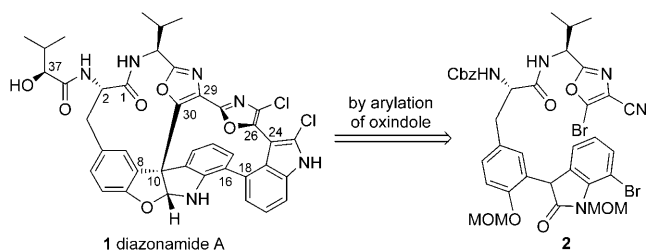


## Natural Products

# A Concise Formal Synthesis of Diazonamide A by the Stereoselective Construction of the C10 Quaternary Center\*\*

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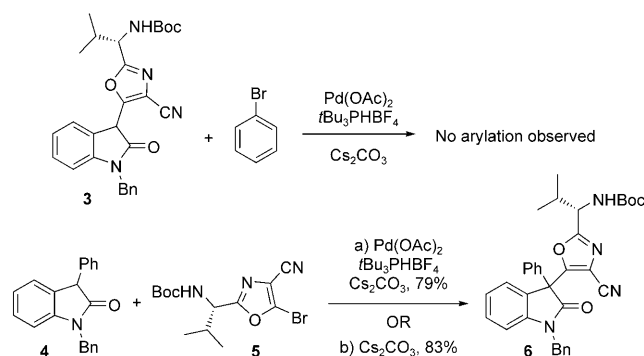
Diazonamide A (**1**, Scheme 1) is a marine natural product with potent antimitotic activity and an unusual architecture.<sup>[1]</sup> Its mode of action has been studied, and although it displayed



**Scheme 1.** The structure and retrosynthesis of diazonamide A. Cbz = phenylmethoxycarbonyl, MOM = methoxymethyl.

differential cytotoxicity in an NCI COMPARE<sup>[2]</sup> screen that is consistent with a tubulin-active agent,<sup>[3]</sup> recent studies by Harran, Wang, McKnight, and co-workers suggest a unique mode of action involving the mitochondrial matrix enzyme, ornithine  $\delta$ -amino transferase (OAT).<sup>[4]</sup> Prior to these studies, OAT had no known mitotic function, and diazonamide A does not inhibit the amino transferase activity of this enzyme; however, it disrupts the interaction of OAT with mitotic-spindle-promoting proteins. These same authors showed that a close synthetic analogue of diazonamide A, which lacks the two chlorine substituents, retained the cytotoxicity of the natural product, but did not display overt toxicity nor did it cause weight loss, a change in overall physical appearance, or show any evidence of causing neutropenia in mice.<sup>[4a]</sup> The limited supply, unique biological activity, and structural complexity of diazonamide A renders this molecule and analogues thereof important targets for chemical synthesis.

The synthetic challenge posed by diazonamide A lies, in great part, in the stereoselective construction of the highly hindered quaternary C10, which has attracted the attention of numerous synthetic groups.<sup>[5]</sup> These efforts have resulted in three total syntheses by Nicolaou et al.<sup>[6a-d]</sup> and Harran et al.,<sup>[6e]</sup> and a formal total synthesis by Magnus and co-workers.<sup>[6f]</sup> We have studied a new approach wherein we construct the C10 quaternary carbon using the arylation of a 3-aryloxindole.<sup>[7]</sup> We initially chose to study this construction using a palladium-catalyzed arylation,<sup>[8]</sup> and performed a model study to examine the order of bond formation in the synthesis of this subunit. We studied these reactions using 3-substituted oxindoles **3** and **4**, which were arylated with bromobenzene and bromooxazole **5**,<sup>[9]</sup> respectively, using modified Hartwig conditions<sup>[10]</sup> ( $\text{Pd}(\text{OAc})_2$  or  $[\text{Pd}(\text{dba})_2]$ ,  $t\text{Bu}_3\text{PHBF}_4$ <sup>[11]</sup> in toluene at reflux; Scheme 2). We found that



**Scheme 2.** Arylation of 3-aryloxindoles **3** and **4**. Boc = *tert*-butoxycarbonyl.

whilst the combination of substrate **3** and bromobenzene did not provide the desired product, substrate **4** reacted cleanly with bromooxazole **5** to produce compound **6** in 79% yield.

This method can be used to readily form a highly hindered quaternary carbon atom. In an effort to optimize this reaction, we incrementally reduced the catalyst loading from 5%; surprisingly, the reaction proceeded even in the absence of palladium with no decrease in yield. This indicated that the reaction proceeded via an  $\text{S}_{\text{N}}\text{Ar}$  mechanism in the absence of palladium (Scheme 2).<sup>[12]</sup> We are currently examining further applications of this reaction for the formation of quaternary carbon centers.

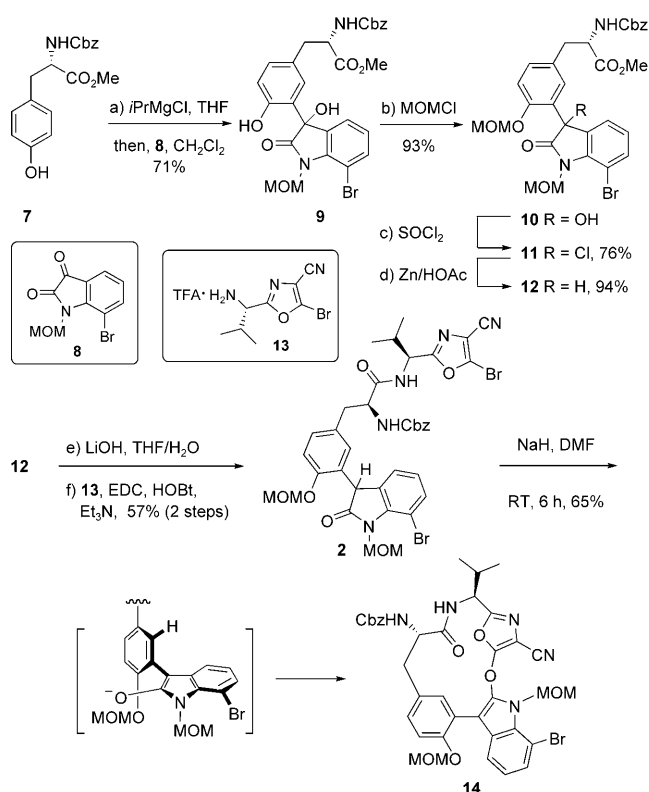
To apply this reaction to the synthesis of diazonamide A, we prepared the bis(MOM)-protected cyclization precursor, **2** (Scheme 3). *N*-Cbz-L-tyrosine methyl ester (**7**)<sup>[13]</sup> was treated with  $i\text{PrMgCl}$ , and the resulting phenoxide was coupled with

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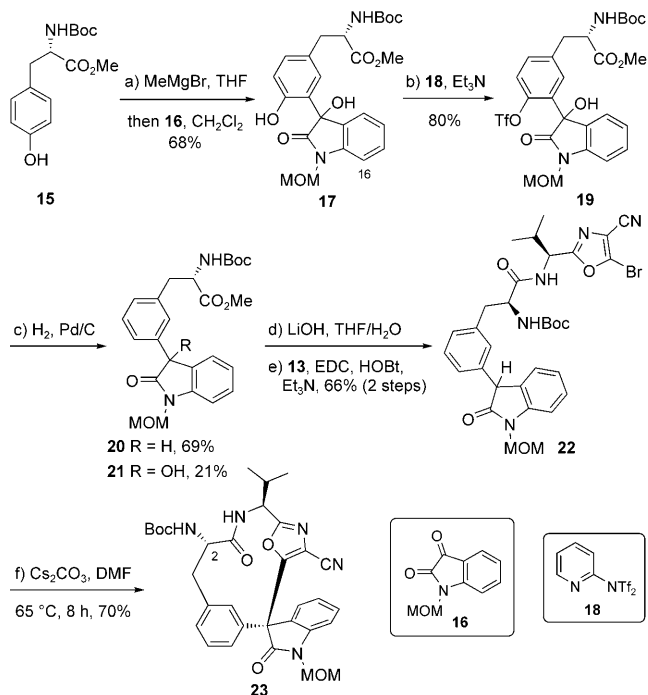
**Scheme 3.** Preparation and cyclization of bis(MOM)-protected oxindole **2**. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBT = 1-hydroxy 1H-benzotriazole, DMF = *N,N*-dimethylformamide.

*N*-MOM-7-bromoisatin (**8**) to provide alcohol **9**.<sup>[14,15]</sup> The phenolic hydroxy group of compound **9** was then protected (MOMCl) and the tertiary alcohol was reduced (SOCl<sub>2</sub> then Zn/HOAc) to provide oxindole **12**.<sup>[15]</sup> Saponification of the methyl ester of **12**, followed by amidation of the resulting carboxylic acid with aminooxazole **13** (EDC/HOBT) provided cyclization precursor **2**.<sup>[15]</sup>

The cyclization of **2** was studied under a variety of conditions with variations in the base, solvent, and temperature. The formation of a cyclic product was observed under many conditions (e.g., NaH in DMF, RT, 65 %); however, we were disappointed to find that in all cases only O-arylation product **14** was formed (Scheme 3).

We hypothesized that the desired C arylation was hindered by the *ortho* substituent of the tyrosine moiety, which prevented the formation of a coplanar enolate, as shown in Scheme 3. The orthogonal aryl group would thereby cause the carbon center to be too hindered to approach the bromooxazole. To test this hypothesis, we synthesized cyclization precursor **22**, which lacks an *ortho* substituent and should be capable of adopting a planar conformation with the enolate. The synthesis of **22** was similar to that of **2**, but required the reduction of the tyrosine phenol group. Typical hydrogenolysis conditions were not compatible with the Cbz protecting group on the nitrogen atom attached to C2 or the bromine atom at C16, so the Cbz was replaced with a Boc group, and the bromine group was not installed. Therefore, compound

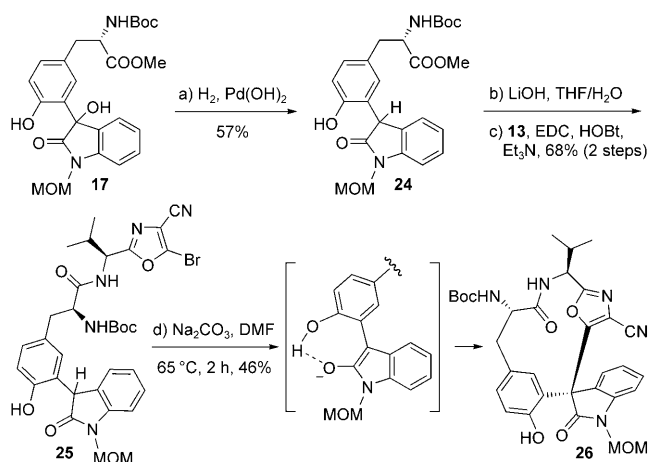
**17**<sup>[15]</sup> was prepared by addition of *N*-Boc-L-tyrosine methyl ester (**15**)<sup>[16]</sup> to *N*-MOM-isatin (**16**), and the phenolic hydroxy group of the product was converted into the triflate with Comins' reagent (**18**)<sup>[17]</sup> to provide **19**<sup>[15]</sup> (Scheme 4). This



**Scheme 4.** Cyclization of substrate **22**, which lacks an *ortho* substituent on the tyrosine moiety. Tf = trifluoromethanesulfonyl.

compound was then subjected to hydrogenolysis (Pd/C, H<sub>2</sub>) to provide the doubly reduced product **20**<sup>[15]</sup> in 69 % yield along with the partially reduced byproduct **21** in 21 % yield. These compounds were separated, and **20** was saponified with LiOH and coupled with aminooxazole **13** to provide cyclization precursor **22**.<sup>[15]</sup> Subjection of compound **22** to Cs<sub>2</sub>CO<sub>3</sub> in DMF at 65 °C provided the desired C-arylated cyclization product **23** in 70 % yield. The stereochemistry of this product was assigned by analogy to that of **34** (see below) and no other stereoisomers were observed by NMR spectroscopy.

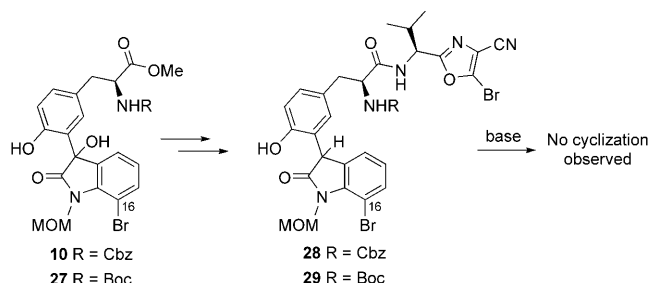
This result suggests that an arene that has no *ortho* functionalization can lie in the same plane as the oxindole enolate and undergo cyclization at the carbon center. However, we still required a method for the synthesis of the C-arylated product that contained the tyrosine hydroxy group. We reasoned that we could force co-planarity of the tyrosine arene and the oxindole enolate by taking advantage of hydrogen bonding between the phenol of the tyrosine and the enolate alkoxide. This is expected to be a strong interaction owing to the acidity of the phenol group and the basicity of the enolate. Cyclization precursor **25**<sup>[15]</sup> was therefore synthesized from **17** by reduction of the tertiary hydroxy group (H<sub>2</sub>/Pd(OH)<sub>2</sub>/C) followed by saponification (LiOH) and EDC/HOBT coupling with **13** (Scheme 5). We were pleased to find that compound **25** underwent cyclization in 46 % yield upon treatment with Na<sub>2</sub>CO<sub>3</sub> in DMF at 65 °C to provide the



**Scheme 5.** Cyclization of free-phenol substrate **25**.

desired C-arylation product **26** as a single diastereomer (Scheme 5; the stereochemistry was assigned by analogy to that of **34**). More reactive bases, such as  $\text{Cs}_2\text{CO}_3$  or  $\text{LiHMDS}$ , were unsatisfactory as they provided complex mixtures.

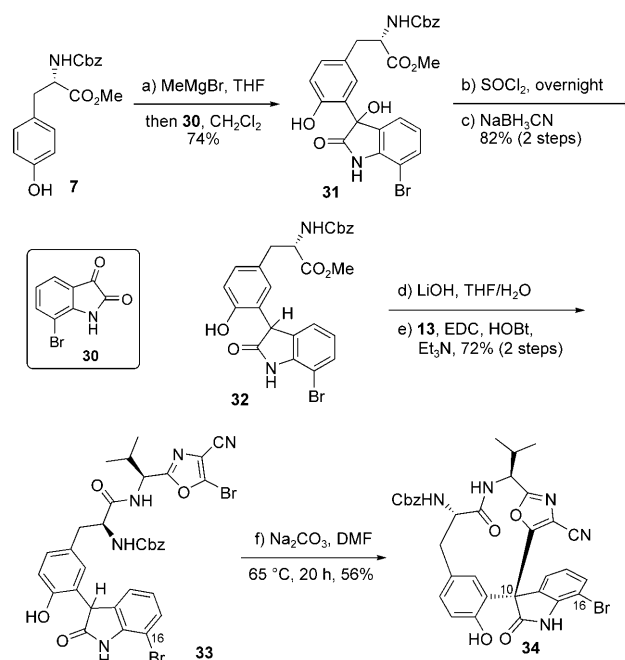
For this cyclization reaction to be viable for the synthesis of the natural product, we required a handle at C16 to allow the formation of the C16–C18 bond. Therefore, we prepared cyclization precursors **28**<sup>[15]</sup> and **29**<sup>[15]</sup> which contained a bromine substituent at C16, from compounds **10** and **27**, respectively, using a route analogous to that shown in Scheme 3. Unfortunately, we did not obtain the desired cyclization products under a variety of conditions; in all cases either recovered starting material or decomposition products were observed (Scheme 6). We hypothesize that these cycli-



**Scheme 6.** Attempted cyclization of substrates **28** and **29**.

zation reactions are inhibited by the conformation of the MOM group, which is presumably influenced by the steric bulk of the bromine atom at the C16 center. Therefore, we studied cyclization precursor **33**, which lacks the *N*-MOM protecting group.

Synthesis of **33**<sup>[15]</sup> proceeded by the addition of *N*-Cbz-L-tyrosine methyl ester (**7**) to 7-bromoisatin (**30**) to provide **31**<sup>[15]</sup> in 74% yield (Scheme 7). This was followed by reduction of the resulting tertiary alcohol by using the procedure reported by Nicolaou et al. ( $\text{SOCl}_2$  then  $\text{NaCNBH}_3$ )<sup>[6c,d]</sup> to provide **32**<sup>[15]</sup> in 82% yield over two steps.

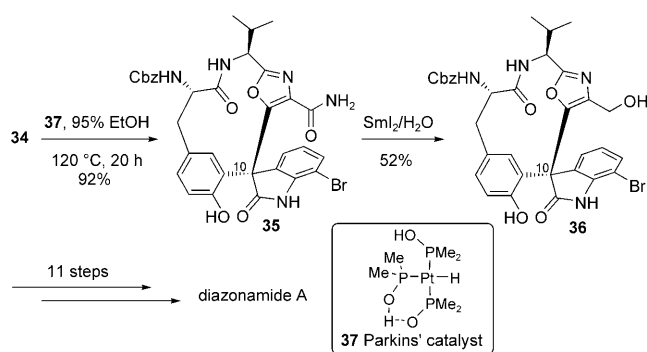


**Scheme 7.** Cyclization of unprotected phenol/oxindole **33**.

Saponification followed by coupling of the resulting acid with aminooxazole **13** provided cyclization precursor **33** in 72% yield over two steps. We were delighted to find that subjection of **33** to  $\text{Na}_2\text{CO}_3$  in DMF at 65 °C for 20 hours provided the desired C-cyclized product in 56% yield. The stereochemistry of the product was determined by X-ray crystallography, and was found to be consistent with the natural product.<sup>[18]</sup> We observed no other isomers in this reaction; the remainder of the material was determined by mass spectrometry to be a mixture of starting material and an unidentified non-isomeric side-product, which contains two bromine atoms, that co-elutes with the starting material. Under the same conditions, other carbonate bases either afforded comparable yields ( $\text{K}_2\text{CO}_3$ , 40–50%), no reaction ( $\text{Li}_2\text{CO}_3$ ), or a complex mixture of products ( $\text{Cs}_2\text{CO}_3$ ). Acetonitrile provided comparable yields to DMF whilst DMA (*N,N*-dimethylacetamide) and DMSO (dimethyl sulfoxide) provided slightly diminished yields (circa 40%).

Compound **34** was then converted into **36**<sup>[6a,b]</sup> using a two-step sequence involving hydrolysis of the nitrile to form carboxamide **35** using Parkins' catalyst (**37**)<sup>[19]</sup> in 95% ethanol in a sealed tube at 120 °C (92%). This step was followed by reduction to the primary alcohol using  $\text{SmI}_2$  and  $\text{H}_2\text{O}$  (52%, Scheme 8).<sup>[20]</sup> The Nicolaou group has reported the conversion of this intermediate into diazonamide **A** by an 11-step sequence,<sup>[6a,b]</sup> and as such, this synthesis constitutes a formal total synthesis of diazonamide **A**.

In conclusion, a formal total synthesis of diazonamide **A** has been described. The key step in this synthesis is the diastereoselective intramolecular arylation of a 3-aryloxindole by an  $\text{S}_{\text{N}}\text{Ar}$  reaction to form the hindered C10 quaternary stereocenter in an efficient and stereoselective fashion. Interestingly, the cyclization occurs under very mild conditions using sodium carbonate as the base, such that no



**Scheme 8.** Correlation with the first synthesis of diazonamide A by Nicolaou and co-workers.

protecting groups are required on the phenol or oxindole nitrogen groups.

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