Nicolaou's observation that the incorrect stereochemistry at C10 yields no product.

The original plan for the synthesis of diazonamide A was to construct **5** with a halogen substituent at the C7 position of the indole (C16 in diazonamide numbering). However, all attempts at removing the Cbz (valine) and benzyl (tyrosine) protection groups proved fruitless; the halogen was removed under hydrogenolysis conditions at a greater rate than acid or free amine formation.

Consequently, two modifications were implemented (Scheme 4). First, the oxindole nitrogen protection group was changed from -Bn to -MOM. Additionally, the C16−C18 bond was formed early in the synthetic sequence. In the event, 7-bromo-1-methoxymethyl-1,2-dihydroindol-2-one (**17**)[14] was transformed to the corresponding boronate ester (**18**) and coupled via palladium catalysis with 4-bromo-*N*,*N*′-(bis-*tert*-butoxycarbonyl)tryptamine (**19**)[16] to afford bisindole compound **20** (80%). Acylation of the oxindole followed our published protocol[14] to afford **21** in 58% yield. Finally, the C10 quaternary center is established as before, giving the desired fragment **22** bearing the CDEFG ring system of the natural product with suitable functionality to complete the synthesis. Although the C10 stereochemistry in **22** is not confirmed, it is assumed that the trityl group again dictates the outcome of the coupling reaction, as described in Figure 2.

In conclusion, a highly stereoselective route to the C10 quaternary center of diazonamide A has been developed. Further progress to the total synthesis of **2** is ongoing in this laboratory and will be reported in due time.

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

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