The Diazonamides: The Plot Thickens**

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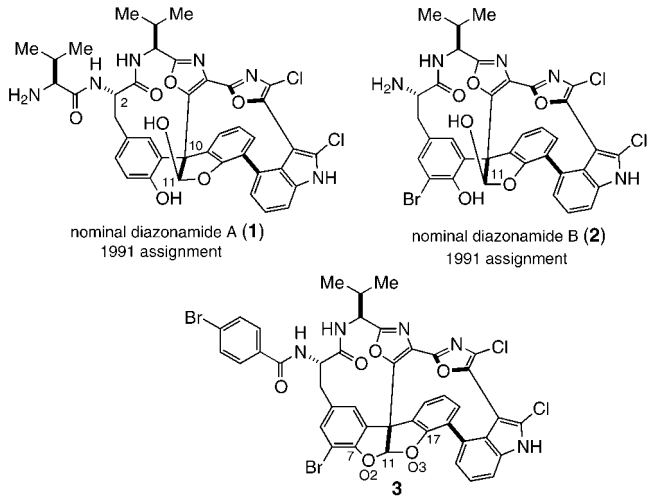
The role of total chemical synthesis as a tool for the structure elucidation of natural products has been largely supplanted by X-ray crystallographic and NMR spectroscopic methods. For the most part, in this respect, synthesis has remained indispensable only as a means to confirm absolute or relative stereochemical assignments, in particular when the imprimatur of an X-ray crystallographic assignment is absent. Thus, it seems quite striking that, in this day and age, synthesis studies lead to a significant structural revision of a new class of biologically active natural products. The disclosure in 1991 of diazonamides A and B (Scheme 1) immediately aroused the attention of the scientific community as a consequence of the unusual structures of these natural products and their impressive activity against human cancer-cell lines. That the structure elucidation was carried out using modern spectroscopic means and was crowned by X-ray crystallographic analysis of a simple derivative of diazonamide B (**3**) would seem to have foreclosed any doubt on the assignment and provided a green light to subsequent studies, focused exclusively on devising a workable synthesis strategy. The synthetic community rose to the challenge, crafting a number of innovative strategies to key intermediates to the presumed structure of diazonamides A and B.[1]



Scheme 1. Original assignments of the structures of nominal diazonamides A (**1**) and B (**2**) as well as the crystographically determined structure of the *p*-bromobenzamide derivative **3**.

Recently, Harran and co-workers at South Western Medical Center at Dallas documented the successful synthesis of **1**.[2] Not only is their strategy notable for its innovation and expediency, but also for an important revelation: the structure of diazonamides was incorrectly assigned. Herein we provide a brief account of the synthetic work by Harran as well as the accompanying detective work which allowed the subsequent corrected assignment to be made.[3] Moreover, despite the fact that, in retrospect, the assigned structure was incorrect, analysis of the studies reported and strategies developed to date are included, as there is much to be learned from them. These include the strategies documented by the groups of Magnus,[4] Nicolaou,[5] Vedejs,[6] Wipf,[7] and Wood.[8]

The piquant story commences with the isolation of diazonamides A and B from the colonial ascidian *Diazona chinensis*. Diazonamide A possesses potent in vitro activity against HCT-116 human colon carcinoma and B-16 marine melanoma cancer-cell lines (IC_{50} values less than 15 ng mL^{-1}).[9] Transformation of diazonamide B to the corresponding *p*-bromobenzamide **3** provided a crystalline derivative suitable for X-ray crystallographic analysis. The diphenylacetal group in **3** was thought to result from the net dehydration occurring during derivatization. On the basis of a small coupling of the C11 proton to a D_2O-exchangeable proton, diazonamide B was thus assigned as the hemiacetal at the C11 atom. The spectroscopic similarity in ^1H and ^{13}C NMR, UV, and IR spectra indicated the same polycyclic nucleus for the diazonamide A framework. Incorporation of a valine residue at the C2 amino group reconciles the proposed structure with the observed high-resolution mass spectrum, in which it had also been assumed that, during HRMS measurement, loss of water converts the hemiacetal into the acetal. Given the spectroscopic data amassed, the structural assignment was deemed to be established fact. The shortage of natural material with which to perform further pharmacological studies as well as the unprecedented molecular architecture, whose retrosynthetic deconvolution and subsequent reconstitution would result in innovative reactions, render the diazonamides ideal targets for synthesis studies. The

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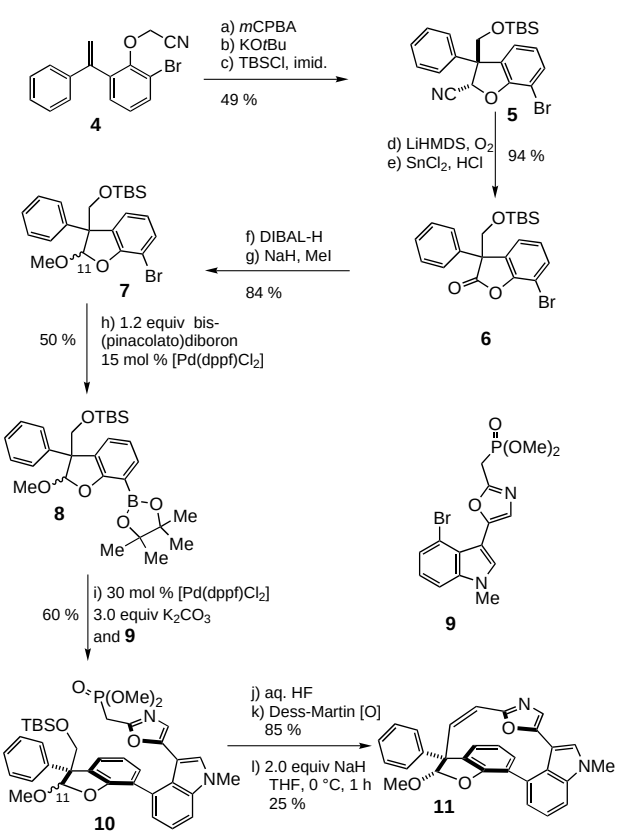
key problems associated with the core stem from the halogenated heterocyclic framework found in a single atropisomeric form and the triaryl acetaldehyde at its epicenter at the C10 atom.

The construction of the quaternary C10 center and the heterocyclic core in a single atropisomeric form was addressed in an early model system by Nicolaou (Scheme 2). Treatment

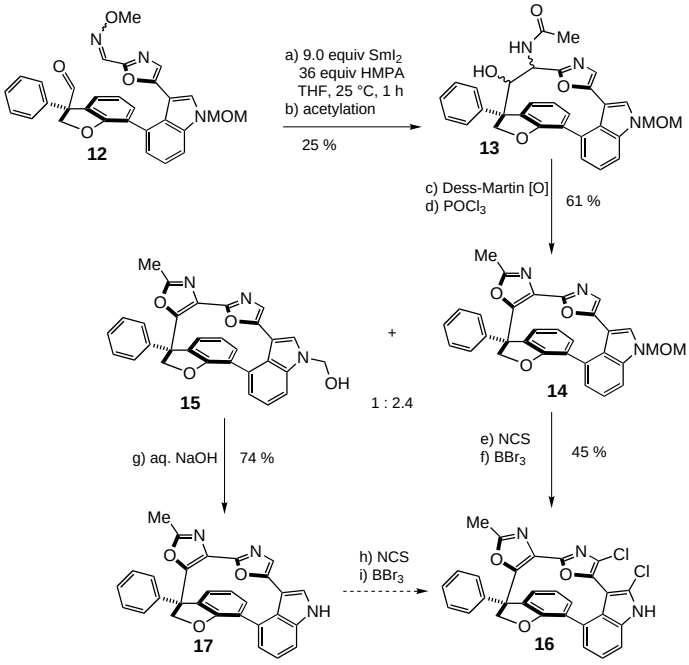


Scheme 2. Horner–Wadsworth–Emmons cyclization strategy (Nicolaou et al.).

of diaryl alkene **4** with *m*CPBA affords an epoxide which subsequently undergoes regioselective nucelophilic 5-*exo-tet* opening[10] by the nitrile enolate to furnish a cyanoalcohol which is protected to yield **5**. Following oxidation to the benzofuranone **6** and lactone semireduction, methylation proceeds to give **7** as a stereoisomeric mixture. As subsequently observed, see below, the stereochemistry of the lactol was critical in the subsequent macrocylization.

After converting the aryl bromide **7** into the boronate **8** using the method developed by Ishiyama et al.,[11] Suzuki coupling of **8** to the phosphonate **9** affords **10** in 30% overall yield from **7**, as a mixture of four isomers which arises from C11 epimers and atropisomerism. The protected alcohol group in **10** is converted into the corresponding aldehyde, which undergoes Horner–Wadsworth–Emmons cyclization at 0°C to give the desired macrocycle **11** as a single atropisomer and a single epimer at the C11 center in 25% yield. It is interesting to note that only one of the diastereomeric starting aldehydes participates in the ring closure. Thus, in analogy with the classic synthesis of erythronolide,[12] the success or failure of the macrocyclization is coupled to stereochemical features of the intervening chain.

In a subsequent approach, Nicolaou et al. examined a strategy in which ring closure is effected using an intramolecular pinacol cyclization reaction of an aldehyde and an oxime (Scheme 3). To avoid the problems observed in the



Scheme 3. Pinacol–cyclization strategy (Nicolaou et al.).

earlier route arising from the stereochemistry at the C11 center, the dihydrobenzofuran **12** was synthesized. Treatment of the aldehyde/oxime with SmI_2 in HMPA/THF gives an aminoalcohol, which on N-acetylation furnishes **13** in 25% overall yield. Oxidation and oxazole formation provides **14** and **15** as a 2.4:1 mixture. Chlorination and indole deprotection of **14** provides **16** in 45%. Conversion of **15** into **17** (74% yield) gives access to additional quantities of **16**.

In the route of Wipf et al., a related disconnection plan is envisioned for the construction of the macrocycle, albeit with a distinct, innovative approach to the precursors (Scheme 4). After establishing a synthesis of benzofuranone **19**, Wipf utilizes a clever application of the Chang rearrangement[13] to afford the protected amino ketone **21**, which is subsequently converted into the requisite oxazole. Thus, deprotonation of **20** at $-78\,^{\circ}C$ with LDA cleanly provides aminoketone **21** in superb yield (78%) through smooth rearrangement of the intermediate carbanion. In the three steps that follow, bisoxazole **22** is efficiently obtained.

In the approach of Vedejs et al., the same region of the molecule is chosen for retrosynthetic unraveling of the macrocycle, which in the synthetic direction relies on a Dieckmann-like cyclization reaction (Scheme 5). The preparation of the cyclization precursor commences with oxidation of **23** and acylation of the resulting **24** with methylchloroformate (57% yield) using the method of Black et al.,[14] a

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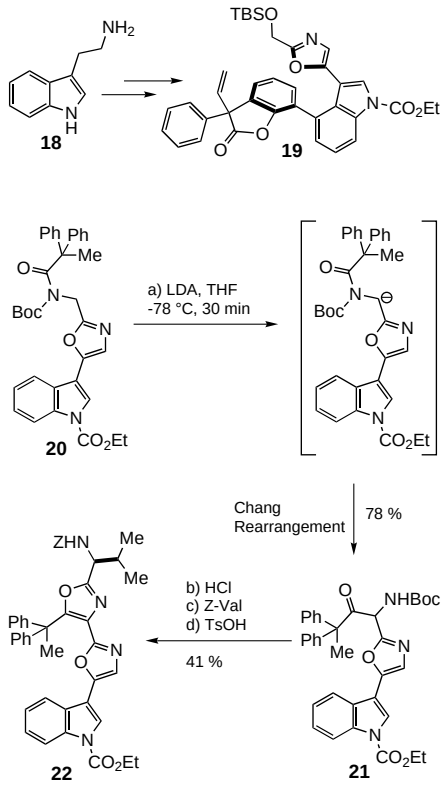
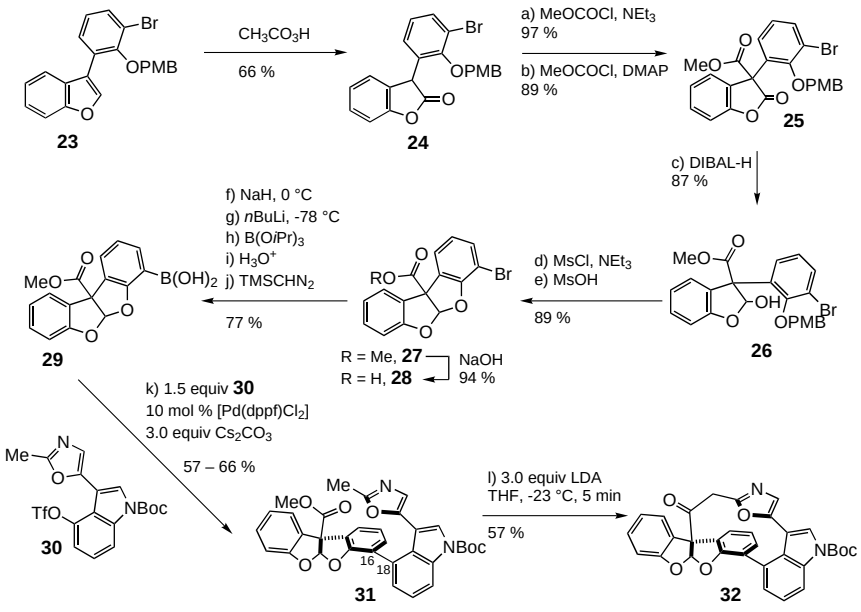
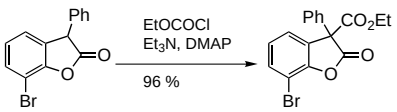


Scheme 4. Modified Chang rearrangement (Wipf et al.).



Scheme 5. Imino-Dieckmann cyclization (Vedejs et al.).

synthetic step similar to that documented by Moody et al. in simple model studies toward the diazonamides [Eq. (1)].[15]

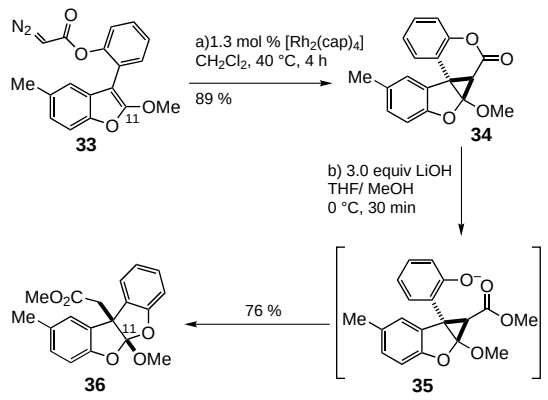


(1)

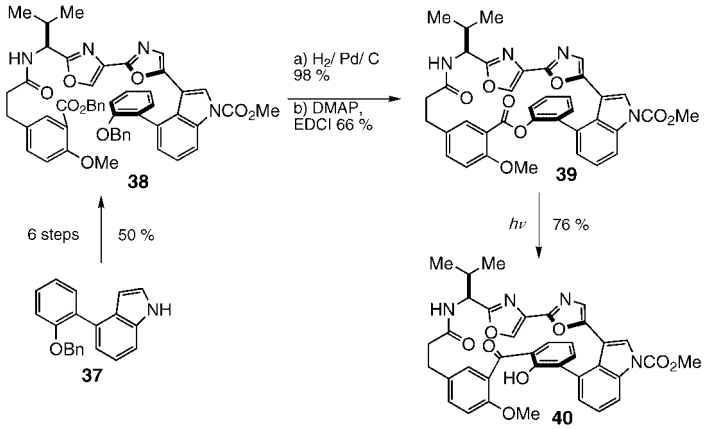
Chemoselective reduction of the resulting lactone **25**, mesylation, and subsequent treatment with methanesulfonic acid furnishes the requisite dibenzoacetal **27** in 77% yield. The required aryl boronic acid **29** is prepared in 72% overall yield from **27** by saponification of the methyl ester, halogen–lithium exchange and treatment with triisopropyl borate, hydrolysis of the boronic ester, and reintroduction of the methyl ester. In the subsequent Suzuki coupling, aryl boronic acid **29** is allowed to react with aryl triflate **30** by utilizing catalytic $[Pd(dppf)Cl_2]$ and Cs_2CO_3 as the base. The use of this base led to significant rate acceleration and improved yields to 57–66%. NMR spectroscopic studies reveal that the two atropisomers interconvert at room temperature, with a value for the barrier of rotation around the C16–C18 biaryl axis of $\Delta G^{\ddagger} = 15.5\ \mathrm{kcal\,mol^{-1}}$. This result is noteworthy, considering the lack of ready interconversion at room temperature between atropisomers **10** in an earlier synthesis (Scheme 2). Treatment of **31** with LDA leads to he Dieckmann-like reaction, which furnishes the expected macrocycle **32** in 57% yield as a single atropisomer.X-ray crystallographic analysis established that the cyclization affords an intermediate with the desired stereochemistry.

In the studies of Nicolaou and Vedejs discussed above, enolate chemistry was relied upon for the installation of the quaternary center at C10; by contrast Wood et al. documented a clever and elegant approach in a model study. Intramolecular cyclopropanation of a benzofuran, followed by an anion-induced ring fragmentation, leads to a key structure (Scheme 6). The diazoacetate **33** is subjected to rhodium(II)-catalyzed cyclopropanation to afford pentacycle **34** in excellent yield (89%). Subsequent treatment of **34** with LiOH initiates ring opening and rearrangement to the orthoester **36**, which incorporates the requisite quaternary center. The use of a transition-metal-catalyzed cyclopropanation reaction opens the possibility to prepare the key precursors in an optically active form; indeed, preliminary work using Doyle's catalyst[16] revealed that the optically active cyclopropane **34** can be formed in 45% *ee*.

A significant departure from the macrocyclization strategies that involve carbanionic intermediates is proffered by the bold, innovative strategy developed by Magnus et al. In this approach, photo-Fries rearrangement of **39** was used for the construction of the diazonamide framework. The precursor lactone **39** is efficiently synthesized in only eight linear steps from indole **37** (Scheme 7). Following debenzylation of **38** (98%), the macrolactone **39** was obtained, by using the Keck modification[17] of the Steglich esterification[18] procedure, in 66% yield, as a 1.5:1 mixture of atropisomers. The macrolactone underwent photo-rearrangement to afford **40** as two atropisomers (2:1) in 76% yield.



Scheme 6. Cyclopropanation – ring-opening strategy (Wood et al.).

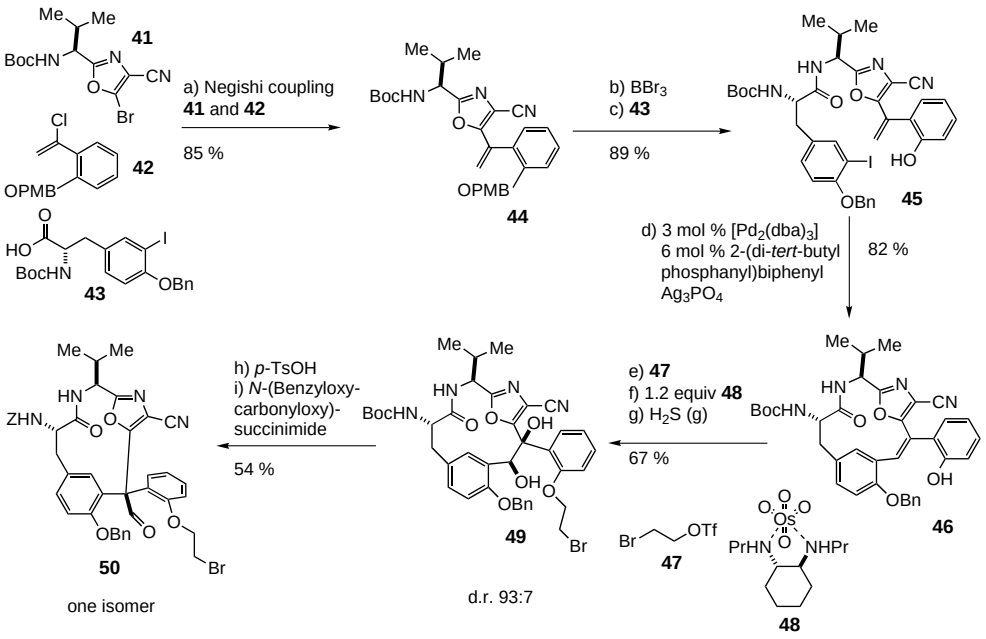


Scheme 7. Photo-Fries rearrangement strategy (Magnus et al.).

In the Harran approach, the problem of forming the macrocycle is efficiently tackled by focusing on the triaryl acetaldehyde epicenter. In this elegant, imaginative strategy, introduction of the core macrocycle is effected in a highly convergent manner by construction of the bond-linking rings **E** and **F** (Scheme 1), by proceeding from advanced, densely functionalized fragments. The selection of this key bond disconnection was critical, leading to the successful development of a synthesis of the nominal diazonamide A (**1**).

The bromooxazole **41** and the vinylchloride **42** were coupled by use of a Negishi coupling reaction[19] in 85 % yield (Scheme 8). Following removal of the *N*-Boc- and *O*-PMB protecting groups, the iodotyrosine derivative **43** participated in amide-bond formation to furnish **45**. In the ring-closing reaction, Heck coupling of the iodoolefin **45** afforded the macrocyclic framework **46** in a remarkable 82 % yield. An important observation from the study of the cyclization reaction is that the use of 2-(di-*tert*-butylphosphanyl)biphenyl generated a robust Pd complex that allows the reaction to be executed with low catalyst loading; moreover, all other phosphane ligands used inhibit the reaction. A working hypothesis that guided the development of the successful cyclization is a mechanistic model in which macrocyclization is facilitated by proceeding from **45** through a preorganized intermediate involving a palladium(II) phenoxide. After derivatization of the phenol **46** as its 2-bromoethyl ether, the latter was treated with the dihydroxylation reagent **48**, (formed with OsO_4 and (1*S*,2*S*)-*N*,*N*′-bis(3,3-dimethylbutyl)cyclohexane-1,2-diamine[20]) to afford the glycol **49** in 67 % overall yield. The use of this osmium reagent is necessary to override the intrinsic bias of the molecule to undergo dihydroxylation with opposite-face selectivity and to ensure that the correct stereochemistry is established (93:7 d.r.). Pinacol rearrangement of the diol **49** under acidic conditions then furnished the triaryl acetaldehyde **50** as a single stereoisomer in excellent yield (54 %) after amine carbamoylation.

Conversion of the nitrile into the desired substituted oxazole, along with the necessary functionalization of the core, was effectively carried out (ten steps, 8.4 % yield) to give the aryl bromide **51** (Scheme 9). This aryl bromide is then the precursor for a second macrocyclization reaction which is carried out by a clever application of the photochemical method developed by Witkop et al.[21] A possible reaction pathway is an intramolecular photoinduced electron transfer from the indole chromophore to the adjacent bromoarene and biradical collapse to form the C16–C18 bond. It has to be pointed out that this macrocyclization, which is carried out in 32 – 40 % yield, forms **52** as a single atropisomer, thus the asymmetry associated with the diazonamide polycycle follows



Scheme 8. Early steps of the total synthesis of nominal **1** (Harran et al.).

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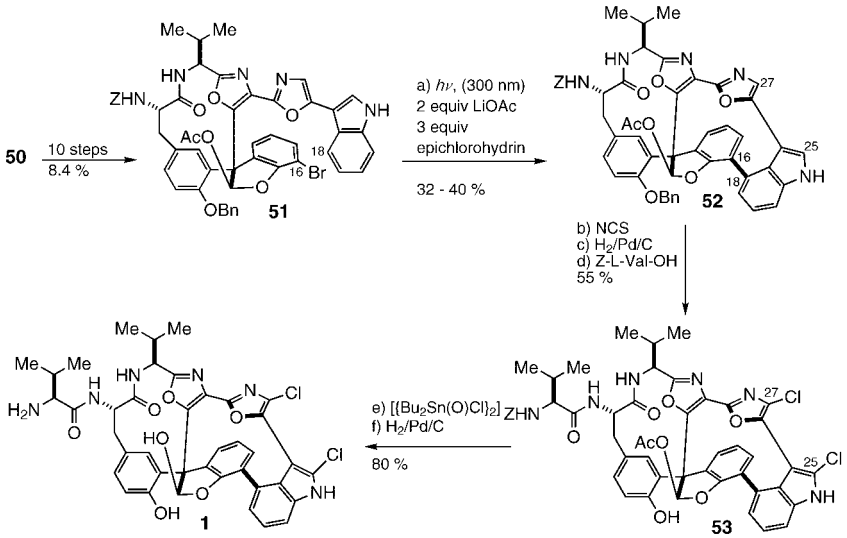
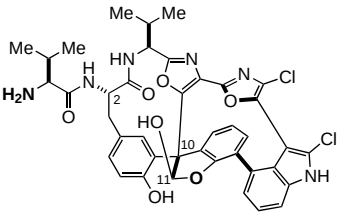


Scheme 9. Late steps of the total synthesis of nominal **1** (Harran et al.).

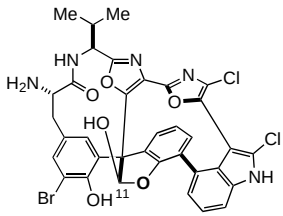
from the stereochemical control in the early steps of the route. Chlorination of **52** with *N*-chlorosuccinimide at C27 and C25 proceeded smoothly. Stannoxane-catalyzed deacetylation of the acetyl hemiacetal and final hydrogenolysis (80%) culminated in the total synthesis of the nominal diazonamide A (**1**).

Surprisingly, subsequent structural analysis revealed that the material obtained from the synthesis study differed from that isolated from natural sources. Thus, both the ^{1}H NMR spectrum and the notable chemical instability of the synthetic material were telling; the synthetic material consists of a 4:1 mixture of C11 lactol epimers, a feature that was not observed with the natural product. Moreover, in contrast to the behavior of diazonamide A, the susceptibility of the synthetic material to degradation prevented further detailed characterization. Harran et al. reasoned that a correct structure for diazonamide A would need to reconcile the observed exact mass of 765.1998 amu with a closely related polycyclic framework. Careful reexamination of the original characterization procedure was critical, as acidic hydrolysis of diazonamide A had not yielded valine as anticipated.[22] Thus, the first feature that seemingly had to be corrected was the fact that the C2 side chain of diazonamide A might have been misassigned. Detailed NMR spectroscopic analysis then suggested that the C2 side chain incorporates a hydroxy group rather than an amino group, as originally assigned. This $NH_2 \rightarrow OH$ exchange requires a adjustment to correct for the corresponding 1-Dalton increase in molecular mass.

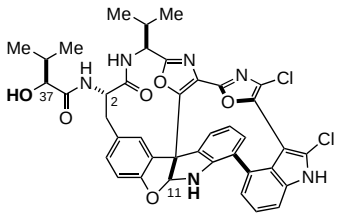
In an impressive logical breakthrough, it was reasoned that the observed exact mass of 743.0340 amu for natural diazonamide B (**55**) is more consistent with the molecular formula of $C_{35}H_{25}N_6O_4Cl_2Br$ ($[M^+ + H] = 743.0576$) than with the mass corresponding to the structure originally assigned to diazonamide B (**2**) ($[M+H]^+ - H_2O = 744.0416$) with the formula $C_{35}H_{26}N_5O_6Cl_2Br$. This can be reconciled with the crystallographic data if a protonated nitrogen atom in diazonamide B was mistaken for an oxygen atom. Careful analysis of the X-ray crystallographic data is revealing: the observed C7–O2 bond length of 1.371 Å does not deviate from common aryl C–O bond lengths, whereas the length of the C17–O3 bond (1.433 Å) is longer than the maximal value (1.409 Å) observed for similar bond types. The large thermal motion of the O3 atom also suggests an element with fewer electrons and a larger covalent radius. Based on these results and on a ^{1}H – ^{15}N NMR correlation spectrum (HSQC) of diazonamide A, Harran et al. then concluded that the structure of the diazonamides is more properly assigned as the C11 diaryl aminal. Thus structures **54** and **55** are most consistent with the available data. Of course, the absolute stereochemistry of the α-hydroxy acid side chain at C2 remains to be assigned, a feature which current synthetic efforts will surely secure.



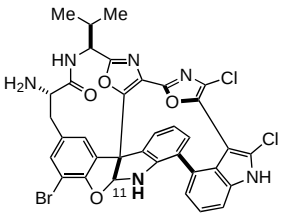
nominal diazonamide A (**1**)
1991 assignment



nominal diazonamide B (**2**)
1991 assignment

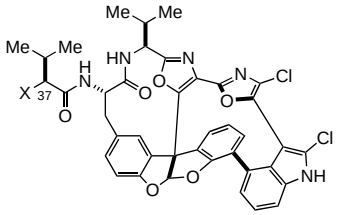


(–)-diazonamide A (**54**)
2001 assignment



diazonamide B (**55**)
2001 assignment

Given the fact that, within experimental error, model compound **56** (prepared from (*S*)-hydroxy isovaleric acid) and diazonamide A (**54**) are equipotent in in vitro cytotoxicity assays, Harran has suggested that the natural product is of the *S* configuration at the C37 center. The synthetic alcohol **56** is about 16 times more potent than its C37 epimer and more than 50 times more potent than the corresponding amine **57** in



56 X = OH
57 X = NH_2

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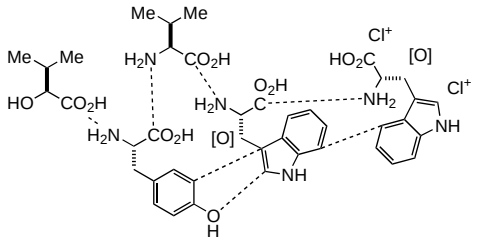
the inhibition of the growth of human ovarian adenocarcinoma OVCAR-3 in vitro.

While analyzing the correct structure of diazonamide A, Harran et al. have speculated about its biosynthesis. Retrospectively, it is plausible that the diazonamide polycycle is biosynthetically constructed from four natural amino acids (Scheme 10). In this respect, the core can be traced back to an oxidized ditryptophan unit which is oxidatively coupled to a tyrosine residue.



Scheme 10. Biosynthesis proposed by Harran et al. [O] = oxidation.

The scientific merit of the studies by various research groups outlined above rests above all in the discoveries and contributions made in the field of synthetic methods. However, one cannot help but also confess some amazement: The diazonamide story reminds us that the synthetic chemistry of natural products at the cutting edge can be counted on to have surprises in store for its practitioner, not only in the hidden treasures it reveals but also in the impact on biology. The revised structures will again challenge organic chemists as targets for synthesis. The modular aspects of the strategies reported to access the nominal diazonamides are certainly flexible enough to provide potential access routes to the natural product. However, anyone who has partaken in a synthetic challenge of this magnitude knows that even the slightest structural change in an advanced intermediate of a synthetic route can have substantial repercussions for the success or failure of the route. The $NH_2 \rightarrow OH$ exchange in the revised diazonamide structure cannot be considered trite, and one can look forward to continuing studies into this synthetic challenge and its culmination.

Abbreviations

cap	caprolactamate
*m*CPBA	*meta*-chloroperbenzoic acid
dba	*trans,trans*-dibenzylideneacetone
Dess – Martin [O]	Dess – Martin periodinane
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HMPA	hexamethylphorphoramide
imid.	imidazole
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
NCS	*N*-chlorosuccinimide
PMB	*p*-methoxybenzyl
TBAF	tetra-*n*-butylammonium fluoride
TBSCl	*tert*-butyldimethylsilyl chloride
TMS	trimethylsilyl
TsOH	*p*-toluenesulfonic acid
Z	benzyloxycarbonyl

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Encapsulated Lanthanides as Luminescent Materials

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Dedicated to Professor Roald Hoffmann on the occasion of his 65th birthday

Materials which embed organic dyes, rare earth ions, complexes, or quantum dots in a matrix with specifically tailored chemical and optical properties provide a challenging approach to novel chemical and optical applications. These materials have the potential to be used in microoptics, optoelectronics, laser materials, solar cells, sensors, battery electrodes, and photocatalysis. In this article we focus on lanthanides encapsulated in zeolites, glass films derived from sol – gel processes, and semiconductors.

The research work on the unique luminescent properties of rare earth elements hosted in different matrixes is strongly motivated by their technological importance in optoelectronic devices.[1] The materials emit over the entire spectral range of interest: near infrared (NIR; Nd^{3+}, Er^{3+}), red (Eu^{3+}, Pr^{3+}, Sm^{3+}), green (Er^{3+}, Tb^{3+}), and blue (Tm^{3+}, Ce^{3+}). Their optical transitions involve 4f orbitals, which are well shielded from their chemical environment by $5s^2$ and $5p^6$ electrons. The f-f transitions are parity forbidden and, as a result, the absorption coefficients are very low and the emissive rates are slow, which results in long-lived and linelike emission bands. As a consequence, direct excitation of the lanthanide ions is unfavorable. The comparatively fast thermal relaxation of the excitation energy is a problem when using lanthanide ions for luminescence. This nonradiative relaxation may occur by interaction of the electronic levels of the lanthanide ion with suitable vibrational modes of the environment.[2] The efficiency of these processes depends on the energy gap between the ground and excited states as well as the vibrational energy of the oscillators. For example, when solvents containing OH groups are coordinated to lanthanide ions, efficient nonradiative deactivations take place through vibronic coupling with the vibrational states of the OH oscillators. Replacement of the OH oscillators by low-frequency OD oscillators, diminishes the vibronic deactivation pathway.[3] Different ways to overcome the difficulties of low absorptivity and thermal relaxation have been used. We show the apparently most important ones in Figure 1:

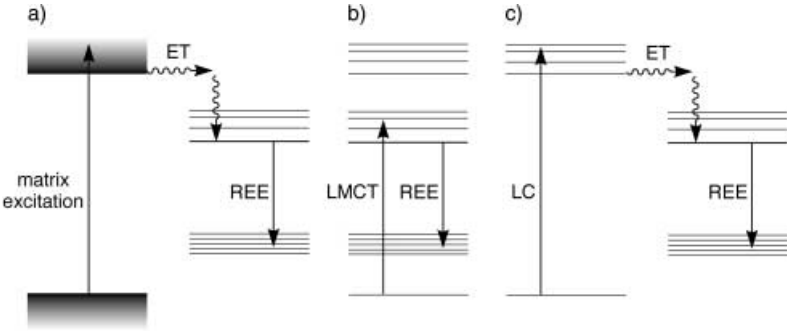

Figure 1. Three paths to efficient lanthanide luminescence (ET = energy transfer; REE = rare earth emission; LMCT = ligand → metal charge transfer absorption; LC = ligand-centered absorption). a) A matrix is excited above the band-gap energy and, after energy transfer, the lanthanide ion emits. b) Ligand → metal charge-transfer absorption can lead to an excited lanthanide ion which luminesces. c) Ligand-centered absorption excites a ligand which transfers its electronic excitation energy to a lanthanide ion that fluoresces.

a) matrix excitation followed by energy transfer to the lanthanide ion, b) ligand → metal charge transfer followed by lanthanide f-f emission, and c) ligand-centered absorption followed by energy transfer to the lanthanide ion.

We first discuss the use of coordinating ligands as sensitizers. After absorption of light by the ligands, the electronic excitation energy is transferred and results in a luminescence of the lanthanide ion (see Figure 1c). A possibility, given by Vögtle, Balzani, and co-workers, is to use a specially designed dendrimer which is able to play the role of the ligand for the lanthanide ions but which is also capable of working as an

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