Total Synthesis of Diazonamide A

The Second Total Synthesis of Diazonamide A**

K. C. Nicolaou, Paraselli Bheema Rao, Junliang Hao, Mali Venkat Reddy, Gerasimos Rassias, Xianhai Huang, David Y.-K. Chen, and Scott A. Snyder*

Unique and challenging molecular motifs within secondary metabolites have long presented synthetic chemists with golden opportunities for discovery, whether simply as a source of inspiration for creative strategies and tactics, or as a stringent testing ground that reveals weaknesses in the power of existing methods.[1] Among recent isolates, the natural product diazonamide A (**1**, Scheme 1)[2] perhaps constitutes one of the best affirmations of this statement as its unprecedented molecular architecture has stimulated the development of numerous inventive synthetic approaches.[3–13] Last year, these efforts provided dividends in the form of the first laboratory synthesis of diazonamide A.[14] Herein, we report the second total synthesis of this formidable target by our group through an entirely distinct route.

The retrosynthetic blueprint that guided this new campaign is defined in Scheme 1. The critical difference from our previous strategy[14] is a reversed order for the construction of the daunting macrocyclic domains of the target, that is, forming the heterocyclic core first, and then generating the 12-membered AG macrolactam system. Accordingly, we initially set intermediate **3** as the crucial subgoal structure of the program, for which we assumed that application of a route based on C_{16}–C_{18} biaryl coupling of advanced building blocks **6** and **7** to access an intermediate such as **5**, followed by macrocyclization through a heteropinacol coupling/oxime-cleavage cascade reaction, could provide a functionalized platform (**4**) for eventual conversion into this advanced compound through a Robinson–Gabriel cyclodehydration reaction. The constrained AG macrolactam could then be formed from an amino acid derivative obtained from **4**. Subsequent chlorination, aminal formation, several func-

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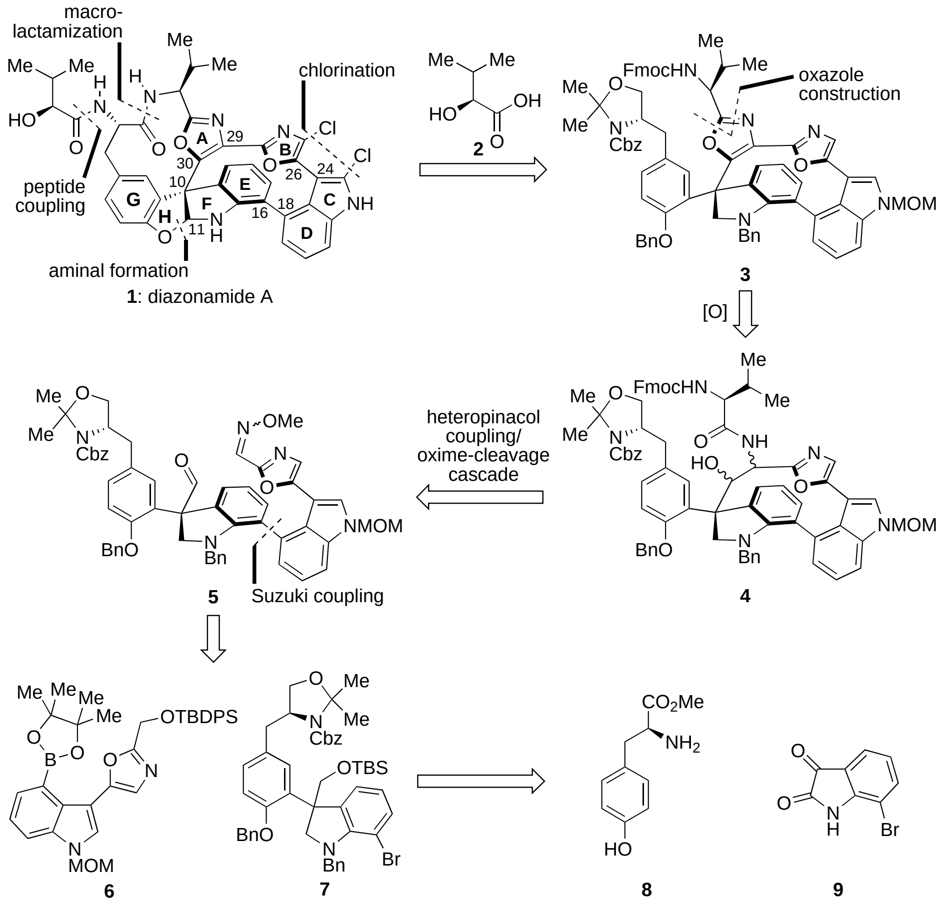
[*] Prof. Dr. K. C. Nicolaou, Dr. P. Bheema Rao, Dr. J. Hao,
Dr. M. V. Reddy, Dr. G. Rassias, Dr. X. Huang, Dr. D. Y.-K. Chen,
S. A. Snyder
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, American Biosciences, the National Institutes of Health (USA), predoctoral fellowships from the National Science Foundation and Pfizer (S.A.S.), and a postdoctoral fellowship from The Skaggs Institute for Chemical Biology (X.H.).

DOI: 10.1002/ange.200351112

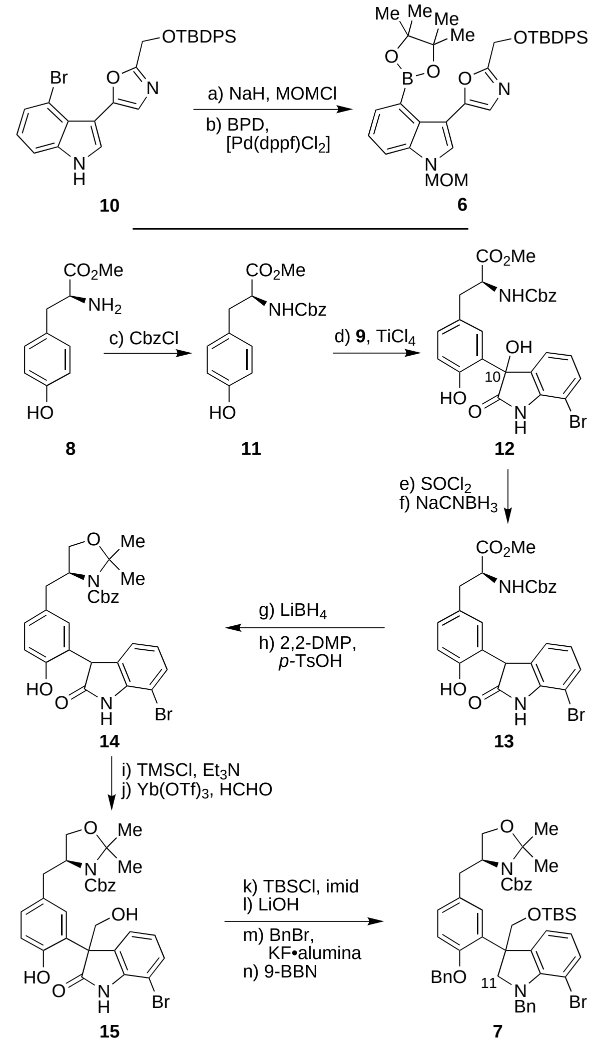


Scheme 1. Structure of diazonamide A (**1**) and general retrosynthetic analysis.

tional-group manipulations, and a final chain extension with (*S*)-hydroxyisovaleric acid (**2**) would complete the total synthesis of diazonamide A (**1**). Although an ambitious plan, we had faith that the operations expected to afford intermediate **3** could be reduced to practice based on a series of model studies that demonstrated their viability in the context of the originally proposed, but incorrect, structure of diazonamide A.[15]

We first needed to prepare indole–oxazole **6** and functionalized EFG-ring system **7**. As shown in Scheme 2, the first of these targets was quite easily accessed from the previously reported **10**[15a] (available in six steps from 4-bromoindole) through initial protection of its indole nitrogen atom with a MOM ether followed by subsequent reaction with BPD and [Pd(dppf)Cl$_2$]·CH$_2$Cl$_2$[16] to afford boronate ester **6**. With these two steps proceeding in a combined yield of 80 %, effort was then directed towards the assembly of **7**, starting with the protection of commercially available tyrosine methyl ester (**8**) as a benzyl carbamate (Cbz) to afford **11** in 94 % yield. Although a conventional beginning, this operation served an important purpose as it set the stage for a subsequent TiCl$_4$-promoted merger with 7-bromoisatin (**9**), an event which gave rise to **12** bearing most of the desired functionality of the targeted EFG fragment **7** in 58 % yield.[17] Indeed, the only major structural element that separated **12** from **7** was appropriate functionalization of its C10 quaternary center. Thus, to fix this deficiency, the newly generated tertiary alcohol was exchanged for a hydrogen atom to form **13** via an intermediate chloride in 76 % yield. The upper tyrosine portion was converted into an acetonide (see **14**) in nearly quantitative yield through reduction of the methyl ester (LiBH$_4$, THF) followed by *p*-TsOH-catalyzed reaction with 2,2-dimethoxypropane. The required hydroxymethyl group at C10 was then installed onto this lactam intermediate **14** through a two-step protocol developed by Padwa et al. for the addition of such groups to carbon atoms adjacent to lactones,[18] affording **15** as an equimolar mixture of both C10 stereoisomers in 70 % yield. Since these diastereomeric compounds could not be separated at this juncture, they were carried forward as a mixture in the hope that eventually the incorporation of a suitable functional group would confer sufficient differences in their physical properties to allow their separation.

With the architectural skeleton **15** of the EFG fragment now completed, only protecting- and functional-group manipulations remained before we could attempt Suzuki coupling with **6**. These alterations were accomplished over four steps (see Scheme 2) starting with silylation of the free primary alcohol group of **15** with TBSCl and imidazole in CH$_2$Cl$_2$, conditions that also led to protection of the free A-ring phenol (84 % yield). Since the latter event was unintended, subsequent treatment with LiOH served to excise this



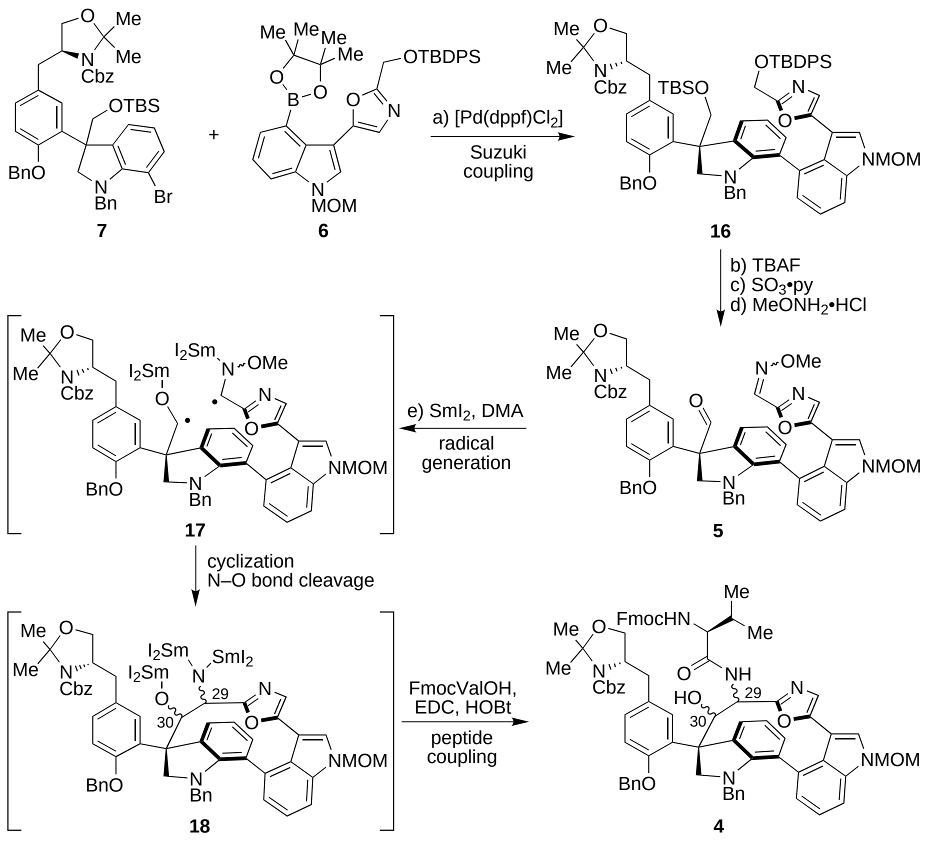
Scheme 2. Synthesis of indole–oxazole **6** and advanced EFG fragment **7**: a) NaH (2.0 equiv), THF, 0 °C, 5 min, then MOMCl (2.0 equiv), 0 °C, 10 min, 94 %; b) BPD (2.5 equiv), [Pd(dppf)Cl_2]·CH_2Cl_2 (0.1 equiv), KOAc (5.0 equiv), 1,4-dioxane, 95 °C, 6 h, 85 %; c) CbzCl (1.1 equiv), aqueous $NaHCO_3$, $CHCl_3$, 25 °C, 3 h, 94 %; d) **9** (1.1 equiv), $TiCl_4$ (1.0 M in CH_2Cl_2, 1.0 equiv), CH_2Cl_2, 25 °C, 10 h, 58 % (70 % based on recovered **11**); e) $SOCl_2$, 25 °C, 10 h, 90 %; f) $NaCNBH_3$ (3.0 equiv), MeCN, 0→25 °C, 5 h, 84 %; g) $LiBH_4$ (3.0 equiv), 0→25 °C, THF, 2 h, 95 %; h) 2,2-DMP (10 equiv), *p*-TsOH (0.1 equiv), acetone, 25 °C, 2 h, 98 %; i) TMSCl (4.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, 0 °C, 1.5 h; j) HCHO (37 % in H_2O, 5.0 equiv), Yb(OTf)$_3$ (0.1 equiv), THF, 25 °C, 24 h, 70 % over two steps; k) TBSCl (3.0 equiv), imid (6.0 equiv), CH_2Cl_2, 25 °C, 6 h, 84 %; l) LiOH (3.0 equiv), DMF, 25 °C, 5 h; m) BnBr (4.0 equiv), KF·alumina (8.0 equiv), DME, 25 °C, 12 h, 95 % over two steps; n) 9-BBN (0.5 M in THF, 5.0 equiv), THF, 65 °C, 36 h, 72 %. BPD = bis(pinacolato)diboron, MOM = methoxymethyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Cbz = benzyloxycarbonyl, TBDPS = *tert*-butyldiphenylsilyl, 2,2-DMP = 2,2-dimethoxypropane, *p*-TsOH = *p*-toluenesulfonic acid, TMS = trimethylsilyl, Tf = trifluoromethylsulfonyl, TBS = *tert*-butyldimethylsilyl, imid = imidazole, 9-BBN = 9-borabicyclo[3.3.1]nonane.

superfluous group. Finally, both the lactam nitrogen atom and the free phenol group were protected with a benzyl group upon reaction with BnBr and KF·alumina in DME (95 % overall for two steps), and the carbonyl group of the lactam was then fully reduced with excess 9-BBN in refluxing THF to afford **7** in 72 % yield. Although the excision of the oxygen atom of the lactam in this final operation might seem wasteful, as we have already demonstrated that a carbonyl group at C11 can enable the construction of the FH aminal system of diazonamide A, it was forced upon us by the fact that this functionality did not prove compatible with the next series of steps.[19] Therefore, although removing this group facilitated our objectives in the short term, it would have to be reintroduced to complete the target molecule.

Pressing forward nonetheless, initial Suzuki coupling between aryl halide **7** and boronate **6** proceeded without incident in the presence of [Pd(dppf)Cl_2]·CH_2Cl_2 and K_2CO_3 in DME at reflux as shown in Scheme 3, affording **16** in 78 % yield after 12 h. From this intermediate, aldehyde–oxime **5** was then formed in 78 % overall yield through a tandem deprotection/oxidation sequence using TBAF and SO_3·py, followed by selective capture of the more reactive aldehyde with $MeONH_2$·HCl upon stirring in DMSO at ambient temperature. As such, the stage was now set to examine the crucial heteropinacol cyclization cascade sequence anticipated for macrocycle formation with concomitant installation of a suitable precursor functionality for the requisite second oxazole. Most gratifyingly, a modified form of our previously reported protocol[15b] for this reaction proceeded smoothly as treatment of **5** with a premixed complex of SmI_2 (9.0 equiv) and DMA (36 equiv)[20] in THF at ambient temperature, followed by quenching with aqueous NH_4Cl, extraction, solvent removal, and subsequent peptide coupling with a solution of Fmoc-protected L-valine, EDC, and HOBt in DMF, gave rise to **4** in a reproducible yield of 45–50 %.[21] Overall, this outcome accounts for an average efficiency of 79 % per step based on the three distinct operations of pinacol cyclization, N–O bond scission, and peptide-bond formation effected during this one-pot conversion.

Having established a functionalized C_{29}–C_{30} bridge through this powerful cascade, the A-ring oxazole in **3** (Scheme 4) was then generated in an overall yield of 33 % through initial oxidation of the relatively hindered alcohol group of **4** with TPAP and subsequent Robinson–Gabriel cyclodehydration of the resultant ketoamide with a mixture of $POCl_3$ and pyridine (1:2) at 70 °C.[22] Although the material throughput for this sequence is modest, it accurately reflects the severely strained and highly hindered nature of the diazonamide heteroaromatic system. In fact, experimentation with numerous oxazole-forming protocols revealed that only the indicated reagent combination could accomplish this task in any measurable yield.[23] As such, this finding suggests that this cyclodehydration protocol may prove to be useful when more conventional techniques fail.

With the complete heteroaromatic core of diazonamide A finally in place, the next step toward diazonamide A (**1**) was the formation of the second macrocyclic subunit through lactamization, a transformation for which we anticipated few difficulties based on the literature precedent for such ring closures.[24] Indeed, our initial forays along these lines were encouraging, as **3** (see Scheme 4) was readily converted into **19** in 83 % overall yield through HF-mediated cleavage of the acetonide, generation of a free acid from the resultant alcohol



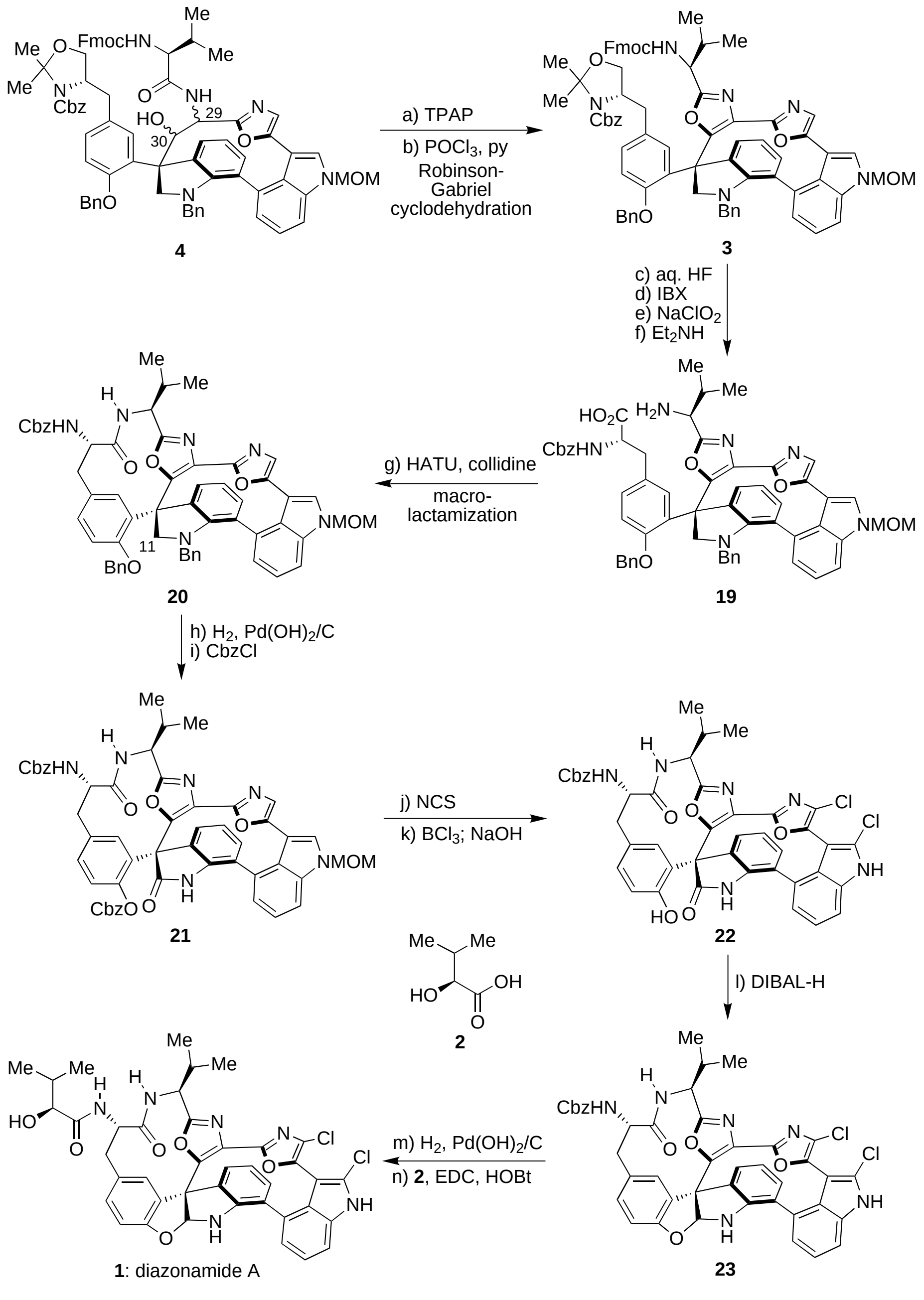
Scheme 3. Construction of the fully functionalized heterocyclic core **4** of diazonamide A through Suzuki and heteropinacol coupling reactions: a) **6** (1.0 equiv), **7** (1.2 equiv), [Pd(dppf)Cl$_2$]·CH$_2$Cl$_2$ (0.2 equiv), K$_2$CO$_3$ (5.0 equiv), DME, 85 °C, 12 h, 78 %; b) TBAF (6.0 equiv), THF, 45 °C, 2.5 h, 94 %; c) Et$_3$N (10 equiv), SO$_3$·py (8.0 equiv), DMSO/CH$_2$Cl$_2$ (1:1), 0 °C, 2 h, 91 %; d) MeONH$_2$·HCl (5.0 equiv), DMSO, 25 °C, 20 min, 91 %; e) SmI$_2$ (0.1 M in THF, 9.0 equiv), DMA (36 equiv), THF, 25 °C, 1 h, then saturated aqueous NH$_4$Cl, 25 °C, 10 min; solvent removal, then FmocValOH (3.0 equiv), EDC (3.0 equiv), HOBt (3.0 equiv), DMF, 25 °C, 10 h, 45–50 % overall, ca. 79 % per synthetic operation in the cascade sequence. DME = ethylene glycol dimethyl ether, TBAF = tetra-*n*-butylammonium fluoride, DMSO = dimethyl sulfoxide, DMA = *N,N*-dimethylacetamide, Fmoc = 9-fluorenylmethoxycarbonyl, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole, DMF = *N,N*-dimethylformamide.

through a two-stage oxidation protocol, and finally Et$_2$NH-induced lysis of the Fmoc protecting group.[25] Unfortunately, initial attempts to form the macrolactam from this advanced compound **19** met with significant resistance despite an almost exhaustive screening of peptide-forming reagents, leading in all cases either to decomposition or dimerization (even when the reaction was run at low concentration).[26] Eventually, we found that **20** could be obtained in yields of 10–15 % when **17** was treated with HATU and collidine for several days at ambient temperature in DMF/CH$_2$Cl$_2$ (1:2) at a final concentration of 1.0×10^{-4} M.[27] Significantly, apart from completing the second highly strained macrocyclic domain, this step also served to resolve the previously formed mixture of C10 epimers, as only material with the stereochemical disposition of **20** resulted (which matched the absolute configuration of diazonamide A).[28]

Having constructed both macrocycles of the target molecule, we then faced the challenge of completing the structure by introducing the final aminal ring system. Thus, in advance of oxidation at C11 to enable the synthesis of this motif, we attempted to remove the two benzyl ethers attached to **20** through a standard hydrogenation reaction facilitated by an excess of Pd(OH)$_2$/C (Pearlman catalyst). Amazingly, however, following subsequent reaction of the intermediate product with benzyl chloroformate, all spectral data indicated that although the debenzylations had occurred as intended, the indoline ring had been oxidized to an oxindole as expressed in **21**! As such, the conditions employed for the hydrogenation reaction had served both to formally reduce as well as oxidize the substrate **20**.[29] We are currently investigating the mechanism behind this puzzling transformation. Although a complete picture has not yet been painted, initial studies have revealed that this reaction requires an excess of Pd(OH)$_2$/C and that it is probably substrate-specific, as application of the same conditions to **7** (cf. Scheme 2) served only to excise its benzyl ethers. It is, therefore, conceivable that both the rigidity of the substrate and the neighboring phenolic group play a crucial role in this process.

After this fortuitous conversion, the completion of diazonamide A (**1**) required only a few finishing touches, starting with the installation of the two chlorine substituents. This goal was smoothly accomplished through an electrophilic aromatic substitution reaction using NCS as the chlorine source at 60 °C in a mixture of THF and CCl$_4$ (1:1), a reaction that proceeded with complete atropselectivity as a result of the constraints of the macrocyclic system. Next, the long resilient MOM protecting group was excised from the C-ring indole through a one-pot, two-step protocol involving initial reaction with BCl$_3$ to selectively cleave its methyl group, followed by exposure to NaOH to expel the residual hydroxymethyl group as a molecule of formaldehyde. These conditions also served to selectively cleave the Cbz group residing on the phenol, thereby generating **22** in 75 % overall yield from **21** and providing an intermediate which intersected our early total synthesis.[14] Gratifyingly, the spectral data of **21** perfectly matched those of the previously obtained compound.[30] As such, application of the same three steps which we had already developed to complete diazonamide A (**1**) from this advanced intermediate served to finish the second total synthesis of this intricate molecule in comparable yields to those of the first.

In summary, our group has chartered a second path to the marine-derived antitumor agent diazonamide A (**1**) through an approach that featured a SmI_2-induced heteropinacol coupling cascade to fashion the 12-membered heterocyclic core of the target and an unprecedented oxidation of an indoline to an oxindole using $Pd(OH)_2/C$. Equally significant as the gathered knowledge from this particular campaign, the complementary nature of our two total syntheses now affords routes capable of delivering simplified structural analogues of either macrocyclic domain. We expect that examination of such compounds will reveal clear structure–activity relationships for the diazonamide class that could potentially instigate new pathways of investigation in the field of cancer chemotherapy. Explorations along these lines, as well as a full account of our synthetic studies in the diazonamide A area, will be reported in due course.



Scheme 4. Final stages and completion of the second total synthesis of diazonamide A (**1**): a) TPAP (1.0 equiv), NMO (5.0 equiv), molecular sieves (4 Å), CH_2Cl_2, 25 °C, 4 h, 62%; b) $POCl_3$/pyridine (1:2), 70 °C, 6 h, 35% (53% based on recovered starting material); c) aqueous HF (48%, 3.0 equiv), MeCN, 0 °C, 2 h, 95%; d) IBX (5.0 equiv), DMSO, 25 °C, 4 h; e) $NaClO_2$ (5.0 equiv), NaH_2PO_4 (5.0 equiv), resorcinol (5.0 equiv), DMSO/H_2O (10:1), 25 °C, 1 h, 89% over two steps; f) Et_2NH/THF (1:5), 25 °C, 4 h, 98%; g) HATU (2.0 equiv), collidine (6.0 equiv), DMF/CH_2Cl_2 (1:2, 1.0×10^{-4} M), 25 °C, 7 d, 10–15%; h) H_2 (1.0 atm), $Pd(OH)_2/C$ (20 wt%, excess), EtOH, 25 °C, 10 h; i) CbzCl (5.0 equiv), aqueous $NaHCO_3$/1,4-dioxane (1:2), 25 °C, 12 h, 35% over two steps; j) NCS (4.0 equiv), CCl_4/THF (1:1), 60 °C, 2 h; k) BCl_3 (1.0 M in CH_2Cl_2, 5.0 equiv), CH_2Cl_2, −78 °C, 10 min, then aqueous NaOH (15%, excess), THF, 25 °C, 12 h, 75% over two steps; l) DIBAL-H (1.0 M in toluene, 10 equiv, added portionwise), THF, −78→25 °C, 3 h, 56%; m) H_2 (2.0 atm), $Pd(OH)_2/C$ (20 wt%, catalytic), EtOH, 25 °C, 2 h; n) **2** (5.0 equiv), EDC (5.0 equiv), HOBt (5.0 equiv), $NaHCO_3$ (15 equiv), DMF, 25 °C, 12 h, 79% over two steps. TPAP = tetra-*n*-propylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, py = pyridine, IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, HATU = 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, NCS = *N*-chlorosuccinimide, DIBAL-H = diisobutylaluminum hydride.

Received: February 5, 2003 [Z51112]

Keywords: domino reactions · macrocycles · natural products · samarium · total synthesis

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[26] Although molecular models suggested the proximity of the reactive units, the steric hindrance within the system, in combination with the entropic penalties associated with the formation of a 12-membered ring with multiple elements of unsaturation from a far more flexible precursor, were the likely culprits that led to such recalcitrance.

[27] For other syntheses that benefited from this reagent combination, see: a) K. C. Nicolaou, A. E. Koumbis, M. Takayanagi, S. Natarajan, N. F. Jain, T. Bando, H. Li, R. Hughes, *Chem. Eur. J.* **1999**, *5*, 2622–2647; b) T. Hu, J. S. Panek, *J. Org. Chem.* **1999**, *64*, 3000–3001; c) D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. L. Katz, *Angew. Chem.* **1998**, *110*, 2864–2868; *Angew. Chem. Int. Ed.* **1998**, *37*, 2700–2704.

[28] This result, combined with the yields obtained for the macrocyclization steps in our first total synthesis, indicates that the presence of either macrocyclic unit does not favor the formation of the second, once again revealing the truly constrained and compact nature of diazonamide A.

[29] Oxidative cleavage of benzyl ethers has been reported, although none of the substrates possessed nitrogen atoms; for an example, see: J. D. Prugh, C. S. Rooney, A. A. Deana, H. G. Ramjit, *Tetrahedron Lett.* **1985**, *26*, 2947.

[30] Selected data for compound **22**: $R_f = 0.35$ (EtOAc/hexanes = 5:1); $[\alpha]_D^{20}$ (CH_3OH, $c = 0.69$) = −277.25; IR (film): $\tilde{\nu}_{max} = 3260$, 2919, 1713, 1660, 1602, 1496, 1443, 1401, 1302, 1261, 1214, 1155, 1055, 750 cm^{-1}; ^1H NMR (600 MHz, CD_3CN): $\delta = 10.38$ (s, 1H), 8.42 (s, 1H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.42–7.33 (m, 7H), 7.27 (br m, 1H), 7.22 (d, $J = 7.0$ Hz, 1H), 7.10 (d, $J = 7.4$ Hz, 1H), 6.89–6.87 (m, 2H), 6.82 (t, $J = 7.9$ Hz, 1H), 6.77 (d, $J = 7.9$ Hz, 1H), 6.73 (s, 1H), 6.15 (d, $J = 7.9$ Hz, 1H), 5.08 (AB quart, $J = 12.7$ Hz, $\tilde{\nu}_{AB} = 17.1$ Hz, 2H), 4.55 (t, $J = 7.4$ Hz, 1H), 4.24 (ddd, $J = 11.4$, 8.8, 3.1 Hz, 1H), 3.23 (t, $J = 12.7$ Hz, 1H), 2.68 (d, $J = 11.4$ Hz, 1H), 2.00 (m, 1H), 1.01 (d, $J = 6.1$ Hz, 3H), 0.91 ppm (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 174.9$, 173.8, 164.3, 156.3, 154.6, 152.9, 152.8, 143.2, 140.6, 138.0, 135.9, 134.5, 131.6, 130.6, 130.0, 129.4, 129.3, 128.8, 128.6, 128.2, 127.2, 126.9, 124.8, 124.5, 123.2, 122.7, 116.6, 112.4, 98.3, 67.0, 57.8, 57.0, 56.4, 37.8, 31.0, 19.6, 19.0 ppm; HRMS (MALDI): calcd for $C_{43}H_{32}Cl_2N_6O_7^+$: 815.1782 $[M+H^+]$, found: 815.1778.