Natural Product Synthesis

A Concise and Flexible Total Synthesis of (−)-Diazonamide A**

*Anthony W. G. Burgett, Qingyi Li, Qi Wei, and Patrick G. Harran**

Diazonamide A is a potently antimitotic natural product whose structure was originally assigned as polycycle **1** (Figure 1).[1] We recently synthesized this material—only to discover that **1** is neither a natural substance nor, in fact, stable.[2] A reinterpretation of published spectroscopic and X-ray crystallographic data led to the proposal that diazonamide A was actually hydroxy isovaleramide-containing aminal **2**.[3] This revision has been recently confirmed through synthesis.[4] 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

[*] Prof. P. G. Harran, A. W. G. Burgett, Q. Li, Q. Wei
Department of Biochemistry
University of Texas
Southwestern Medical Center at Dallas
Dallas, TX 75390-9038 (USA)
Fax: (+1) 214-648-6455
E-mail: pharra@biochem.swmed.edu

[**] Funding provided by the NIH (RO1-GM60591), the Howard Hughes Medical Institute, the Robert A. Welch Foundation, and unrestricted research awards from AstraZeneca, Eli Lilly, and Pfizer are gratefully acknowledged. P.H. is a fellow of the Alfred P. Sloan Foundation. A.B. thanks the medicinal chemistry section of the ACS for a predoctoral fellowship (sponsor: Aventis Pharmaceuticals). We are indebted to Dr. Nigam Rath (University of Missouri at St. Louis) for his crystallographic analysis of aminal **15**.

 DOI: 10.1002/ange.200352577

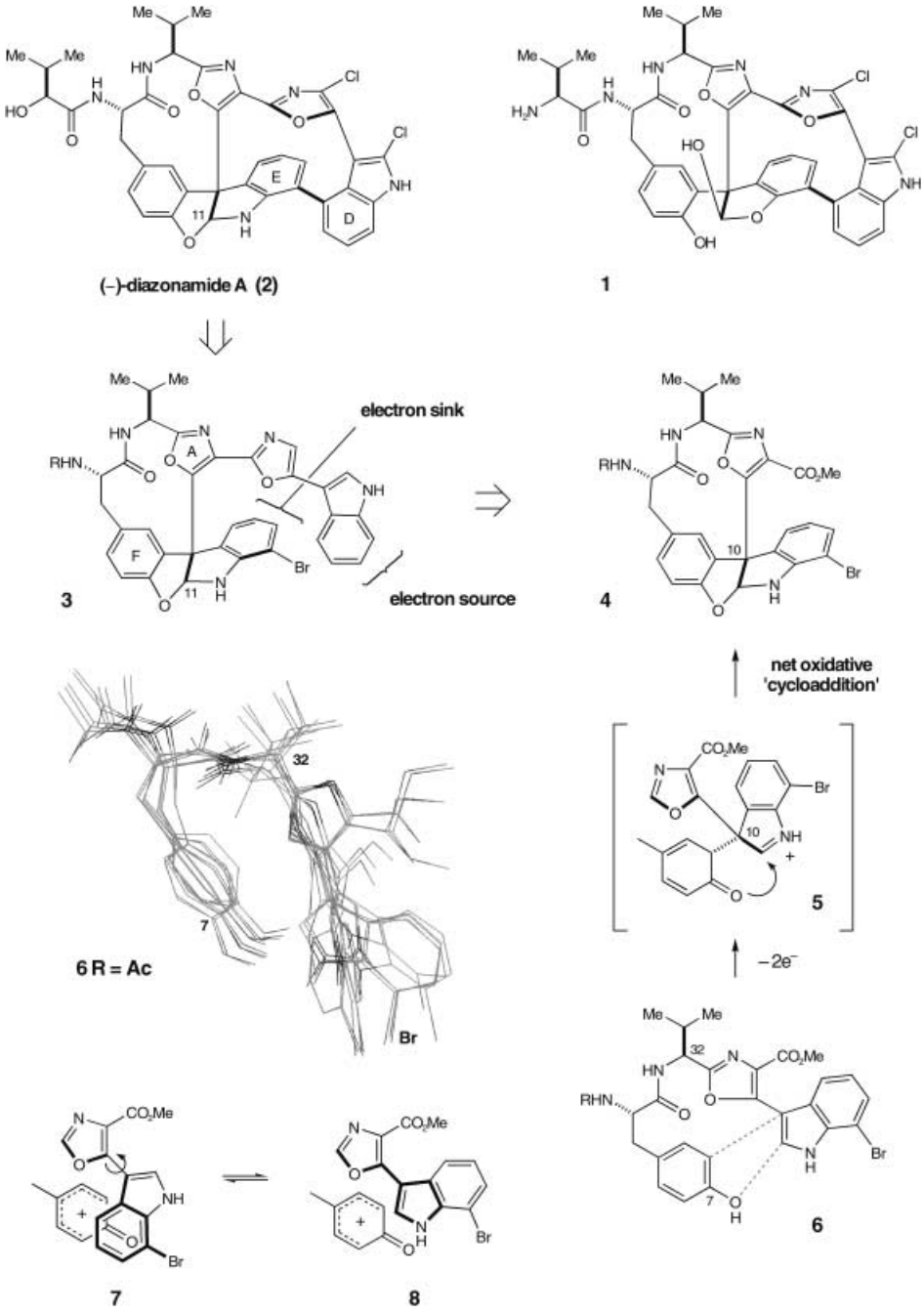


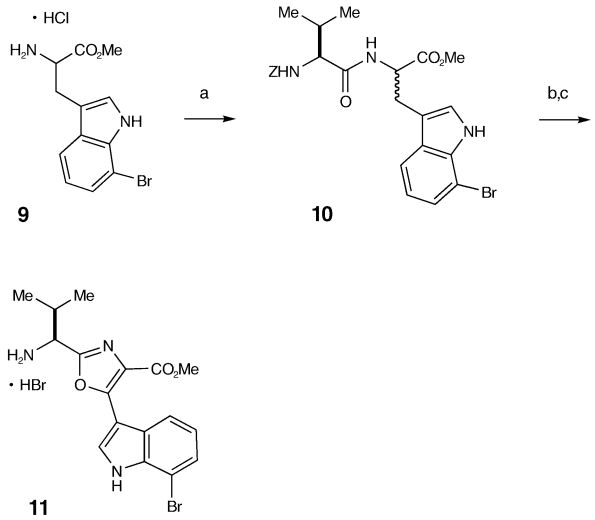
Figure 1. Diazonamide A structure and primary retrosynthesis.

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

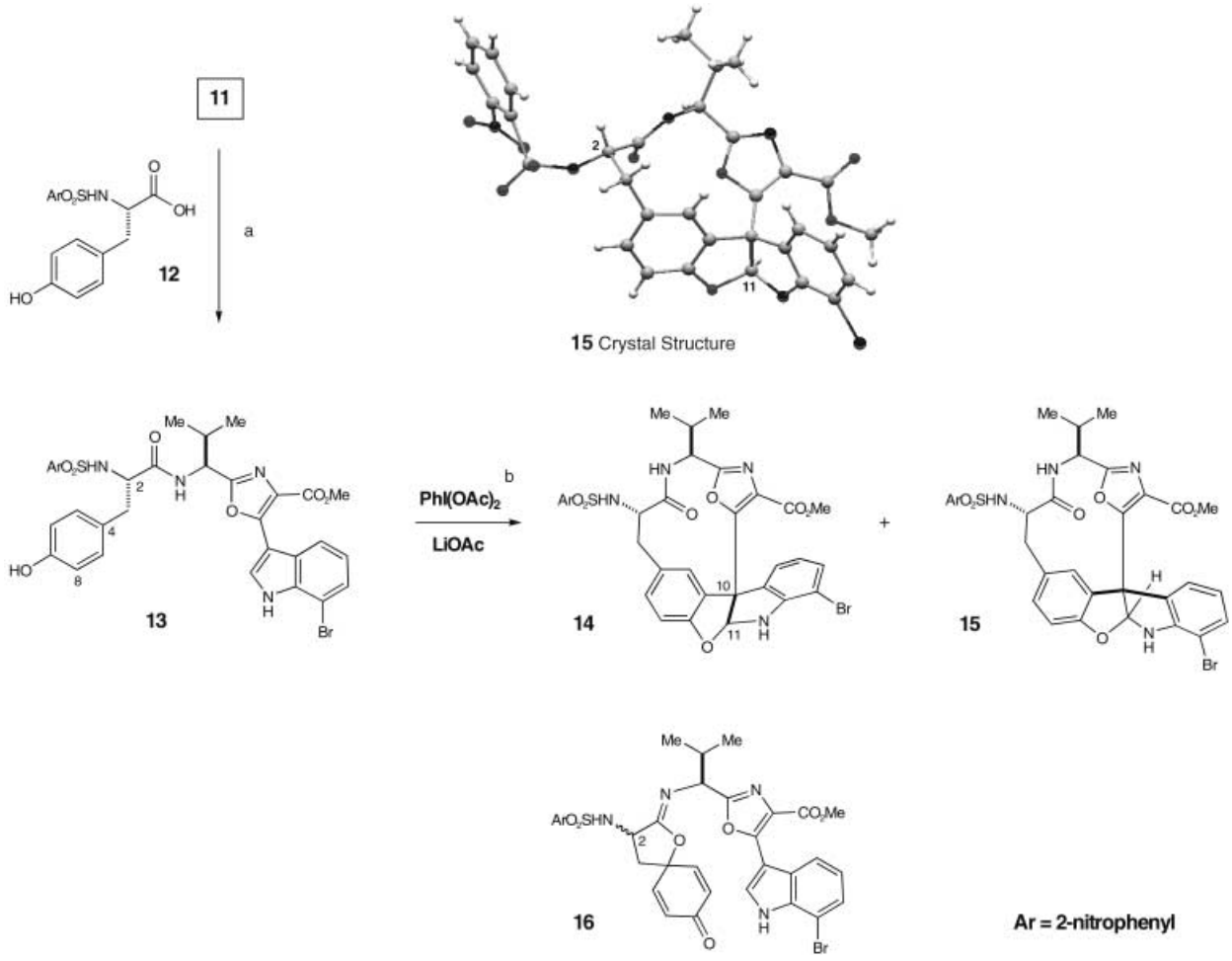
Lessons learned from earlier work proved valuable. Peripheral halogenation and acyl substitution can be installed late on a diazonamide core. In addition, we knew that potentially complicating issues of atropisomerism[5] during assembly of this core could be avoided by forming the D/E biaryl bond intramolecularly 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.[2] From **3**, the problem simplifies to central aminal **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.[6] With respect to stereoinduction in this scheme, calculated conformational preferences for **6** (Figure 1[7]) indicate a left handedness to the display of Cα substituents in its dipeptide segment. To the extent that these computations and, for that matter ground state conformational preference, would be predictive[8]—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[9]) 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[10] (Scheme 1). Treatment of this material with the acid chloride derived from N-Z-[L]-Val-OH[11] provided an epimeric mixture of dipeptides **10**. Yonemitsu oxidation[12] 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**[13] 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 $PhI(OAc)_2$ 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** (≈3:1 favoring **14**[14])



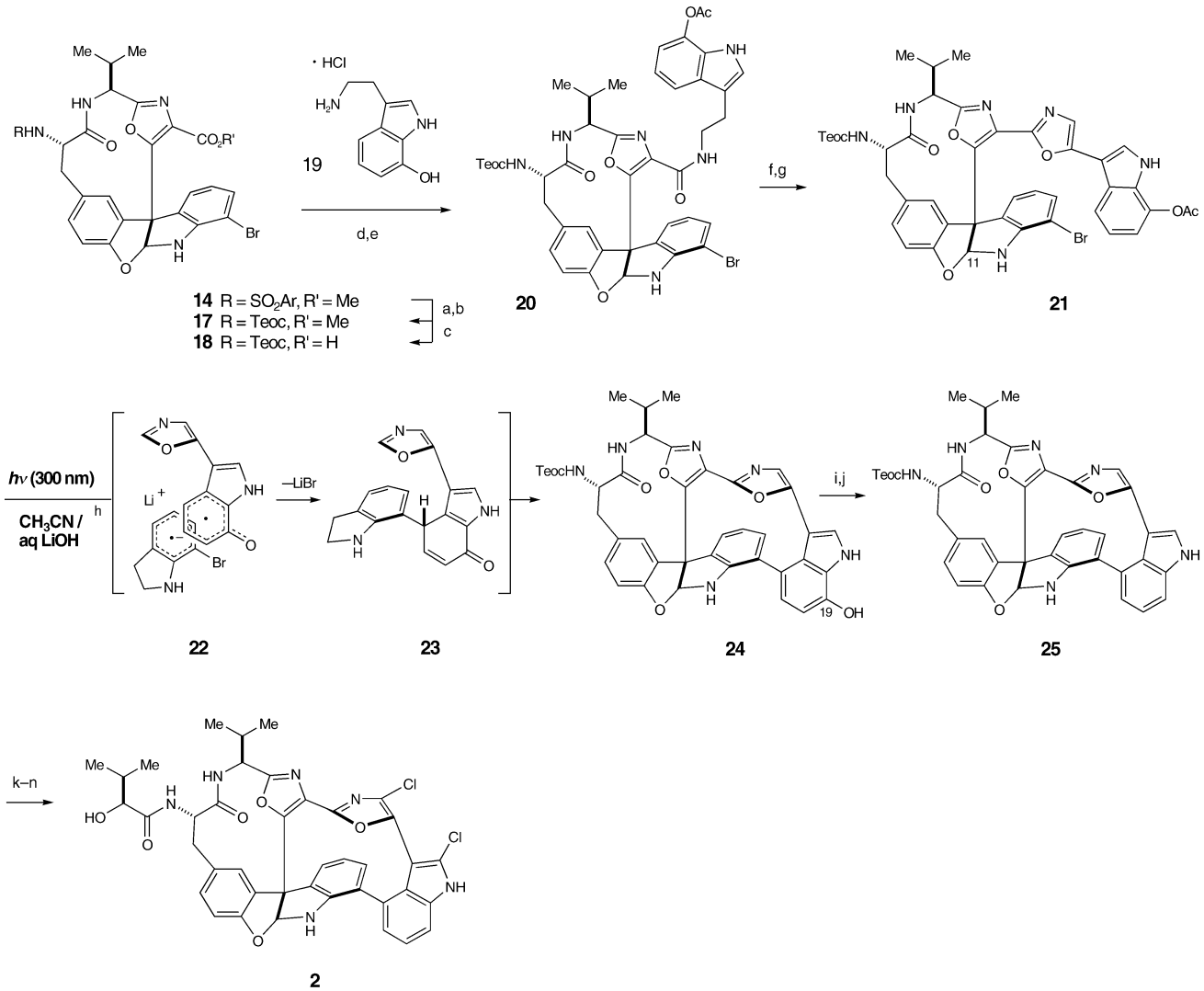
Scheme 1. Reaction conditions: a) N-Z-[L]-Val-OH, 1-chloro-*N*,*N*-2-trimethyl-1-propen-1-amine, CH_2Cl_2 then **9** (0.95 equiv), py (2.0 equiv), 0°C (76%). b) DDQ (2.3 equiv), THF, 70°C, 2 h (90%). c) 33% HBr in glacial AcOH, room temperature, 10 min (94%). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, py = pyridine.



Scheme 2. Reaction conditions: a) TBTU, $(iPr)_2NEt$, DMF, room temperature (91%). b) $PhI(OAc)_2$ (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**.[15] 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.[16] Populated conformations of **13** evidently permit macrolactam formation to compete[17] 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.[18]

The above five-step synthesis of **14** quickly moved our effort to its advanced stages. Three functional group manipulations[19] prepared the molecule to serve as an acylating agent for 7-hydroxytryptamine **19**.[20] Condensation of **17** and **19**, acetylation of the product, and a two-step benzylic oxidation/cyclodehydration sequence[2,21] afforded bis(oxazoyl)indole **21** (Scheme 3). Compound **21** was then dissolved in aqueous CH_3CN 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.[2] As in that photochemistry, we rationalize the chemistry in terms of photoinduced electron transfer[22] 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_2CO_3, DMF, room temperature. b) Teoc-Cl, CH_2Cl_2, aqueous K_2CO_3 (80%—2 steps). c) LiOH, aqueous MeOH (99%). d) **19** (1.1 equiv), TBTU, $(iPr)_2NEt$ (2 equiv), DMF, (91%). e) Ac_2O, py, CH_2Cl_2/THF (95%). f) DDQ (2.2 equiv), 9:1 THF/H_2O (86%). g) PPh_3, $(CCl_3)_2$, Et_3N, CH_2Cl_2, 15 min (55%). h) *hν* (300 nm), 3.0 mM in argon-purged CH_3CN/H_2O (3:1) that contained LiOH (2 equiv), room temperature, 3 h (72%). i) 4-nitrophenyltriflate, K_2CO_3, DMF (87%). j) 20% $Pd(OH)_2$/C, 1 atm H_2, EtOAc/MeOH, room temperature (96%). k) diallyldicarbonate, Et_3N, THF, room temperature; add Teoc-Cl, Et_3N, room temperature; add $[Pd(PPh_3)_4]$ (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) $(Me_2N)_3SSiMe_3F_2$ (5 equiv), DMF, room temperature (95%). n) (*S*)-α-hydroxy isovaleric acid (1.1 equiv), $(EtO)_2P(O)CN$, *N*-methylmorpholine, THF, room temperature (90%).

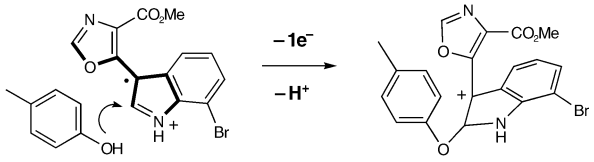
substituent into the synthesis. After reductive removal of this spectator phenol (at C19, through its triflate[23]), the molecule was differentially acylated, carefully chlorinated on its right periphery with perchloro-2,4-cyclohexadien-1-one,[24] and treated with tris(dimethylamino)sulfur trimethyldifluorosilicate[25] to afford desbromo diazonamide B. Phosphoryl cyanide-mediated condensation with commercial (*S*)-α-hydroxy isovaleric acid then delivered (−)-diazonamide **2**. Synthetic **2** has identical spectroscopic characteristics and co-elutes with a sample of natural material[26] 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[27] and this preparation will provide sufficient material and derivatives to explore diazonamide pharmacology in depth.

Received: August 6, 2003 [Z52577]
Published Online: September 30, 2003

Keywords: antimitotic agents · natural products · oxidation · photochemistry · total synthesis

[1] a) N. Lindquist, W. Fenical, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 2303 – 2304; b) N. Lindquist, Ph.D. thesis, University of California San Diego (USA), **1989**.
[2] J. Li, S. Jeong, L. Esser, P. G. Harran, *Angew. Chem.* **2001**, *113*, 4901 – 4904; *Angew. Chem. Int. Ed.* **2001**, *40*, 4765 – 4770.
[3] J. Li, A. W. G. Burgett, L. Esser, C. Amezcua, P. G. Harran, *Angew. Chem.* **2001**, *113*, 4905 – 4909; *Angew. Chem. Int. Ed.* **2001**, *40*, 4770 – 4773.
[4] a) K. C. Nicolaou, P. Bheema Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y.-K. Chen, S. A. Snyder, *Angew. Chem.* **2003**, *115*, 1795 – 1800; *Angew. Chem. Int. Ed.* **2003**, *42*, 1753 – 1758; b) K. C. Nicolaou, M. Bella, D. Y.-K. Chen, X. Huang, T. Ling, S. A. Snyder, *Angew. Chem.* **2002**, *114*, 3645 – 3649; *Angew. Chem. Int. Ed.* **2002**, *41*, 3495 – 3499; c) For a review of efforts aimed at diazonamide synthesis (through 2001) see: T. Ritter, E. M. Carreira, *Angew. Chem.* **2002**, *114*, 2601 – 2606; *Angew. Chem. Int. Ed.* **2002**, *41*, 2489 – 2494; More recent contributions include: d) T. Sawada, D. E. Fuerst, J. L. Wood, *Tetrahedron Lett.* **2003**, *44*, 4919 – 4921; e) I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216 – 4219; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082 – 4085.
[5] a) E. Vedejs, M. A. Zajac, *Org. Lett.* **2001**, *3*, 2451 – 2454; b) K. C. Nicolaou, S. A. Snyder, K. B. Simonsen, A. E. Koumbis, *Angew. Chem.* **2000**, *112*, 3615 – 3620; *Angew. Chem. Int. Ed.* **2000**, *39*, 3473 – 3478.
[6] Ring closure in **5** could also occur via its phenol tautomer.
[7] Geometry optimization of **6** (R = Ac) was performed by using the Amber force field within Macromodel v7.0 (Schrödinger). The result was subjected to a Monte Carlo molecular dynamics simulation. Figure 1 depicts rigid superimposition of the ten lowest energy conformations calculated from this exercise.
[8] J. I. Seeman, *Chem. Rev.* **1983**, *83*, 83 – 134.
[9] a) A. H. Jackson, A. E. Smith, *Tetrahedron* **1968**, *24*, 403 – 413; b) A. H. Jackson, B. Naidoo, P. Smith, *Tetrahedron* **1968**, *24*, 6119 – 6129.
[10] Prepared in two steps from 7-bromoindole and methyl 3-bromopyruvate oxime. See: a) Y. Konda-Yamada, C. Okada, K. Yoshida, Y. Umeda, S. Arima, N. Sato, T. Kai, H. Takayanagi, Y. Harigaya, *Tetrahedron* **2002**, *58*, 7851 – 7861; b) D. E. Davies, T. L. Gilchrist, T. G. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1275 – 1280; c) T. F. Jamison, Ph.D. thesis, Harvard University, **1997**.
[11] U. Schmidt, M. Kroner, U. Beutler, *Synthesis* **1988**, 475 – 477.
[12] Y. Oikawa, T. Yoshioka, K. Mohri, O. Yonemitsu, *Heterocycles* **1979**, *12*, 1457 – 1462.
[13] Prepared from L-tyrosine methyl ester hydrochloride in two steps: 1) 2-nitrophenylsulfonyl chloride, pH 9.0 phosphate buffer/CH_2Cl_2; 2) KOH, aq MeOH (70 %—2 steps).
[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 (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
[15] Analytical HPLC analyses of crude oxidation mixtures show that **14, 15**, and epimers **16** are formed in the ratio 3:1:0.7:0.7. Spirodienones **16** can be purified by preparative HPLC (C_{18}, CH_3CN/H_2O gradient) but partially degrade during flash chromatography on silica gel.
[16] L. Kürti, P. Herczegh, J. Visy, M. Simonyi, S. Antus, A. Pelter, *J. Chem. Soc. Perkin Trans. 1* **1999**, 379 – 380.
[17] We are mindful of another explanation. It is possible that **14** and **15** form as a result of an indolic oxidation. The (**14** + **15**)/**16** ratio may actually reflect two separate pathways operating rather than bifurcation through a common intermediate. For example, one electron oxidation of the indole subunit in **13** would produce a radical cation (e.g. **I**). This species could trap the tethered phenol, relinquish a second electron (to either I^{III} or I^{II}) and the



I **II**

resultant ion (**II**) undergo an internal Friedel-Crafts type alkylation to afford **14**/**15**. While experiments to test these ideas are ongoing, we do note examples of I^{III} oxidations for which related mechanisms might be invoked: a) Y. Kishi, S. Nakatsuka, T. Fukuyama, M. Havel, *J. Am. Chem. Soc.* **1973**, *95*, 6493 – 6495; b) N. A. Braun, M. Ousmer, J. D. Bray, D. Bouchu, K. Peters, E.-M. Peters, M. A. Ciufolini, *J. Org. Chem.* **2000**, *65*, 4397 – 4408.
[18] a) Y. Kita, H. Tohma, K. Kikuchi, M. Inagaki, T. Yakura, *J. Org. Chem.* **1991**, *56*, 435 – 438; b) Y. Tamura, T. Yakura, J. Haruta, Y. Kita, *J. Org. Chem.* **1987**, *52*, 3927 – 3930; c) P. Wipf, Y. Kim, *Tetrahedron Lett.* **1992**, *33*, 5477 – 5480; d) G. Scheffler, H. Seike, E. J. Sorensen, *Angew. Chem.* **2000**, *112*, 4783 – 4785; *Angew. Chem. Int. Ed.* **2000**, *39*, 4593 – 4596.
[19] Cleavage of the 2-nitrophenylsulfonamide: T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373 – 6374.
[20] Prepared just prior to use by hydrogenolyzing commercial 7-benzyloxy tryptamine (Biosynth AG, Switzerland) over $Pd(OH)_2/C$ (1 equiv ethereal HCl, EtOH, 1 atm H_2, >95 % yield).
[21] P. Wipf, F. Yokokawa, *Tetrahedron Lett.* **1998**, *39*, 2223 – 2226.
[22] a) O. Yonemitsu, P. Cerutti, B. Witkop, *J. Am. Chem. Soc.* **1966**, *88*, 3941 – 3945; b) H. G. Theuns, H. B. M. Lenting, C. A. Salemink, H. Tanaka, M. S. Shibata, K. Ito, R. J. J. C. Lousberg,

Heterocycles **1984**, *22*, 2007 – 2011; c) J. Mattay, *Synthesis* **1989**, 233 – 252.
[23] A. P. Kozikowski, W. Tuckmantel, C. George, *J. Org. Chem.* **2000**, *65*, 5371 – 5381.
[24] A. Guy, M. Lemaire, J.-P. Guetté, *Tetrahedron* **1982**, *38*, 2339 – 2346.
[25] a) W. R. Roush, D. S. Coffey, D. J. Madar, *J. Am. Chem. Soc.* **1997**, *119*, 11331 – 11332; b) R. Noyori, I. Nishida, J. Sakata, M. Nishizawa, *J. Am. Chem. Soc.* **1980**, *102*, 1223 – 1225.
[26] We are grateful to Professor William Fenical (Scripps Oceanographic Institute) for a generous gift of natural (−)-diazonamide A.
[27] G. Wang, A. W. G. Burgett, X. Wang, P. G. Harran, unpublished results.

