Published in final edited form as:
Angew Chem Int Ed Engl. 2010 March 22; 49(13): 2397–2400. doi:10.1002/anie.200906318.

A Concise Formal Synthesis of Diazonamide A via the Stereoselective Construction of the C10 Quaternary Center**

Cheng-Kang Mai, **Matthew F. Sammons**[+], and **Tarek Sammakia**
Department of Chemistry and Biochemistry University of Colorado Boulder, CO 80309-0215 (USA)

Diazonamide A (**1**, Figure 1) is a marine-derived natural product with potent antimitotic activity and an unusual architecture.[1] Its mechanism of action has been studied, and though it displays differential cytotoxicity in the NCI COMPARE[2] screen consistent with a tubulin-active agent,[3] recent studies by Harran, Wang and McKnight suggest a unique mechanism of action involving the mitochondrial matrix enzyme, ornithinine δ-amino transferase (OAT).[4] Prior to these studies, OAT had no known mitotic function, and diazonamide A does not inhibit the amino transferase activity of this enzyme, yet it disrupts its interaction with mitotic spindle promoting proteins. These same workers showed that a close synthetic analogue of diazonamide A lacking the two chlorine atoms retains the cytotoxicity of the natural product, but does not display overt toxicity nor does it cause weight loss, change in overall physical appearance, or evidence of neutropenia in mice.[4a] The combination of limited supply, unique biological activity, and structural complexity, 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 C10 quaternary carbon, which has attracted the attention of numerous synthetic groups.[5] These efforts have resulted in three total syntheses by Nicolaou and by Harran, and a formal total synthesis by Magnus.[6] We have studied a new approach wherein we construct the C10 quaternary carbon via the arylation of a 3-aryloxindole.[7] We initially chose to study this construction via a Pd-catalyzed arylation,[8] and embarked on 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 subjected to arylation with bromobenzene or bromooxazole **5**,[9] respectively, using modified Hartwig conditions[10] ($Pd(OAc)_2$ or $Pd(dba)_2$ and t-Bu_3PHBF_4[11] in toluene at reflux, Scheme 1). We found that while the combination of substrate **3** and bromobenzene did not provide the desired product, substrate **4** reacted cleanly with bromooxazole **5** producing compound **6** in 79% yield.

This method can readily form a very hindered quaternary carbon, and in an effort to optimize the reaction, we reduced the catalyst loading from 5% to incrementally lower levels. Surprisingly, we were able to eliminate the Pd entirely with no decrease in yield, indicating that the reaction can proceed via an S_NAr mechanism in the absence of Pd

This work was supported by a generous grant from the National Institutes of Health (GM 48498). We wish to thank Dr. Joseph H. Reibenspies (Texas A&M University) for acquiring the X-ray crystal structure of **34 and Dr. Richard Shoemaker (University of Colorado) for expert assistance with acquiring NMR data.

Correspondence to: Tarek Sammakia.

Fax: (+1) 303-492-0439 Sammakia@colorado.edu.
[+]Current Address: Pfizer Global Research and Development Groton, CT 06340 (USA)

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

(Scheme 1).[12] We are currently examining further applications of this reaction to the formation of quaternary carbon centers.

In order to apply this reaction to the synthesis of diazonamide A, we prepared the bis-MOM protected cyclization precursor **2** (Scheme 2). *N*-Cbz-L-tyrosine methyl ester (**7**)[13] was treated with *i*PrMgCl, and the resulting phenoxide was coupled with *N*-MOM-7-bromoisatin (**8**) to provide alcohol **9**.[14, 15] The phenolic hydroxyl group of compound **9** was then protected (MOMCl) and the tertiary alcohol was reduced ($SOCl_2$ then Zn/HOAc) to provide oxindole **12**.[15] Saponification of the methyl ester of **12** followed by amidation of the resulting carboxylic acid with aminooxazole **13** (EDC/HOBt) provided cyclization precursor **2**.[15]

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 the *O*-arylation product (**14**) was formed (Scheme 2).

We hypothesized that the desired *C*-arylation was hindered by the *ortho*-substituent of the tyrosine moiety, which prevents the formation of a coplanar enolate as shown in Scheme 2. The orthogonal aryl group would thereby render the carbon center too hindered to approach the bromooxazole. We wished to test this hypothesis and therefore 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. Typical hydrogenolysis conditions are not compatible with the Cbz protecting group on the C2 nitrogen or the bromine at C16, so the Cbz was replaced with a Boc group, and the bromine was not installed. Thus, compound **17**[15] was prepared by addition of *N*-Boc-L-tyrosine methyl ester (**15**)[16] to *N*-MOM-isatin (**16),** and the phenolic hydroxyl group of the product converted to the triflate with Comins' reagent (**18**)[17] to provide **19**[15] (Scheme 3). This was then subjected to hydrogenolysis (Pd/C, H_2) to provide the doubly reduced product **20**[15] 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**.[15] Subjection of compound **22** to Cs_2CO_3 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** (vide infra) and no other stereoisomers were observed by NMR.

This result suggests that an arene lacking *ortho*-functionalization can achieve coplanarity with the oxindole enolate and undergo cyclization on carbon. However, we still required a method for the synthesis of the *C*-arylated product bearing the tyrosine hydroxyl 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 due to the acidity of the phenol and the basicity of the enolate. Cyclization precursor **25**[15] was therefore synthesized as shown in Scheme 4 from **17** by reduction of the tertiary hydroxyl group (H_2/Pd(OH)$_2$/C) followed by saponification (LiOH) and coupling with **13** (EDC/HOBt). We were pleased to find that compound **25** underwent cyclization in 46% yield upon treatment with Na_2CO_3 in DMF at 65 °C to provide the desired *C*-arylation product **26** as a single diastereomer (Scheme 4; stereochemistry assigned by analogy to that of **34**). More reactive bases, such as Cs_2CO_3 or LiHMDS, were unsatisfactory as they provided complex mixtures.

In order for this cyclization to be viable for a synthesis of the natural product, we required a handle at C16 to allow for the formation of the C16-C18 bond. We therefore prepared cyclization precursors **28**[15] and **29**,[15] bearing a bromine at C16 starting from compounds

10 and **27,** respectively, by a route analogous to that shown in Scheme 2. Unfortunately, we did not obtain the desired cyclization products under a variety of conditions; in all cases either recovered starting material or decomposition was observed (Scheme 5). We hypothesize that these cyclizations are inhibited by the conformation of the MOM group, which is likely altered due to the sterics of the bromine at C16. We therefore studied cyclization precursor **33** which lacks the *N*-MOM protecting group.

Synthesis of **33**[15] proceeded by the addition of *N*-Cbz-L-tyrosine methyl ester (**7**) to 7-bromoisatin (**30**) to provide **31**[15] in 74% yield (Scheme 6). This was followed by reduction of the resulting tertiary alcohol by Nicolaou's procedure ($SOCl_2$ then $NaCNBH_3$)[6c,d] to provide **32**[15] in 82% yield over two steps. 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 Na_2CO_3 in DMF at 65 °C for 20 hours provided the desired *C*- cyclized product in 56% yield. The stereochemistry of this material was determined by X-ray crystallography and found to be consistent with the natural product.[18] We observed no other isomers in this reaction; the remainder of the material was a mixture of starting material and an unidentified non-isomeric side product bearing two bromine atoms by mass spectrometry that co-elutes with the starting material. Under the same conditions, other carbonate bases either provided comparable yields (K_2CO_3, 40 – 50%), no reaction (Li_2CO_3), or a complex mixture (Cs_2CO_3). Acetonitrile provides comparable yields to DMF while DMA and DMSO provide slightly diminished yields (~40%).

Compound **34** was then converted to **36**[6a,b] by a two step sequence involving hydrolysis of the nitrile to carboxamide **35** using Parkins' catalyst (**37**)[19] in 95% ethanol in a sealed tube at 120 °C (92%). This was followed by reduction to the primary alcohol using SmI_2 and H_2O (51%, Scheme 7).[20] Nicolaou has converted this intermediate to diazonamide A by an 11-step sequence,[6a,b] and as such, this constitutes a formal total synthesis.

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 via an S_NAr reaction, thereby forming 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 protecting groups are required on the phenol or oxindole nitrogen.

References

1. For isolation and structure revision of diazonamide A, see: Lindquist N, Fenical W, Van Duyne GD, Clardy J. J. Am. Chem. Soc. 1991; 113:2303–2304.Li J, Jeong S, Esser L, Harran PG. Angew. Chem. 2001; 113:4901–4906.Angew. Chem. Int. Ed. 2001; 40:4765–4769.Li J, Burgett AWG, Esser L, Amezcua C, Harran PG. Angew. Chem. 2001; 113:4906–4909.Angew. Chem. Int. Ed. 2001; 40:4770–4773.
2. Shoemaker RH. Nat. Rev. Cancer. 2006; 6:813–823. [PubMed: 16990858]
3. Cruz-Monserrate Z, Vervoort HC, Bai R, Newman DJ, Howell SB, Los G, Mullaney JT, Williams MD, Pettit GR, Fenical W, Hamel E. Mol. Pharm. 2003; 63:1273–1280.
4. For biological studies of diazonamide A and analogues, see: Williams NS, Burgett AWG, Atkins AS, Wang X, Harran PG, McKnight SL. Proc. Natl. Acad. Sci. USA. 2007; 107:2074–2079. [PubMed: 17287337] Wang G, Shang L, Burgett AWG, Harran PG, Wang X. Proc. Natl. Acad. Sci. USA. 2007; 104:2068–2073. [PubMed: 17287350] Harran P, Wang X, Wang G. 2007University of Texas SystemUS 2007/0287679 A1
5. For a recent review of the synthesis of diazonamide A, see: Lachia M, Moody CJ. Nat. Prod. Rep. 2008; 25:227–253. [PubMed: 18389137]

6. For the synthesis of diazonamide A, see: Nicolaou KC, Bella M, Chen DY-K, Huang X, Ling T, Snyder SA. Angew. Chem. 2002; 114:3645–3649.Angew. Chem. Int. Ed. 2002; 41:3495–3499.Nicolaou KC, Chen DY-K, Huang X, Ling T, Bella M, Snyder SA. J. Am. Chem. Soc. 2004; 126:12888–12896. [PubMed: 15469286] Nicolaou KC, Rao PB, Hao J, Reddy MV, Rassias G, Huang X, Chen DY-K, Snyder SA. Angew. Chem. 2003; 115:1795–1800.Angew. Chem. Int. Ed. 2003; 42:1753–1758.Nicolaou KC, Hao J, Reddy MV, Rao PB, Rassias G, Snyder SA, Huang X, Chen DY-K, Brenzovich WE, Giuseppone N, Giannakakou P, O'Brate A. J. Am. Chem. Soc. 2004; 126:12897–12906. [PubMed: 15469287] Burgett AWG, Li Q, Wei Q, Harran PG. Angew. Chem. 2003; 115:5111–5116.Angew. Chem. Int. Ed. 2003; 42:4961–4966.Cheung C-M, Goldberg FW, Magnus P, Russell CJ, Turnbull R, Lynch V. J. Am. Chem. Soc. 2007; 129:12320–12327. [PubMed: 17880079]
7. For the arylation of oxindoles, see: Durbin MJ, Willis MC. Org. Lett. 2008; 10:1413–1415. [PubMed: 18321119] Altman RA, Hyde AM, Huang X, Buchwald SL. J. Am. Chem. Soc. 2008; 130:9613–9620. [PubMed: 18588302] For the asymmetric arylation of 3-alkyloxindoles, see: Taylor AM, Altman RA, Buchwald SL. J. Am. Chem. Soc. 2009; 131:9900–9901. [PubMed: 19580273] For a related approach, see: Lin J, Gerstenberger BS, Stessman NYT, Konopelski JP. Org. Lett. 2008; 10:3969–3972. [PubMed: 18702502]
8. Bellina F, Rossi R. Chem. Rev. 2009 ASAP. DOI: 10.1021/cr9000836; Johansson CCC, Colacot TJ. Angew. Chem. 2010; 122:686–718.Angew. Chem. Int. Ed. 2010; 49:676–707.
9. Jeong S, Chen X, Harran PG. J. Org. Chem. 1998; 63:8640–8641.
10. Jørgensen M, Lee S, Liu X, Wolkowski JP, Hartwig JF. J. Am. Chem. Soc. 2002; 124:12557–12565. [PubMed: 12381200]
11. Netherton MR, Fu GC. Org. Lett. 2001; 3:4295–4298. [PubMed: 11784201]
12. Palmer, DC.; Venkatraman, S. The Chemistry of Heterocyclic compounds, Oxazoles: Synthesis, Reactions, and Spectroscopy: Part A. Palmer, DC., editor. Vol. 60. John Wiley & Sons, Inc.; Hoboken, New Jersey: 2003. p. 138-149.
13. Lin S, Yang Z-Q, Kwok BHB, Koldobskiy M, Crews CM, Danishefsky SJ. J. Am. Chem. Soc. 2004; 126:6347–6355. [PubMed: 15149232]
14. Hewawasam P, Erway M. Tetrahedron Lett. 1998; 39:3981–3984.
15. Prepared as a 1:1 mixture of diastereomers.
16. Richter JM, Whitefield BW, Maimone TJ, Lin DW, Castroviejo MP, Baran PS. J. Am. Chem. Soc. 2007; 129:12857–12869. [PubMed: 17900115]
17. Comins DL, Dehghani A. Tetrahedron Lett. 1992; 33:6299–6302.
18. CCDC 753609 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif
19. a Ghaffar T, Parkins AW. Tetrahedron Lett. 1995; 56:8657–8660.b Ghaffar T, Parkins AW. J. Mol. Catal. A: Chem. 2000; 160:249–261.
20. Kamochi Y, Kudo T. Chem. Lett. 1993; 22:1495–1498.

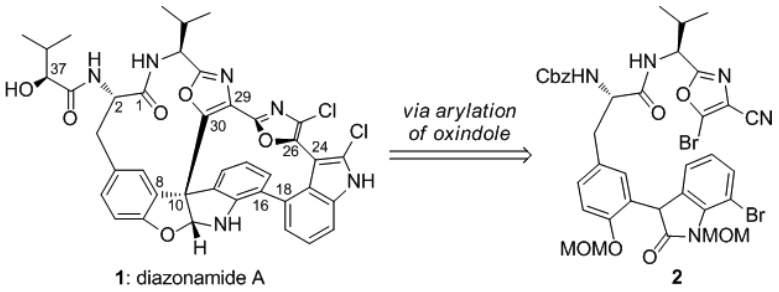
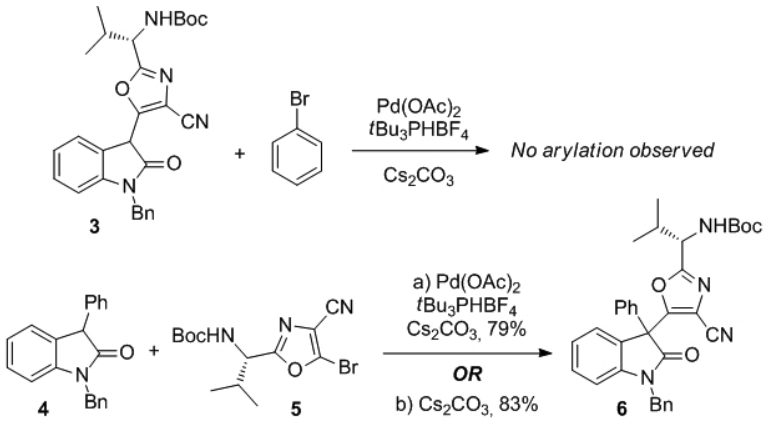
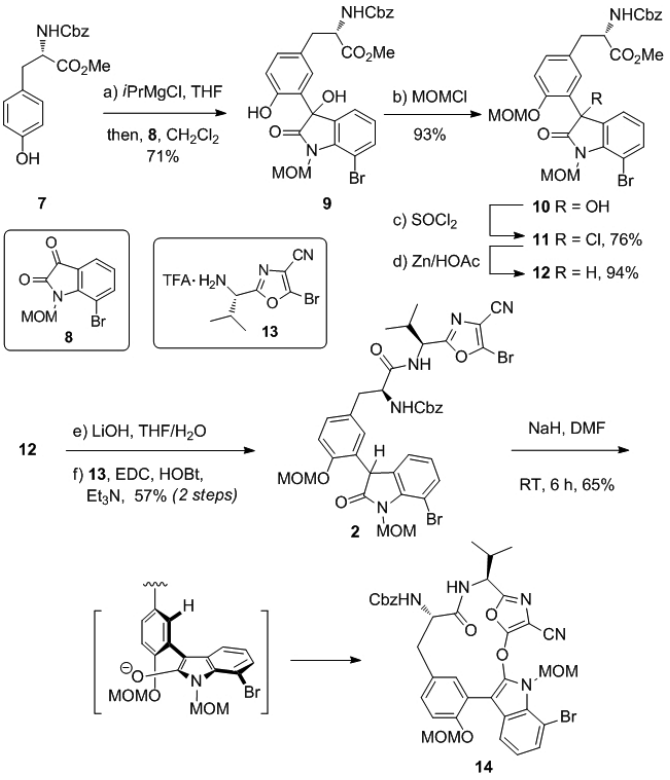


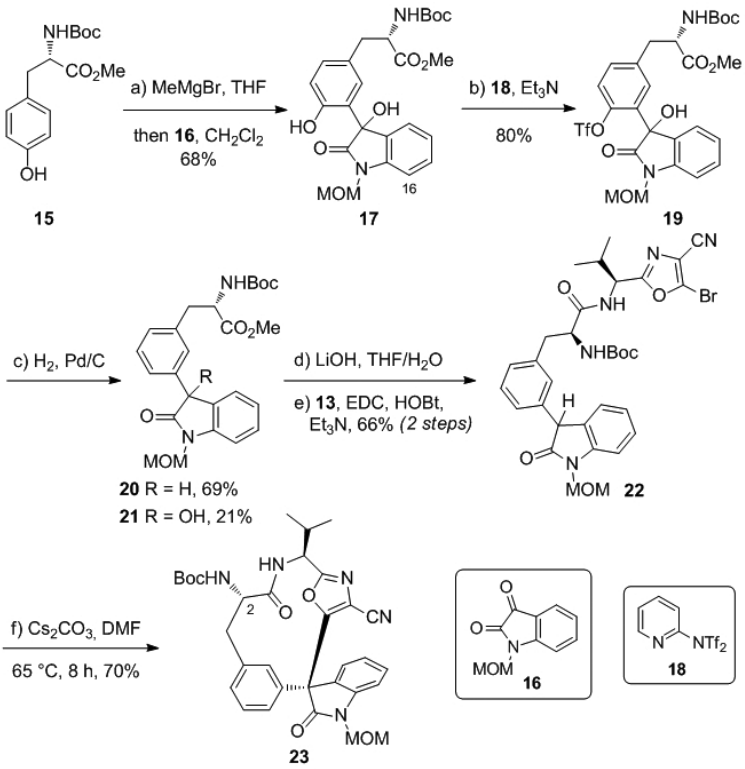
Figure 1.
The structure and retrosynthesis of diazonamide A



Scheme 1.
Arylation of 3-aryloxindoles **3 & 4**.

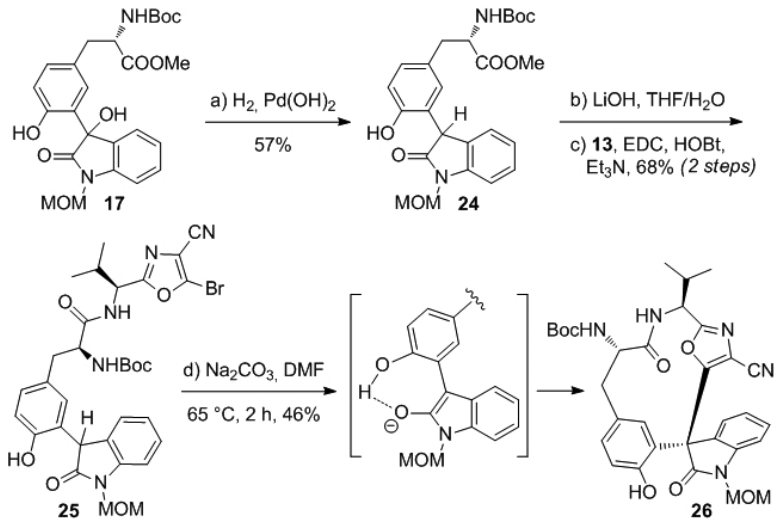


Scheme 2.
Preparation and cyclization of bis-MOM protected oxindole **2**.

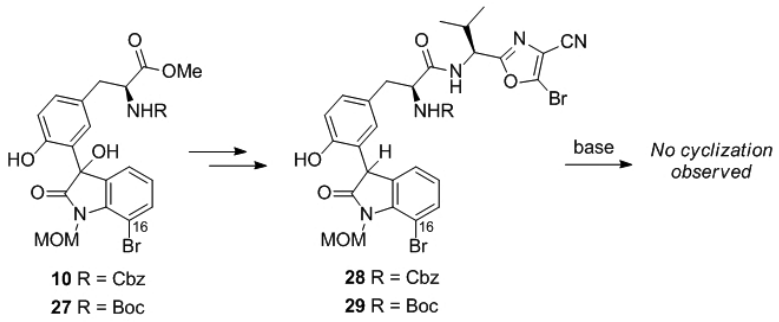


Scheme 3.

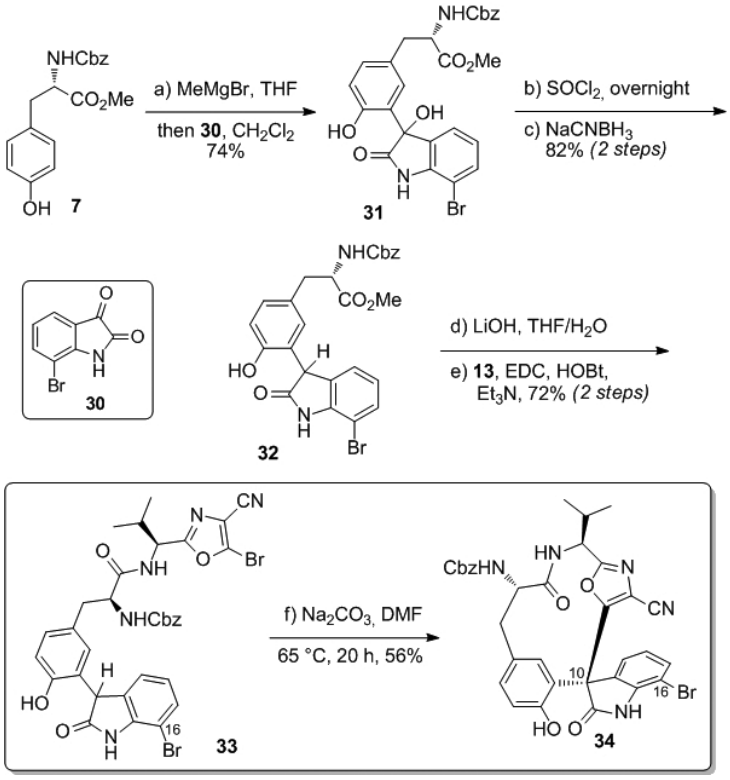
Cyclization of substrate **22** lacking an *ortho*-substituent on the tyrosine moiety.



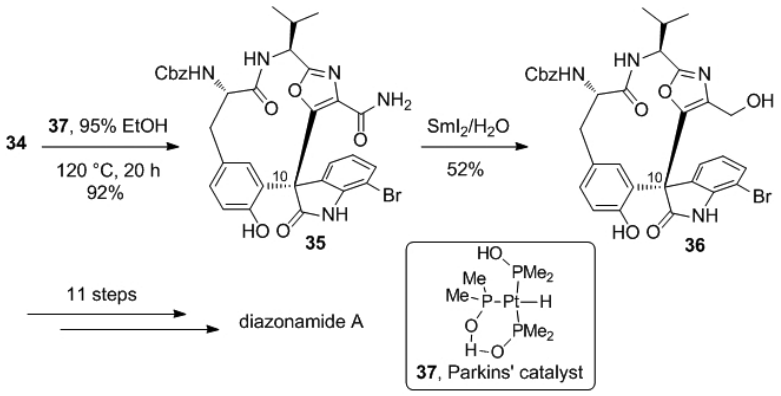
Scheme 4.
Cyclization of free-phenol substrate **25**.



Scheme 5.
Attempted cyclization of substrates **28 & 29**.



Scheme 6.
Cyclization of unprotected phenol-oxindole **33**.



Scheme 7.
Correlation with Nicolaou's First Synthesis of Diazonamide A.