In summary, BDA desymmetrized glycolic acid has proved to be an interesting reagent in one-pot, consecutive, three- and four-component coupling reactions. Highly functionalized α-hydroxy acid derivatives are obtained in good yields and with high diastereoselectivities from simple and readily available starting materials. The simplicity of the method should allow the synthesis of large libraries of compounds with potential biological activity in an easy, fast, clean, and efficient way. Investigations along these lines as well as on the mechanisms of the reactions and the applications of this methodology in the synthesis of natural products are underway in our laboratories.

Experimental Section

Representative procedure for the preparation of **7**: A solution of lithium hexamethyldisilazide in THF (1M, 0.20 mL, 0.20 mmol) was added dropwise to a solution of **1** (0.038 g; 0.20 mmol) in THF (0.5 mL) at $-78\,°C$. The resulting pale yellow solution was stirred for 10 min at the same temperature, and then a solution of coumarin **2b** (0.032 g; 0.22 mmol) in THF (0.5 mL) was added dropwise at $-78\,°C$. After 30 min, a solution of *trans* chalcone **5c** (0.045 g, 0.22 mmol) was added dropwise. The reaction mixture was stirred for a further 30 min at the same temperature, and then a solution of trimethylsilyl chloride (0.31 mL) in methanol (5 mL) was added at $-78\,°C$. The reaction mixture was warmed to room temperature overnight. The solvents were removed in vacuo to give the crude product, which was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to afford pure **7** (0.063 g, 76 %): $[\alpha]_D^{25} = +30.5$; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.75 - 6.69$ (m, 14H; ArH), 4.15 (dd, $J = 5.9$, 3.1 Hz, 1H; C*H*OH), 3.61 (s, 3H; OCH$_3$) 3.48 (d, $J = 6.6$ Hz, 2H; CH$_2$CO), 3.29 (dt, $J = 11.6$, 6.6 Hz, 1H; CHPh), 3.14 (dd, $J = 11.6$, 1.0 Hz, 1H; CHCO$_2$), 2.88 (d, $J = 3.1$ Hz, 1H; OH), 2.81 (d, $J = 5.9$ Hz, 1H; C*H*CHOH; unresolved coupling to CHCO$_2$); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 197.2$, 172.2, 169.2, 152.2, 140.6, 136.7, 133.0, 129.0, 128.4, 127.9, 127.8, 124.6, 117.7, 74.7, 52.6, 49.1, 43.5, 42.9, 39.8; HRMS (EI): calcd for C$_{27}$H$_{24}$O$_6$NNa [M+Na]$^+$: 467.1471, found: 467.1481.

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Total Synthesis of Nominal Diazonamides— Part 1: Convergent Preparation of the Structure Proposed for (−)-Diazonamide A**

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In 1991 Fenical, Clardy and co-workers reported the composition and skeletal stereochemistry of two unique toxins extracted from tissues of the marine invertebrate *Diazona angulata*.[1] The structure of the major isolate, termed diazonamide B (**1b**, Scheme 1), was given from X-ray diffraction measurements on a crystal of derived *p*-bromobenzamide **2**. The acylation of **1b** purportedly caused dehydration of its C11 hemiacetal, which leaves the configuration at this position the one noted ambiguity in an analysis that included designation of absolute stereochemistry. The core of the minor metabolite was subsequently assigned by analogy and a complete proposal (**1a**) made more consistent with available

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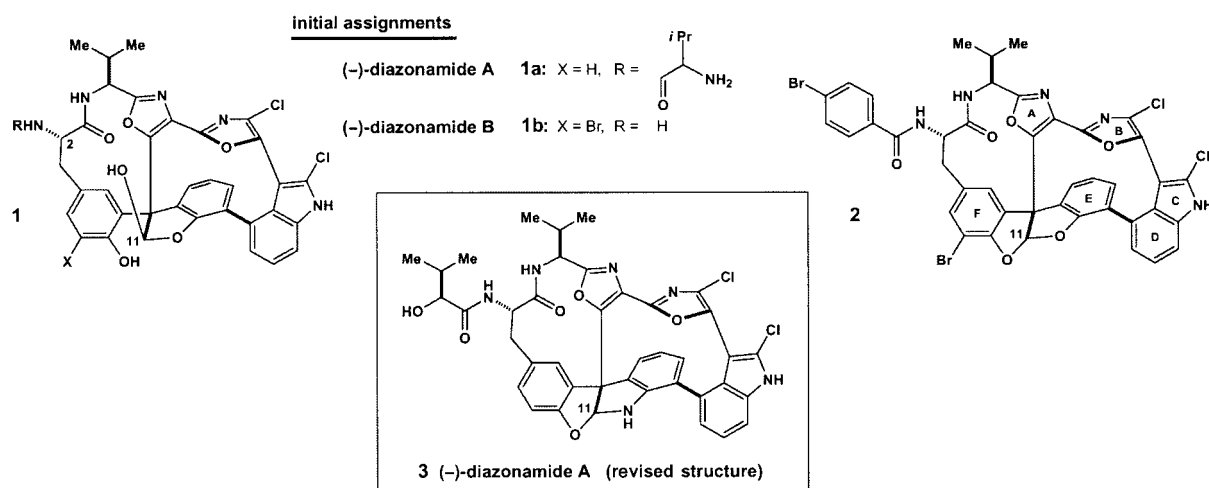
Scheme 1. Diazonamide structure: initial and revised assignments.

data by incorporation of a valine-derived C2-amine append-age (of undetermined configuration).[2] In retrospect, evi-dence argued against this specification.[3] However, in the excitement of uncovering such a remarkable new class of materials and the finding that one of them (namely, diazon-amide A) showed potent antineoplastic activity,[4] certain details were inadvertently overlooked.

In the decade since this report, diazonamide synthesis has become a topic of considerable interest. Numerous laborato-ries have taken on the architectural problem and important progress has been made in key areas.[5] Our own tactics for constructing a diazonamide ring system have likewise evolved steadily.[6] Herein we describe a culmination of these efforts with the preparation of **1a** and **2**. Our doing so makes it clear for the first time that neither is a natural product (or a derivative). Rather, new evidence suggests that the true structure of (−)-diazonamide A is L-α-hydroxyisovaleric acid conjugate **3** (Scheme 1).[3]

Key design elements in our synthesis respond to stereo-chemical challenges provided by the structure of diazon-amides. These have been described elsewhere.[6a,b] Suffice it to say that the completed effort can be broken down into five segments of comparable size, two of which are commercial products and mole quantities of the other three (**4**–**6**, Scheme 2) are readily accessible.[7] For reasons that will become apparent, the macrolactam harboring the central core of the molecule is built first. This begins by treating dibutylzirconocene[8] with α-chloro styrene **6**. The regiode-fined vinyl Zr^{IV} species (**7**, Scheme 2) putatively generated in situ is then cross-coupled with bromide **5** in a process catalyzed by palladium to afford 1,1-disubstituted ethylene **8**. Notably, this variant of Takahashi's modification[9] of a Negishi coupling neither requires nor benefits from a Zr-to-Zn transmetalation prior to addition of the electrophile. The protecting groups on **8** are subsequently removed and the amine produced (**9**) is condensed with tyrosine derivative **4** to afford modified dipeptide **10**. When **10** is exposed to catalytic Pd^0 in the presence of Ag$_3$PO$_4$, cyclic triarylethylene **12** is formed at 75 °C (Scheme 3). This Heck endocyclization is pivotal[10] in that **12** has the content of a diazonamide core and
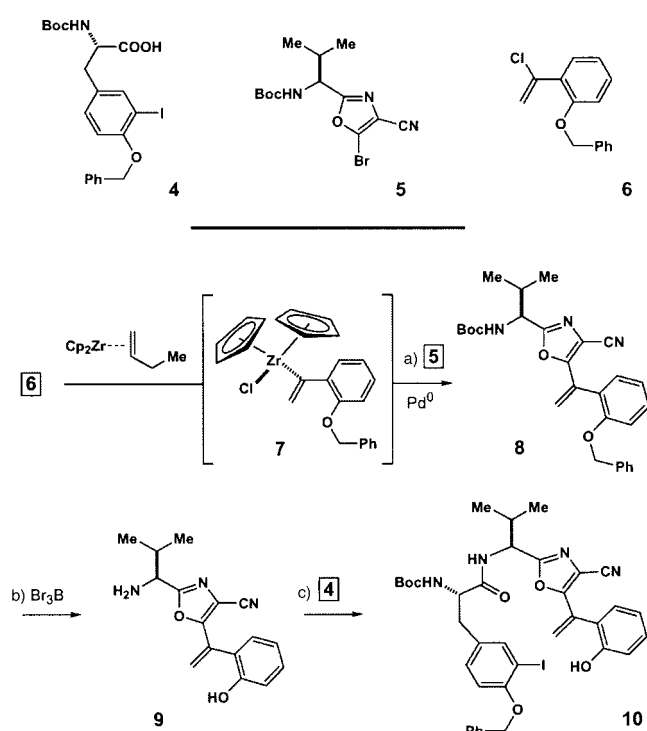
Scheme 2. Reaction conditions: a) [Cp$_2$ZrCl$_2$], nBuLi, THF, −78 °C, then **6**, −78 °C→RT, 3 h; 3.8 mol % Pd(OAc)$_2$, 3.8 mol % P(o-tolyl)$_3$, Ag$_3$PO$_4$, **5**, RT, 8 h, (85%); b) 2.5 equiv BBr$_3$, CH$_2$Cl$_2$, −78 → −20 °C, (quant.); c) **4**, iPr$_2$NEt, TBTU, DMF, RT, (89%). Boc = tert-butoxycarbonyl; TBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoro-borate.

needs only to be oxidatively restructured to reveal this feature. After the C16 phenol is derivatized as its 2-bro-moethyl ether, oxidation is achieved by exposure to the complex formed between OsO$_4$ and (1S,2S)-N,N'-bis(3,3-dimethylbutyl)-cyclohexane-1,2-diamine (namely, **13**).[11] De-composition of incipient Os^{VI} glycolates with H$_2$S provides a 93:7 ratio of diastereomeric *syn*-glycols in which β-isomer **14** is favored—a particularly gratifying outcome for this stereo-chemically mismatched transformation.[12] With **14** in hand, its
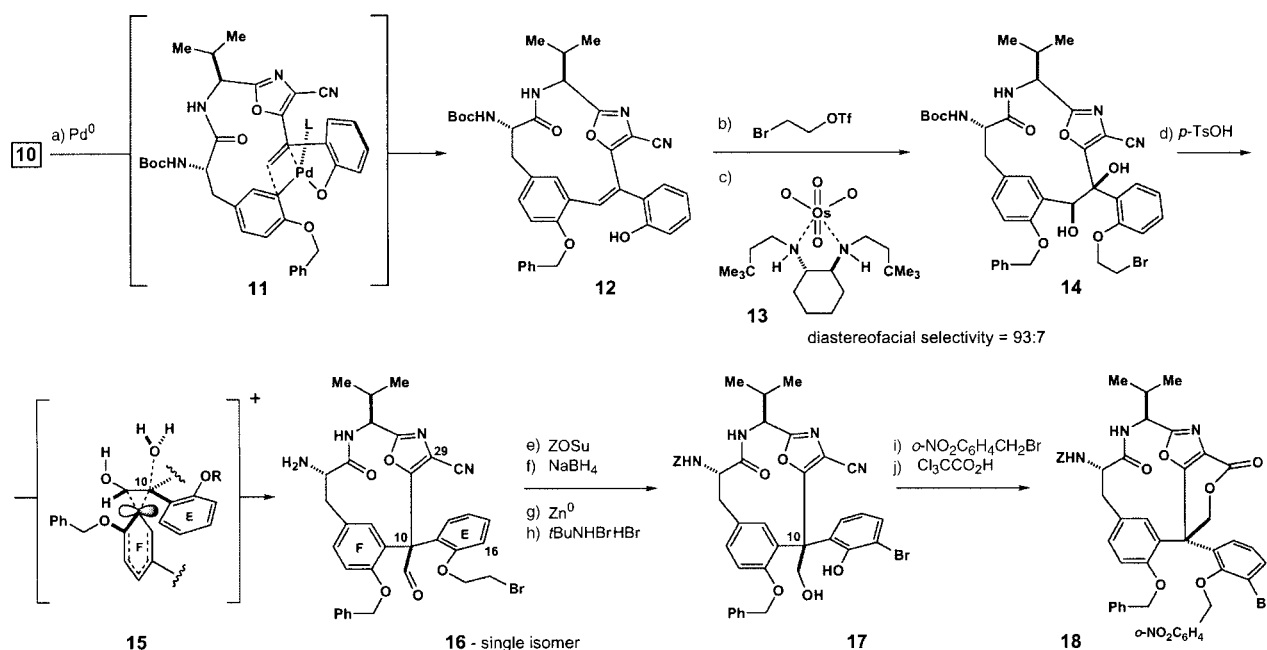
Scheme 3. Reaction conditions: a) 3 mol % [Pd$_2$(dba)$_3$], 6 mol % 2-(di-*tert*-butylphosphanyl)biphenyl, Ag$_3$PO$_4$, THF, 75 °C (82 % based on recovered **10**); b) *t*BuOK, THF, 1.2 equiv 2-bromoethyltriflate, 0 °C; c) 1.2 equiv **13**, toluene, −78 → −25 °C; H$_2$S(g), THF, −50 °C, (67 % from **12**); d) 3 × 1 equiv *p*-TsOH, toluene, 95 °C, 40 min; e) ZOSu, DMF, RT, (54 % from **14**); f) NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH; g) Rieke zinc (excess), 3:1 THF/EtOH, 0 °C, (75 % from **16**); h) *t*BuNH$_2$/Br$_2$ complex, toluene/THF/CH$_2$Cl$_2$, −78 → −20 °C, 10 h (86 %, *ortho:ortho/para* = 5:1); i) *o*-nitrobenzyl bromide, K$_2$CO$_3$, NaI, DMF, (52 %); j) 4.8 equiv Cl$_3$CCO$_2$H, 1 equiv H$_2$O, toluene, 68 °C, (90 %). dba = *trans,trans*-dibenzylideneacetone; Z = benzyloxycarbonyl; Su = *N*-succinimidyl.

restructuring takes the form of a ring-contracting pinacol rearrangement initiated with anhydrous *p*-TsOH. While efficiency is modest for the change, stereochemical communication is near perfect (presumably mediated by phenonium ion **15**)[6b] as triarylacetaldehyde **16** is produced as a single C10 diastereomer. It should be noted that the operations that convert **12** to **16** are our only deliberate stereochemical manipulations. The axial asymmetries of the diazonamide polycycle can now be made an artifact of their assembly.[13] Following carbamoylation of the C2 amine, reduction of the C10 aldehyde, and degradation of the 2-bromoethyl ether, the resultant E-ring phenol is *ortho*-brominated to afford **17**.[14] Reetherification of the more acidic nucleophile in **17** then provides a product that, when warmed with moist Cl$_3$CCO$_2$H, generates lactone **18**.

Active ester **18** is now a versatile platform on which to launch attempts at completing a target polycycle. While this goal was elusive for some time, nonproductive forays finally gave way to success. Lactone **18** is opened with dimethylaluminum amide **19** which was derived in situ from tryptamine and AlMe$_3$.[6b] The resultant δ-hydroxy amide is oxidized with *n*Pr$_4$NRuO$_4$ and the aldehyde formed (**20**) briefly photolyzed (350 nm) in dilute dioxane solution to provide a crude C11 hemiacetal (Scheme 4). Acylation of this material with Ac$_2$O affords a single diastereomer of acetate **21**.[15] A two-step oxidation/cyclodehydration[5q] protocol then parlays the acyl tryptamine segment of this molecule into bis(oxazoyl)indole **22**—a structure one-bond removed from the target ring system.

Gratifyingly, UV irradiation of degassed solutions of **22** (300 nm, 5.0 × 10^{-3} M in 3:1 CH$_3$CN/H$_2$O) results in loss of HBr and the formation of internal arylation product **25**. A

single regioisomeric biaryl (one atropdiastereomer) is isolated from this reaction although there is competing production of uncyclized materials lacking bromine. One mechanism to interpret this Witkop-type cyclization[16] invokes intramolecular photo-induced electron transfer from the indole chromophore to the adjacent bromo arene. Mesolytic elimination of bromide from the resultant radical-ion pair **23**, biradical collapse, and prototropy in 4*H*-indole **24** would give **25**. A benefit realized by including Li$^+$ ions into the medium,[17] the inability of 4-methyl-2,6-di(*tert*-butyl)phenol to inhibit the reaction, and the observation that materials chlorinated at C25 and C27 do not photocyclize similarly are consistent with this view.[18]

With **25** in hand, completion of a putative diazonamide is straightforward. The right periphery of the molecule is oxidized with *N*-chlorosuccinimide to afford dichloride **26** directly (Scheme 5).[6a] This material is then partially hydrogenolyzed and the product amine reacylated with Z-L-Val-OH. Stannoxane-catalyzed deacetylation of the acetyl hemiacetal[6a] and a final hydrogenolysis provides **1a**—the structure originally proposed for (−)-diazonamide A.[1a]

Remarkably, this material is different from a sample of natural (−)-diazonamide A,[19] particularly by qualitative measures such as its stability to handling[20] and its mobility on a thin-layer chromatography plate. The former issue is most troubling. Mass spectrometry indicates that late synthetic intermediates begin to decompose through net C10 deformylation almost immediately after unmasking a free C11 hemiacetal. The process completes upon attempted preparative HPLC purification of **1a** under conditions identical to those used to isolate natural (−)-diazonamide A.[2] In addition, a second degradation pathway available in this series
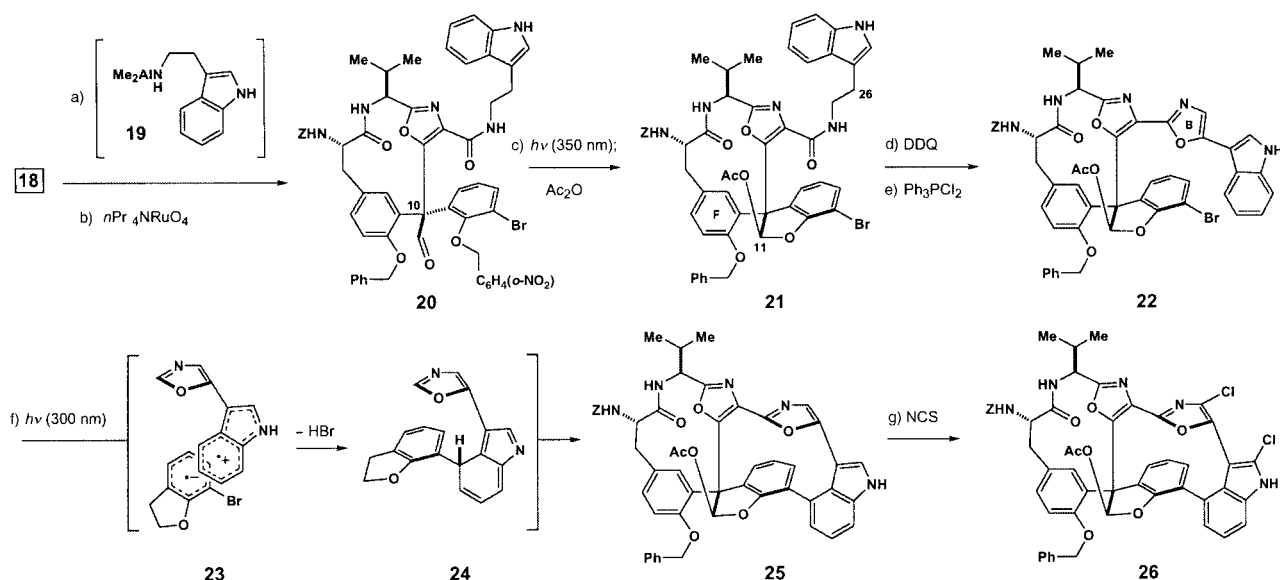
Scheme 4. Reaction conditions: a) 1.3 equiv **19**, toluene/CH$_2$Cl$_2$, 0°C →RT, (83%); b) 5 mol% nPr$_4$NRuO$_4$, 1.5 equiv NMO, 4 Å MS, CH$_2$Cl$_2$, (78%); c) $hν$ (350 nm), 0.003 M in degassed dioxane; excess Ac$_2$O, pyridine, DMAP, CH$_2$Cl$_2$, (85%); d) 2.2 equiv DDQ, 9:1 THF/H$_2$O, (89%); e) (Cl$_3$C)$_2$, Ph$_3$P, Et$_3$N, THF, (68%); f) $hν$ (300 nm), 2 equiv LiOAc, 3 equiv epichlorohydrin, 0.005 M in 3:1 CH$_3$CN/H$_2$O, (32–40%); g) 2 equiv NCS, THF, 32°C, 10 h, (60%). NMO = 4-methylmorpholine-N-oxide; DMAP = 4-dimethylaminopyridine; DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; NCS = N-chlorosuccinimide.
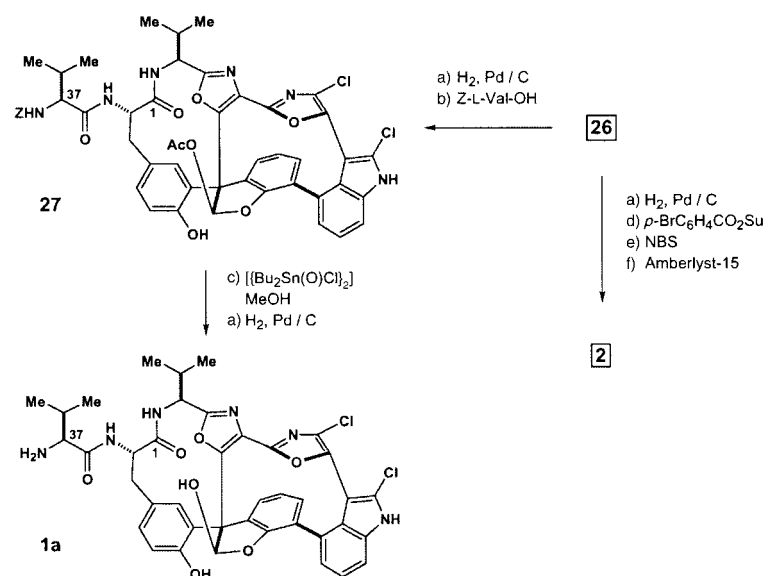
Scheme 5. Reaction conditions: a) 1 atm H$_2$, 10% Pd/C, MeOH, RT, (quant.); b) Z-L-Val-OH, TBTU, iPr$_2$NEt, DMF, (92%); c) 40 mol% [{Bu$_2$Sn(O)Cl}$_2$], toluene/MeOH 70°C, (80%); d) p-BrC$_6$H$_4$CO$_2$Su, DMF, RT, (79%); e) NBS, iPr$_2$NH, CH$_2$Cl$_2$/THF, (48%); f) Amberlyst-15, 4 Å MS, 1:4 CH$_3$CN/CH$_2$Cl$_2$ (54–85%). NBS = N-bromosuccinimide.

appears as a result of the cleavage of the strained macrolactam ring through diketopiperazine formation that involves the C37 amine and the C1 amide carbonyl.[21] These observations, and compelling spectroscopic data,[3] suggest a misassignment of the C2 amine appendage. However, this is not the whole story. We have synthesized the reported derivative of diazonamide B (**2**, Scheme 5) whose crystallographic characterization formed the basis of initial diazonamide assignments. While fully consistent with our designation, ^{1}H-NMR data for synthetic **2** is subtly different from that reported for material derived from natural (−)-diazonamide B.[2] The X-ray structure of C11 diphenyl acetal **28** (Figure 1)[22] makes it very likely that the heterocyclic skeletons shown for synthetic **1a** and **2** are correct—a result which leaves the true constitution of natural diazonamides in doubt. A solution to this puzzle requires reinterpretation of data collected on natural isolates as well as new insights. The communication directly following this one provides both.[3]

Experimental Section

2 (synthetic): $R_f = 0.72$ (35% EtOAc/benzene); $[\alpha]_D^{25} = -108.8°$ ($c = 0.32$, MeOH); IR (film): $\tilde{v} = 3281, 2965, 1660, 1651, 1644, 1538, 1479, 1063, 752$ cm^{-1}; ^{1}H NMR (400 MHz, [D$_4$]MeOH, 25°C): $\delta = 7.79$ (d, $J = 8.4$ Hz, 2H), 7.66 (d, $J = 8.4$ Hz, 2H), 7.52 (s, 1H), 7.51 (s, 1H), 7.48 (dd, $J = 0.8, 8.4$ Hz, 1H), 7.38 (app t, $J = 8.4$ Hz, 1H), 7.24 (m, 2H), 7.11 (dd, $J = 1.2, 7.6$ Hz, 1H), 6.97 (app t, $J = 7.6$ Hz, 1H), 6.93 (s, 1H), 4.99 (d, $J = 6.0$ Hz, 1H), 4.76 (dd, $J = 2.8, 12.0$ Hz, 1H), 3.60 (app t, $J = 12.0$ Hz, 1H), 2.92 (dd, $J = 3.2, 12.8$ Hz, 1H), 2.36–2.28 (sym 6-line m, 1H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, [D$_4$]MeOH, 25°C): $\delta = 174.9, 168.6, 163.4, 159.7, 156.5, 154.8, 152.9, 141.9, 139.9, 136.7, 134.5, 134.4, 133.6, 133.0, 132.7, 130.7, 130.6, 130.6, 130.2, 129.6, 129.2, 128.8, 127.5, 126.4, 125.4, 124.5, 124.17, 124.16, 122.7, 119.5, 112.5, 104.0, 98.0, 63.1, 58.4, 56.6, 37.9, 31.6, 19.5, 18.8; ES-MS: calcd for C$_{42}$H$_{27}$Br$_2$Cl$_2$N$_5$O$_6$ [M^++H]: 925.98, found: 926.04; calcd for C$_{42}$H$_{27}$Br$_2$Cl$_2$N$_5$O$_6$ [M^- − H]: 923.96, found: 923.96; HR-FAB-MS: calcd for C$_{42}$H$_{27}$Br$_2$Cl$_2$N$_5$O$_6$ [M^++Li]: 931.9865, found: 931.9878.

27: $R_f = 0.25$ (50% EtOAc/benzene); $[\alpha]_D^{25} = -211.8°$ ($c = 0.40$, MeOH); IR (film): $\tilde{v} = 3270, 2966, 1766, 1658, 1651, 1514, 1205, 1048, 754$ cm^{-1}; ^{1}H NMR (400 MHz, [D$_4$]MeOH, 25°C): $\delta = 8.75$ (s, 1H), 7.43 (d, $J = 8.0$ Hz, 1H) 7.38–7.30 (m, 6H), 7.15 (d, $J = 7.6$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 6.84–6.75 (m, 4H), 6.54 (d, $J = 1.2$ Hz, 1H), 5.11 (s, 2H), 4.50 (dd, $J = 2.4, 11.2$ Hz, 1H), 4.47 (d, $J = 8.8$ Hz, 1H), 3.97 (d, $J = 6.8$ Hz, 1H), 3.22 (app t, $J = 12.8$ Hz, 1H), 2.66 (dd, $J = 2.4, 12.8$ Hz, 1H), 2.08–1.98 (m, 2H), 1.84 (s, 3H), 1.07 (d, $J = 6.4$ Hz, 3H), 0.96–0.93 (m, 9H); ^{13}C NMR (75 MHz, [D$_4$]MeOH, 25°C): $\delta = 173.5, 172.3, 169.0, 163.8, 157.4, 156.5, 154.1, 154.0,$
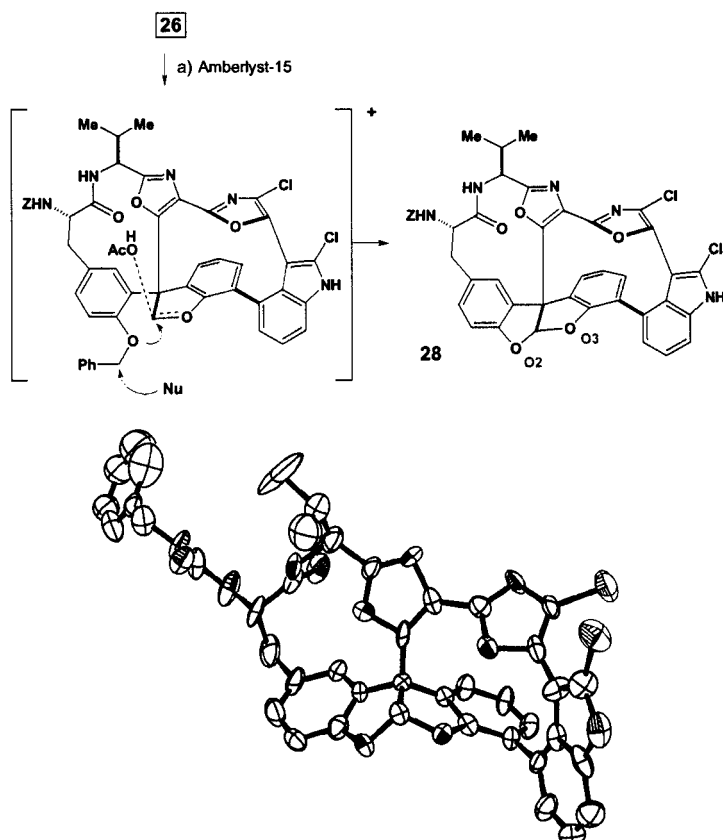
Figure 1. Preparation and X-ray structure (ORTEP; 30% probability thermal ellipsoids) of diphenyl acetal **28**. a) Amberlyst-15, 4 Å MS, 1:4 CH_3CN/CH_2Cl_2.

153.8, 140.9, 137.0, 135.3, 133.5, 132.2, 130.0, 129.1, 128.3, 127.9, 127.8, 127.8, 127.7, 127.1, 126.5, 126.3, 126.0, 124.2, 123.4, 122.8, 122.7, 121.6, 121.3, 117.1, 110.8, 100.7, 97.5, 66.5, 60.7, 59.2, 56.7, 55.2, 37.0, 31.1, 30.2, 19.4, 19.1, 18.4, 18.2, 17.5; ES-MS: calcd for $C_{50}H_{44}Cl_2N_6O_{10}$ $[M^++H]$: 959.26, found: 959.25; calcd for $C_{50}H_{44}Cl_2N_6O_{10}$ $[M^--H]$: 957.24, found: 957.26.

1a: $R_f = 0.10$ (10% $MeOH/CH_2Cl_2$); ^1H NMR (major C11 epimer; 400 MHz, $[D_6]DMSO$, 25°C): $\delta = 9.77$ (s, 1H), 8.95 (d, $J = 6.4$ Hz, 1H), 8.26 (br s, 1H), 7.86 (d, $J = 5.6$ Hz, 1H), 7.58 (d, $J = 5.6$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 1H), 7.31 (app t, $J = 8.0$ Hz, 1H), 7.10 (d, $J = 7.2$ Hz, 1H), 7.20 (dd, $J = 1.3, 8.0$ Hz, 1H), 6.78 (d, $J = 8.4$ Hz, 1H), 6.73 (dd, $J = 2.0, 6.8$ Hz, 1H), 6.66–6.62 (m, 2H), 6.34 (d, $J = 1.3$ Hz, 1H), 4.47 (app t, $J = 8.4$ Hz, 1H), 4.38 (dd, $J = 6.4, 8.4$ Hz, 1H), 3.16 (br s, 1H), 3.04 (app t, $J = 12.0$ Hz, 1H), ≈ 2.48 (1H; obscured by residual solvent signal), 1.91–1.96 (m, 2H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 7.2$ Hz, 3H), 0.82 (d, $J = 7.2$ Hz, 3H); ES-MS: calcd for $C_{40}H_{36}Cl_2N_6O_7$ $[M^++H]$: 783.21, found: 783.31; calcd for $C_{40}H_{36}Cl_2N_6O_7$ $[M^--H]$: 781.20, found: 781.25; HR-FAB-MS: calcd for $C_{40}H_{36}Cl_2N_6O_7$ $[M^++Li]$: 789.2183, found: 789.2198.

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[12] An intrinsic facial bias in this ring system leads to undesired *syn-α*-glycolate stereochemistry (d.r. $\approx 6:1$) upon stoichiometric dioxyosmylation with OsO_4/p-(dimethylamino) pyridine in THF solvent.

[13] It is possible to assign stereochemistry to each of the three chiral biaryl axes in **1a**. In principle, the structure could exist in 2^3 atropdiastereomeric forms. However, geometry dictates that six of these are prohibitively high in energy. When assembled, only the ring network depicted and its enantiomer are relevant. Our synthetic pathway selects for one.

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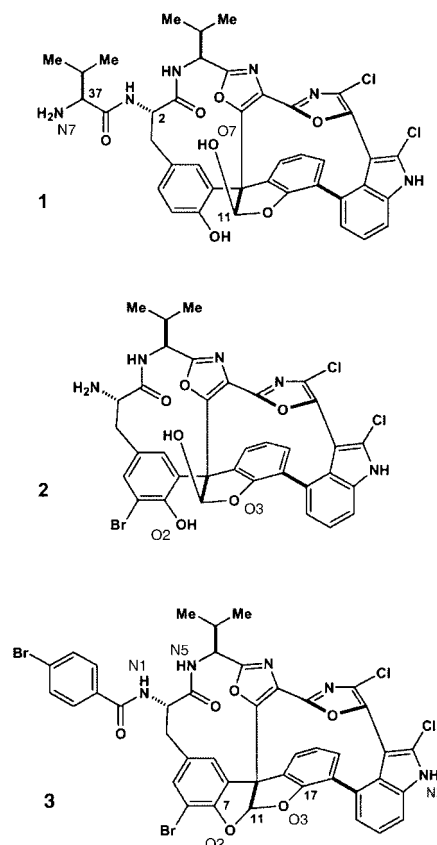
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[18] A non-chain radical mechanism that involves C16−Br bond homolysis and intramolecular addition of the resultant aryl radical to the indole nucleus cannot, at this point, be ruled out.

[19] We are grateful to Professor William Fenical (Scripps Institute of Oceanography) for a generous gift of natural (−)-diazonamide A.

[20] Synthetic **1a** appears (¹H NMR) as an ≈4:1 mixture of C11 epimers. However, unpredictable degradation prevents detailed characterization of these materials. Protected derivative **27** is serviceable with respect to handling and analysis.

[21] Diketopiperazine formation appears to be a competing pathway when a C37 Fmoc-amine-protected congener of **27** is treated with DBU in THF. Fmoc = fluorenylmethyloxycarbonyl.

[22] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-174087. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Scheme 1. Initial diazonamide structure assignments.

Total Synthesis of Nominal Diazonamides— Part 2: On the True Structure and Origin of Natural Isolates**

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In the preceding communication we described a fully synthetic pathway to the structure proposed for (−)-diazonamide A (**1**, Scheme 1).[1] This material is not identical to the natural product, which raises the obvious question: What is the true structure of diazonamide A? Herein we provide an answer. In addition, we report that defined synthetic entity **8** induces, with equal potency, a toxic phenotype in cell culture indistinguishable from that produced by natural (−)-diazonamide A.

Spectroscopic data for the heterocyclic cores of diazonamides A and B are nearly identical.[2] So when the crystal structure of a *p*-bromobenzamide derivative of diazonamide B was reported as **3**,[2a] the diazonamide A assignment

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seemed only to require reconciling its exact mass (765.1998 amu)[3] within the same framework. The molecular formula $C_{40}H_{35}N_6O_6Cl_2$ is consistent with this mass ($\Delta −$ 0.3 ppm) although it was thought to reflect a desiccated form of the molecule as a result of a C11 hemiacetal that loses water during HRMS analysis. Likewise, the C11 diphenylacetal reported in **3** was thought a result of net dehydration occurring during derivatization of diazonamide B with *p*-bromobenzoyl chloride. Hemiacetal functionality was considered a necessary part of both natural products to accommodate a small vicinal coupling between C11H and an exchangeable, one-proton resonance just over $\delta = 7$ in ¹H NMR spectra ([D₆]DMSO). The diazonamide A assignment (**1**) was then completed by incorporation of a terminal valine residue which emanates from the C2 amine. In the context of a C11 hemiacetal, this designation does coincide with the high resolution mass measurement but, unfortunately, with little else.

Acid digests of diazonamide A do not produce valine.[2b] ¹H NMR (360 MHz, [D₆]DMSO) indicates the presence of two isopropyl groups in the molecule, but the N7 protons are reported as a sharp, one-proton doublet at $\delta = 5.46$. This resonance is, in turn, coupled (5.9 Hz) to the C37 methine hydrogen at $\delta = 3.75$.[4] In a triacetate derivative, the C37 proton shifts downfield to $\delta = 5.11$, although it now appears as a doublet rather than the more complex pattern one might expect for a C37 acetamide.[5] Moreover, in non-acetylated material, C37 resonates at $\delta = 76.9$ (50 MHz, [D₄]MeOH)— considerably downfield from the corresponding carbon atom