

Natural Product Synthesis **A Concise and Flexible Total Synthesis of  
(–)-Diazonamide A\*\***

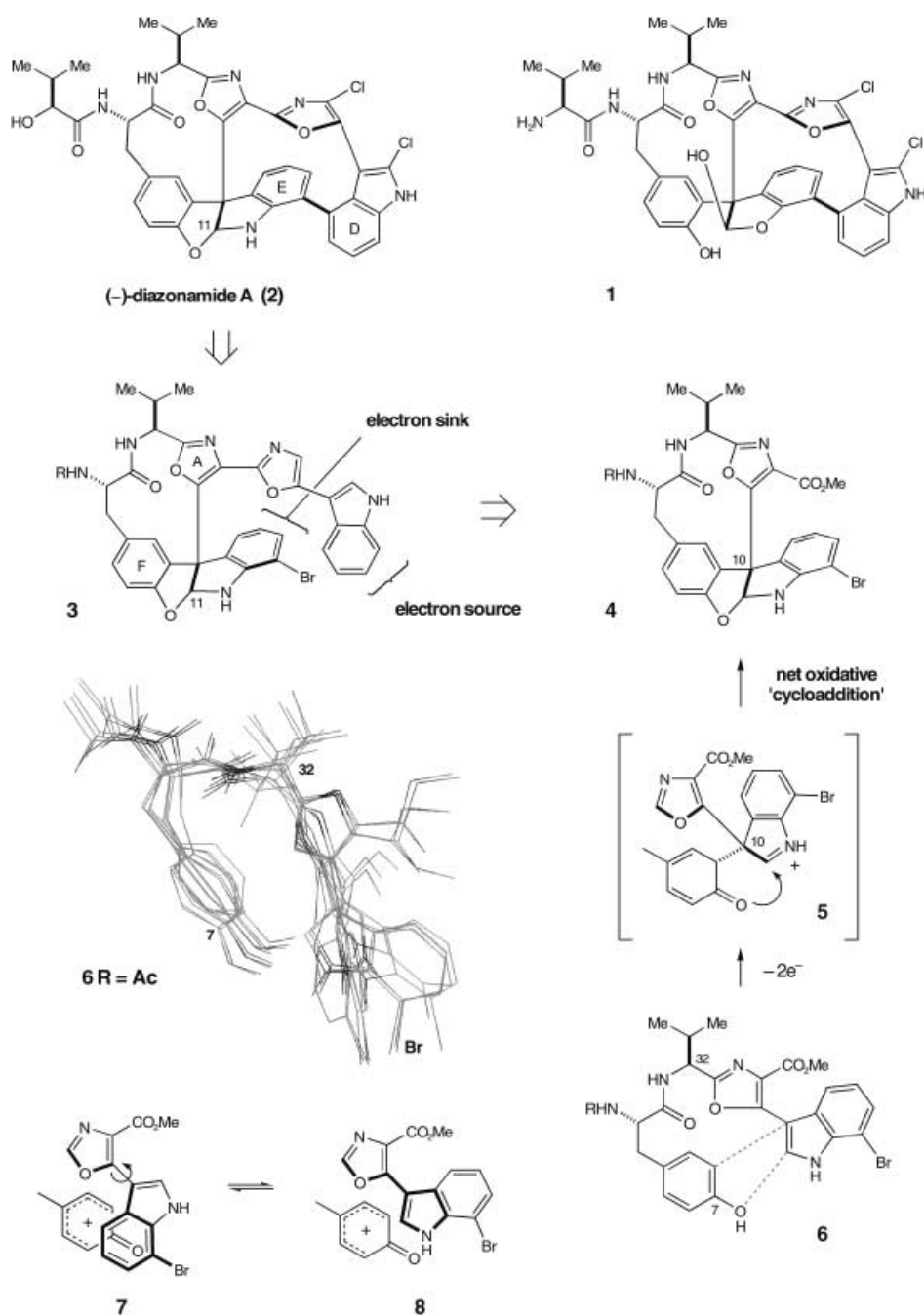
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Patrick G. Harran\**

Diazonamide A is a potently antimitotic natural product whose structure was originally assigned as polycycle **1** (Figure 1).<sup>[1]</sup> We recently synthesized this material—only to discover that **1** is neither a natural substance nor, in fact, stable.<sup>[2]</sup> A reinterpretation of published spectroscopic and X-ray crystallographic data led to the proposal that diazonamide A was actually hydroxy isovaleramide-containing aminal **2**.<sup>[3]</sup> This revision has been recently confirmed through synthesis.<sup>[4]</sup> We felt that the differences between **1** and **2**, while seemingly subtle, provided for a very different synthetic problem. Therefore, minor adaptations of the route used to prepare **1** were not pursued. Rather, we developed and

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**Figure 1.** Diazonamide A structure and primary retrosynthesis.

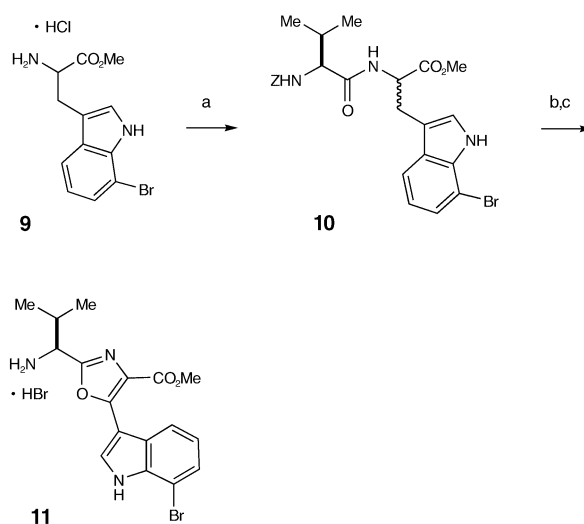
describe here a new sequence—one that generates natural diazonamide A in a particularly concise manner and along lines possibly relevant to its biosynthesis.

Lessons learned from earlier work proved valuable. Peripheral halogenation and acyl substitution can be installed late on a diazonamide core. In addition, we knew that potentially complicating issues of atropisomerism<sup>[5]</sup> during assembly of this core could be avoided by forming the D/E biaryl bond intramolecularly in the context of a pre-existing, correctly configured A/F macrolactam. This implicated seco halide **3** as a penultimate target—a position from which photoinduced electron transfer mediated elimination of HBr could complete the diazonamide ring system.<sup>[2]</sup> From **3**, the

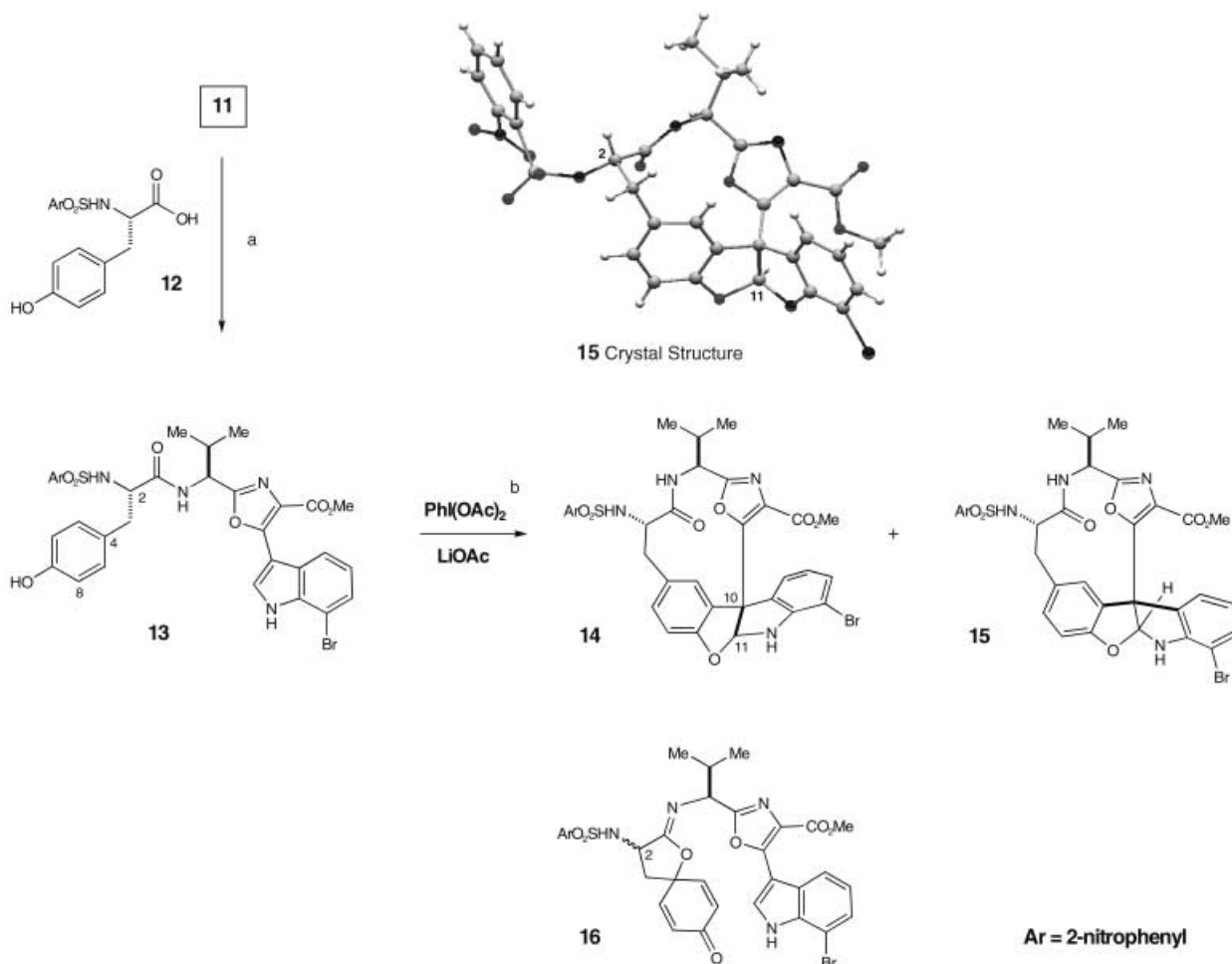
problem simplifies to central amination **4**. The dihydrobenzofuro[2,3b]indole subunit of this molecule is viewed as a remnant of oxidation. In particular, of a linear peptidyl precursor (e.g. **6**) wherein, for example, heterolytic oxidation of the phenol could initiate an annulation involving phenoxenium ion capture by the tethered indole and ring closure (as indicated) within the resultant cyclohexadienone-linked indoleninium species.<sup>[6]</sup> With respect to stereoinduction in this scheme, calculated conformational preferences for **6** (Figure 1<sup>[7]</sup>) indicate a left handedness to the display of C $\alpha$  substituents in its dipeptide segment. To the extent that these computations and, for that matter ground state conformational preference, would be predictive<sup>[8]</sup>—an electron deficient

intermediate generated from the phenol would situate itself beneath (as shown in Figure 1) the indole unit as they approached within the bonding distance. Kinetic C10 stereochemistry in **5** would thus reflect whether nucleophilic attack (by the indole at its 3-position<sup>[9]</sup>) had occurred from *s-cis* rotamer **8** or its *trans* counterpart **7**; the former producing a desired result. While our ability to predict such a preference was limited, the construction itself could be evaluated readily.

An oxidation substrate was synthesized beginning with racemic 7-bromotryptophan methyl ester<sup>[10]</sup> (Scheme 1). Treatment of this material with the acid chloride derived from N-Z-[L]-Val-OH<sup>[11]</sup> provided an epimeric mixture of dipeptides **10**. Yonemitsu oxidation<sup>[12]</sup> of the mixture gave one 3-oxazoylindole product whose carbamate then degraded in HBr/AcOH to give crystalline amine salt **11**. Condensation of **11** with L-tyrosine-derived sulfonamide **12**<sup>[13]</sup> subsequently completed the content of a diazonamide aminal (Scheme 2)—a fact made strikingly clear by the observation that adding **13** to a cold trifluoroethanol solution of PhI(OAc)<sub>2</sub> is sufficient to generate target lactam **14**—presumably through mechanistic events related to those outlined in Figure 1. As currently performed, aminal **14** is produced alongside its C10-(*R*),C11-(*S*) diastereoisomer **15** ( $\approx$  3:1 favoring **14**<sup>[14]</sup>)



**Scheme 1.** Reaction conditions: a) N-Z-[L]-Val-OH, 1-chloro-N,N-dimethyl-1-propen-1-amine, CH<sub>2</sub>Cl<sub>2</sub> then **9** (0.95 equiv), py (2.0 equiv), 0°C (76%). b) DDQ (2.3 equiv), THF, 70°C, 2 h (90%). c) 33% HBr in glacial AcOH, room temperature, 10 min (94%). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, py = pyridine.

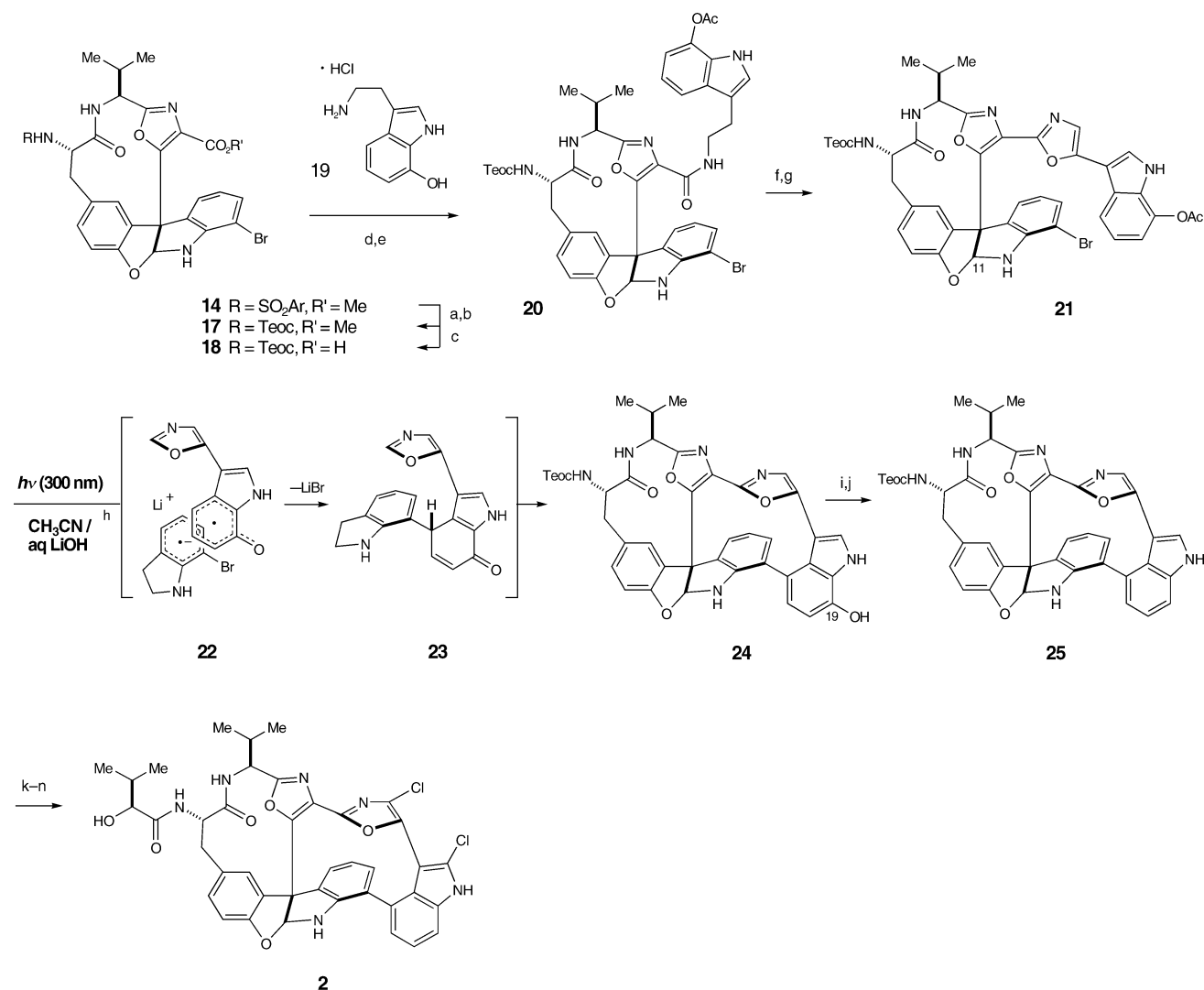


**Scheme 2.** Reaction conditions: a) TBTU, (*i*Pr)<sub>2</sub>NEt, DMF, room temperature (91%). b) PhI(OAc)<sub>2</sub> (1.1 equiv), LiOAc (2.0 equiv), 2,2,2-trifluoroethanol, inverse addition, -20°C, 10 min. (20–25% **14**, 7–8% **15**, ~15% **16** (1:1)). TBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

and comparable amounts of epimeric spirodienones **16**.<sup>[15]</sup> Notably, C2-epi-**13** (derived from D-tyrosine) does not cyclize similarly nor does **16** convert to **14/15** when resubjected to the reaction conditions. These data are consistent with the (**14**+**15**)/**16** ratio being a result of kinetic competition between nucleophilic attack at C8 and C4 of an intervening phenoxenium ion.<sup>[16]</sup> Populated conformations of **13** evidently permit macrolactam formation to compete<sup>[17]</sup> with an ostensibly favored, more conventional medium-ring spiroannulation manifold. The latter has been exploited in various contexts following Kita's seminal demonstrations of the method.<sup>[18]</sup>

The above five-step synthesis of **14** quickly moved our effort to its advanced stages. Three functional group manipulations<sup>[19]</sup> prepared the molecule to serve as an acylating agent for 7-hydroxytryptamine **19**.<sup>[20]</sup> Condensation of **17** and **19**, acetylation of the product, and a two-step benzylic

oxidation/cyclodehydration sequence<sup>[2,21]</sup> afforded bis(oxa-zoyl)indole **21** (Scheme 3). Compound **21** was then dissolved in aqueous CH<sub>3</sub>CN that contained LiOH and allowed to stand for 20 minutes. The resultant lithium phenoxide solution was degassed and photolyzed (Rayonet, 300 nm) to produce biaryl **24** (single atropdiastereomer) in good yield. This result is a significant improvement over our earlier D/E biaryl bond synthesis.<sup>[2]</sup> As in that photochemistry, we rationalize the chemistry in terms of photoinduced electron transfer<sup>[22]</sup> between the indole chromophore and the adjacent bromoarene—leading initially to a radical ion pair capable of mesolytic elimination of bromide. The incipient biradical can then internally collapse and the resultant indolenone (**23**) tautomerize to generate **24**. Additional electron density in the indole subunit benefits the process tremendously, in fact, more than enough to justify bringing an otherwise superfluous



**Scheme 3.** Reaction conditions: a) PhSH, Na<sub>2</sub>CO<sub>3</sub>, DMF, room temperature. b) Teoc-Cl, CH<sub>2</sub>Cl<sub>2</sub>, aqueous K<sub>2</sub>CO<sub>3</sub> (80%—2 steps). c) LiOH, aqueous MeOH (99%). d) **19** (1.1 equiv), TBTU, (iPr)<sub>2</sub>NEt (2 equiv), DMF, (91%). e) Ac<sub>2</sub>O, py, CH<sub>2</sub>Cl<sub>2</sub>/THF (95%). f) DDQ (2.2 equiv), 9:1 THF/H<sub>2</sub>O (86%). g) PPh<sub>3</sub>, (CCl<sub>3</sub>)<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 15 min (55%). h) *hν* (300 nm), 3.0 mM in argon-purged CH<sub>3</sub>CN/H<sub>2</sub>O (3:1) that contained LiOH (2 equiv), room temperature, 3 h (72%). i) 4-nitrophenyltriflate, K<sub>2</sub>CO<sub>3</sub>, DMF (87%). j) 20% Pd(OH)<sub>2</sub>/C, 1 atm H<sub>2</sub>, EtOAc/MeOH, room temperature (96%). k) diallyldicarbonate, Et<sub>3</sub>N, THF, room temperature; add Teoc-Cl, Et<sub>3</sub>N, room temperature; add [Pd(PPh<sub>3</sub>)<sub>4</sub>] (5 mol%), morpholine (5 equiv), 0°C, 20 min (78% overall). l) 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (2.5 equiv), DMF, room temperature, 24 h (30–50%). m) (Me<sub>2</sub>N)<sub>3</sub>SSiMe<sub>3</sub>F<sub>2</sub> (5 equiv), DMF, room temperature (95%). n) (S)-α-hydroxy isovaleric acid (1.1 equiv), (EtO)<sub>2</sub>P(O)CN, N-methylmorpholine, THF, room temperature (90%).

substituent into the synthesis. After reductive removal of this spectator phenol (at C19, through its triflate<sup>[23]</sup>), the molecule was differentially acylated, carefully chlorinated on its right periphery with perchloro-2,4-cyclohexadien-1-one,<sup>[24]</sup> and treated with tris(dimethylamino)sulfur trimethyl difluorosilicate<sup>[25]</sup> to afford desbromo diazonamide B. Phosphoryl cyanide-mediated condensation with commercial (*S*)- $\alpha$ -hydroxy isovaleric acid then delivered (–)-diazonamide **2**. Synthetic **2** has identical spectroscopic characteristics and co-elutes with a sample of natural material<sup>[26]</sup> when a pre-mixture is analyzed by LC/MS.

The synthesis of (–)-diazonamide A described herein converges on the target from five segments in a total of 19 operations (longest linear sequence is nine steps). We have evidence that **2** blocks mitotic cell division by an unprecedented mechanism<sup>[27]</sup> and this preparation will provide sufficient material and derivatives to explore diazonamide pharmacology in depth.

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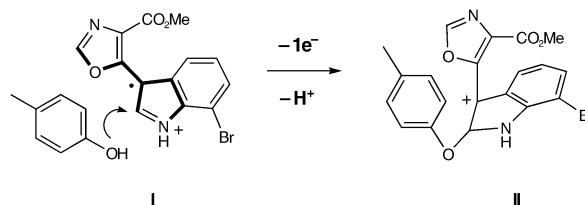
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- [14] C11 stereochemistry, relative to C10, is governed by geometry. Only two *cis*-fused dihydrobenzofuro[2,3b] indole diastereomers are formed. C10-(*R*), C11-(*S*) diastereomer **15** has been characterized by X-ray diffraction (Scheme 2). CCDC-218220 (**15**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).
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