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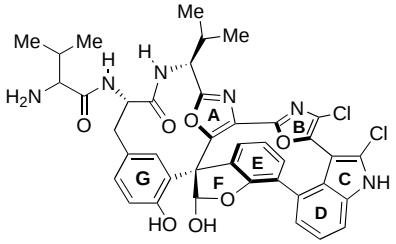
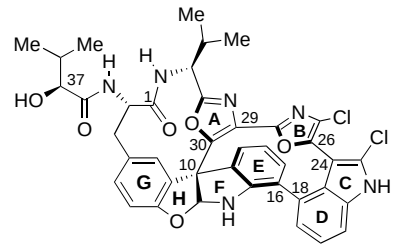
Total Synthesis of Diazonamide A**

K. C. Nicolaou,* Marco Bella, David Y.-K. Chen, Xianhai Huang, Taotao Ling, and Scott A. Snyder

In 1991, Fenical and co-workers reported structure **1** for diazonamide A, a marine natural product which had been isolated from the colonial ascidian *diazona angulata*.[1] A



1: original structure of diazonamide A



2: revised structure of diazonamide A

decade later, Harran and his group synthesized the proposed structure **1** only to prove that it was in error, and advanced structure **2** for diazonamide A instead.[2] In the intervening time, numerous efforts directed at the total synthesis of **1** had been reported;[3–13] no research activities related to the newly proposed structure **2** have yet been disclosed. The appeal of diazonamide A (**2**) stems both from its biological activity (cytotoxicity against several tumor cell lines with IC_{50} values $< 15\ ng\,mL^{-1}$) and its highly strained and unprecedented

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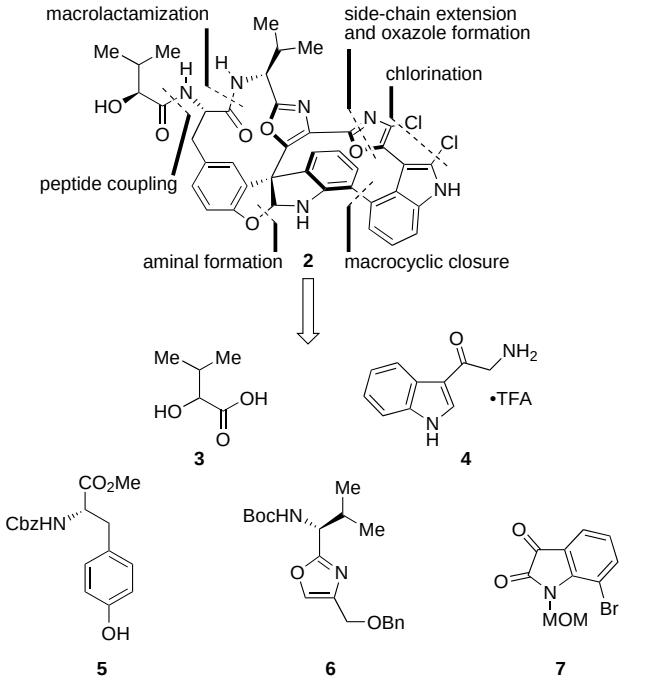
structure. Because of its scarcity from natural sources and its potential as a lead for the development of new chemotherapeutic agents, **2** presents a unique opportunity for chemical synthesis. In this communication, we report a total synthesis of diazonamide A (**2**) which required the development of new synthetic technologies and strategies and which provides a solution to this formidable molecular puzzle.

The revised structure of diazonamide A (**2**) represented a greater synthetic challenge than the one posed by the originally proposed structure (**1**) in that it contains an additional ring (ring H) and a nitrogen atom instead of the oxygen substituent in ring F which leads to a structurally unique aminal moiety. In addition to the rigidity associated with this EFGH tetracyclic system, its quaternary center (C10) preeminently stood as the central cornerstone of any synthetic strategy. The two 12-membered rings of the structure were also expected to pose considerable recalcitrance to formation owing to their severely constrained environments. In all, structure **2**, with its ten exquisitely arrayed rings and unique elements of stereochemistry, amounted to a rare challenge to modern synthetic chemistry.

Scheme 1 presents the blueprint of our strategy towards this target molecule in retrosynthetic format. Thus, excision of the

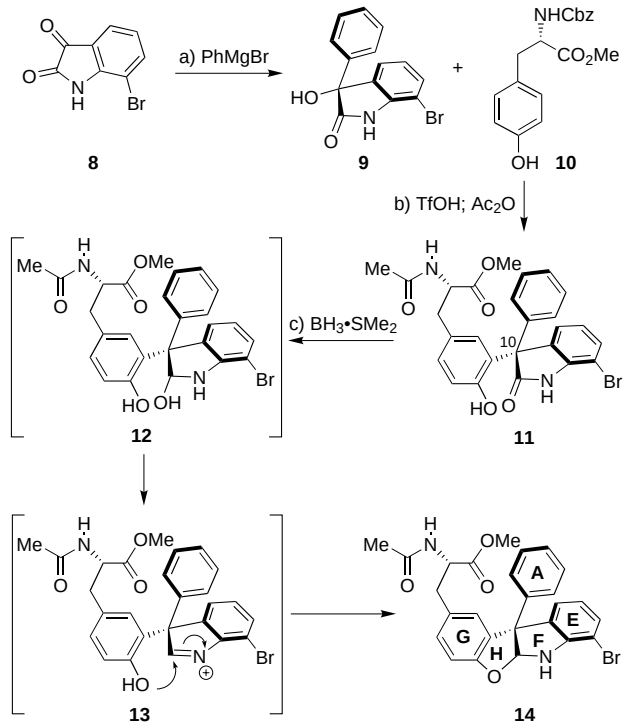


Scheme 1. General retrosynthetic analysis of diazonamide A (**2**). Cbz = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl, MOM = methoxy methyl, TFA = trifluoroacetic acid.

side chain and the chlorine atoms, and rupture of the macrolactam, aminal, oxazole, and bis-aryl ring systems as shown, led to fragments **3**–**7**. In the synthetic direction, the challenge was thus reduced to the following milestone events: a) construction of the required building blocks; b) assembly of the quaternary center with its substituents; c) formation of the 12-membered macrolactam ring system; d) introduction of the indole–oxazole domain; e) closure of the 12-membered polycyclic framework and chlorination; f) fusion of the aminal bicyclic network; and g) attachment of the isovaleric acid side chain (the operations to be executed in that order). The proposed late introduction of the side chain would allow for expedient construction of analogues, including the synthesis of the natural product's epimer at C37 for purposes of structural and biological comparison.

While all of the defined building blocks (**3**–**7**) were readily generated from commercially available starting materials according to literature procedures, the construction of the quaternary center (C10) with its peripheral structural motifs required considerable process development. To this end, the model study depicted in Scheme 2 was designed and executed. Thus, 7-bromoisatin (**8**)[14] was treated with excess PhMgBr to afford tertiary alcohol **9** in 96% yield. Upon mixing compound **9** with tyrosine derivative **10** in the presence of TfOH, and following acetylation of the resultant primary amine (as TfOH cleaved the Cbz group), phenolic lactam **11** emerged in 84% yield as a mixture of diastereomers (ca. 1:1).[15] Exposure of **11** to excess $BH_3{\cdot}SMe_2$ resulted in the formation of the bicyclic aminal system **14** (40% overall yield, unoptimized) containing some of diazonamide A's most challenging structural features, presumably via intermediates **12** and **13** as suggested in Scheme 2.

Prompted by this encouraging set of preliminary results, we then proceeded to apply the developed chemistry to the target molecule **2** as shown in Scheme 3. Having failed to successfully utilize the known oxazole ester derivative **15**[16] in the intended coupling reaction, we resorted to its reduction



Scheme 2. Model studies exploring the generation of the C10 quaternary center: a) PhMgBr (3.0 equiv), THF, 0°C, 96%; b) **10** (1.1 equiv), TfOH (10 equiv), CH_2Cl_2, 0°C, 20 min; then Ac_2O (10 equiv), CH_2Cl_2, 25°C, 5 min, 84%; c) $BH_3{\cdot}SMe_2$ (3.0 equiv), THF, 25°C, 4 h, 40%. TfOH = trifluoromethanesulfonic acid. Note: compounds **11**–**14** are mixtures of C10 epimers (ca. 1:1).

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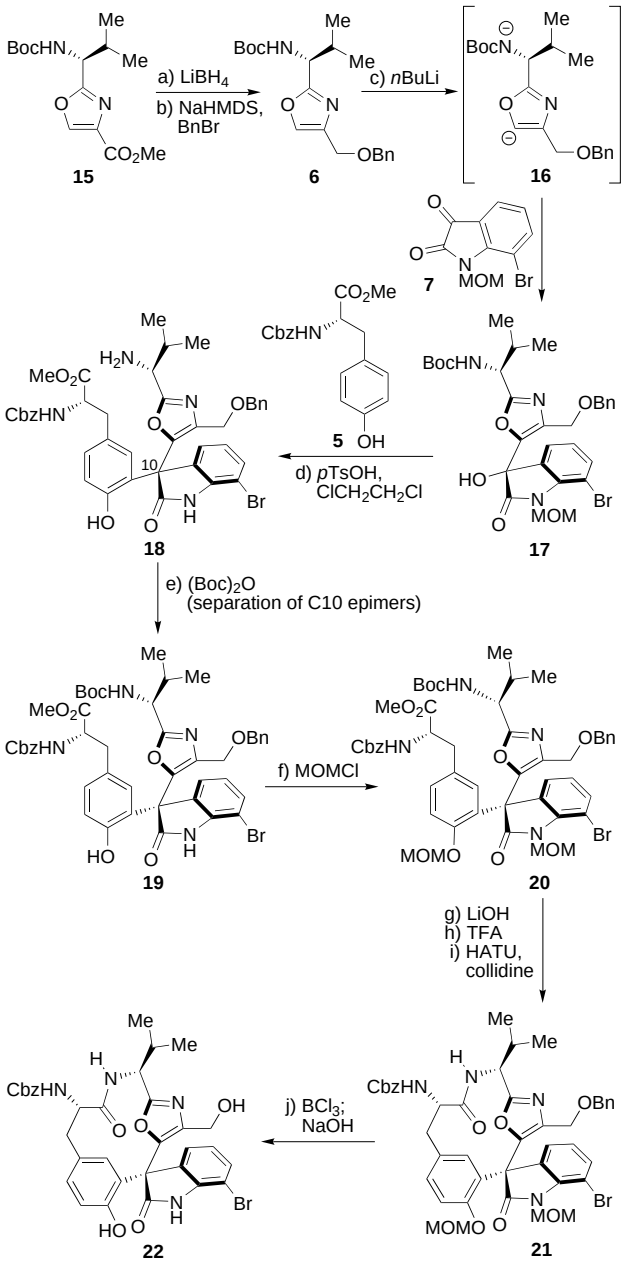
($LiBH_4$) and selective protection (60% overall yield)[17] to afford benzyl ether **6** as an alternative substrate for this process. Reaction of **6** with 2.0 equiv of *n*BuLi in THF at −78 °C resulted in the formation of dianion **16** which was treated with 1.1 equiv of isatin derivative **7**[18] at −78 °C to afford, upon standard workup, tertiary alcohol **17** in 73% yield. The crucial step of establishing the quaternary center assembly with its structural entourage was then accomplished by refluxing **17** with tyrosine derivative **5** (4.0 equiv) in 1,2-dichloroethane in the presence of *p*TsOH to furnish compound **18**, which had lost both the MOM and the Boc protective groups, in 33% yield. It is important to note that the triflic acid conditions utilized successfully in the model study (Scheme 2) failed in this instance; only decomposition products were obtained, which most likely arose from the oxazole moiety. Reprotection of the primary amine in **18** with $(Boc)_2O$ led to two C10 epimers whose chromatographic properties allowed their convenient separation to yield pure **19** and its epimer (not shown). Since the configuration of the quaternary center in these intermediates could not be determined at this stage, both epimers were separately carried forward to the corresponding macrolactams (**22** and its C10 epimer) whose spectroscopic data were suggestive of their structures (see below). The following step involved protection of the phenolic hydroxy group and the oxoindole amide nitrogen atom, an objective which was accomplished by exposing **19** to excess MOMCl and K_2CO_3 to afford compound **20** (94% yield). This precursor (**20**) was then transformed to the coveted macrolactam **21** by first liberating the carboxylic acid (LiOH) and the amino groups (TFA), in that order, and then cyclizing the resultant amino acid through the action of HATU and collidine in DMF/CH_2Cl_2 in 36% overall yield. This challenging formation of the 12-membered ring required high-dilution conditions to minimize formation of dimers and higher oligomers. It should also be noted that MOM protection of the precursor considerably improved the yield of this ring closure as compared to that obtained with unprotected material (i.e., **19**). Furthermore, of the two C10 epimers, only one cyclized smoothly whereas the other led to preferential dimerization even under extremely high dilution conditions. The next step in the sequence required removal of the benzyl group in the presence of the Cbz and the aryl bromine moieties, a challenging task that was accomplished by the use of BCl_3 in CH_2Cl_2 at −78 °C followed by treatment with NaOH. In this reaction, the two MOM groups in **21** were concomitantly cleaved to yield compound **22** in 61% overall yield.[19] At this stage, the ^1H NMR spectroscopic data of the more accessible macrolactam epimer (see Table 1) were reminiscent of those of diazonamide A (**2**). Therefore, we assumed the structure of this epimer to be that of **22** (that is to say, the one corresponding to the targeted natural product).

Having chosen epimer **22** as the most likely candidate to yield diazonamide A (**2**), its further elaboration proceeded as shown in Scheme 4. Thus, selective protection of the phenolic hydroxy group of **22** (Boc_2O), followed by sequential oxidation first with IBX and then with $NaClO_2$, furnished the expected carboxylic acid whose coupling with indole ammonium salt **4** in the presence of EDC and HOBt led to **23** (41% overall yield from **22**). This keto amide was then converted to



Scheme 3. Synthesis of advanced macrolactam **22**: a) $LiBH_4$ (2.0 M in THF, 3.0 equiv), EtOH (10 equiv), Et_2O/THF (2:1), 0→25 °C, 3 h, 83%; b) NaHMDS (1.0 M in THF, 2.0 equiv), THF, −78 °C, 10 min, then TBAI (0.1 equiv), BnBr (10 equiv), −78→25 °C, 24 h, 72%; c) *n*BuLi (2.0 equiv), THF, −78 °C, 20 min, then **7** (1.1 equiv), 10 min, 73%; d) **5** (4.0 equiv), *p*TsOH (4.0 equiv), $ClCH_2CH_2Cl$, 83 °C, 15 min, 33%; e) $(Boc)_2O$ (1.1 equiv), aq. $NaHCO_3$/dioxane (1:2), 25 °C, 2 h, 65%; f) MOMCl (30 equiv), K_2CO_3 (40 equiv), acetone, 0→25 °C, 2 h, 94%; g) LiOH (20 equiv), MeOH/THF/H_2O (2:10:1), reflux, 10 min, 98%; h) TFA, 10 min, 98%; i) HATU (2.2 equiv), collidine (6.6 equiv), DMF/CH_2Cl_2 (1:2, 3.0×10^{-4} M), 25 °C, 12 h, 36%; j) BCl_3 (1.0 M in hexanes, 20 equiv), CH_2Cl_2, −78 °C, 2 h; then THF, sat. aq. $NaHCO_3$, 10% aq. NaOH, 25 °C, 30 min, 61%. NaHMDS = sodium salt of 1,1,1,3,3,3-hexamethyldisilazane, TBAI = tetra-*n*-butylammonium iodide, *p*TsOH = *p*-toluenesulfonic acid, HATU = 2-(1*H*-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

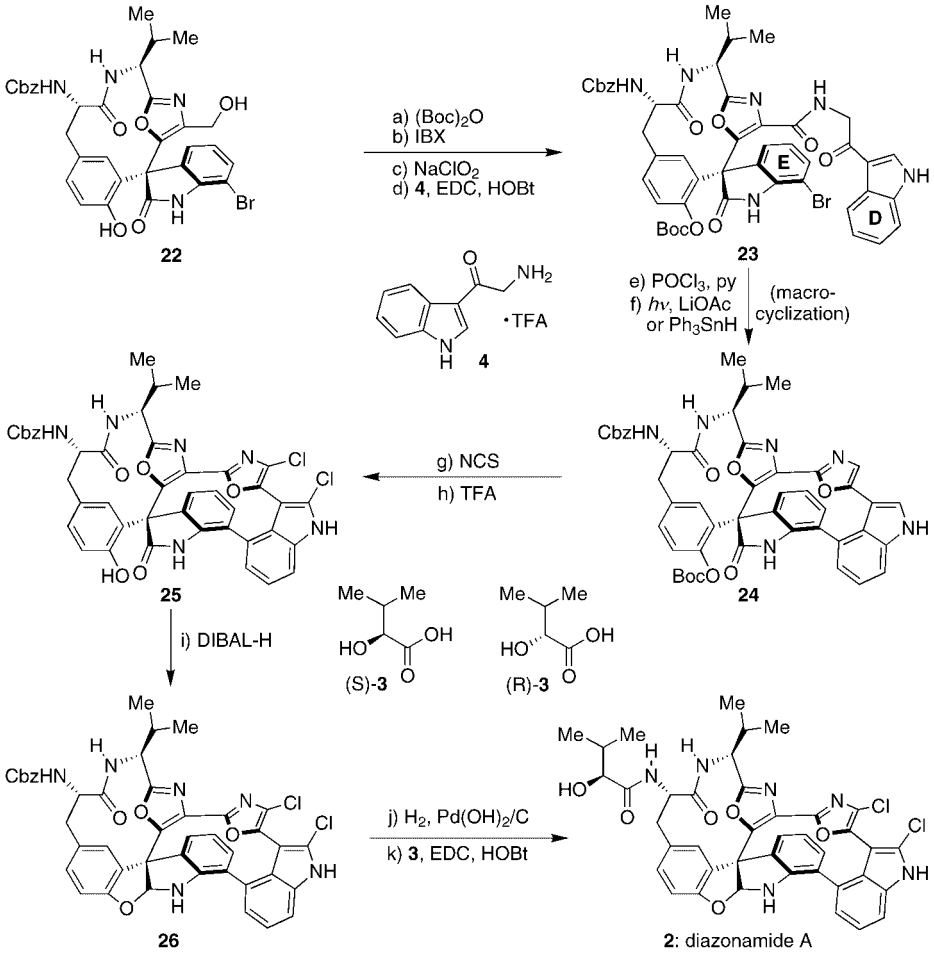
the corresponding oxazole system through a Gabriel–Robinson cyclodehydration effected by a unique set of conditions ($POCl_3$/pyridine)[20] which set the stage for the critical

Table 1. Selected data for compounds **22** and **26**.

22: $R_f = 0.41$ (silica gel, ethyl acetate); IR (film): $\tilde{\nu}_{max} = 3392, 1715, 1649, 1614, 1508, 1455, 1390, 1261, 1220, 1126, 1090, 1020, 750, 597\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN): $\delta = 8.66$ (s, 1H), 7.47 (d, $J = 7.9$ Hz, 1H), 7.37 (m, 4H), 7.34 (m, 1H), 7.27 (br d, 1H), 7.22 (s, 1H), 7.07 (d, $J = 7.4$ Hz, 1H), 7.02 (d, $J = 7.4$ Hz, 1H), 6.90 (t, $J = 7.9$ Hz, 1H), 6.70 (d, $J = 7.9$ Hz, 1H), 6.23 (s, 1H), 6.04 (br d, 1H), 5.07 (AB, $J = 12.3$ Hz, $\tilde{\nu}_{AB} = 21.9$ Hz, 2H), 4.45 (t, $J = 7.4$ Hz, 1H), 4.11 (t, $J = 9.2$ Hz, 1H), 3.63 (qd, $J = 9.2$, 5.7 Hz, 2H), 3.06 (t, $J = 12.7$ Hz, 1H), 2.77 (br s, 1H), 2.62 (d, $J = 12.7$ Hz, 1H), 2.04 (m, 1H), 1.01 (d, $J = 7.4$ Hz, 3H), 0.91 ppm (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 175.5$, 173.4, 164.6, 155.9, 153.0, 144.7, 142.4, 139.0, 138.0, 133.6, 133.0, 130.6, 130.0, 129.3, 128.8, 128.7, 128.6, 127.7, 125.4, 124.2, 116.2, 102.9, 67.0, 57.6, 57.0, 55.8, 38.4, 30.7, 19.6, 19.3 ppm; HR-MS (matrix-assisted laser desorption/ionization, MALDI) for $C_{33}H_{31}BrN_4O_7Na^+$ [M+Na$^+$]: calcd: 697.1268, found: 697.1266

cyclization event required to form the second 12-membered ring of diazonamide A. Most gratifyingly, radical cyclization of this precursor with Ph_3SnH/AIBN induced the desired ring closure to **24**, albeit in low yield (ca. 10%). The efficiency of this ring closure was improved to 30% by resorting to a Witkop-type reaction[21a] based on a literature procedure,[2a] a process that was proven effective in previous instances of macrocycle construction.[21b,c] Significantly, and in contrast to the Ph_3SnH-induced reaction (in which the majority of the substrate was reductively debrominated), the bulk of the remaining material from this process remained unchanged which allowed for productive recycling of recovered starting material. As such, this observation lends further support that this particular macrocyclization reaction proceeds through a mechanism based on intramolecular photo-induced electron transfer from the D-ring indole chromophore to the adjacent benzenoid E-ring,[2a] rather than some exclusively radical-based event in which case the halogen in the starting material would most likely be expelled.

With the establishment of both macrocyclic scaffolds of diazonamide A through the successful generation of **24**, completion of the synthesis required only a few finishing touches (see Scheme 4). First, the two, still missing, chlorine residues were installed at their proper positions by electrophilic aromatic substitution (NCS, 53% yield). Second, the resulting product was exposed to TFA to effect removal of the Boc group and furnish phenolic intermediate **25** (98% yield). Chemoselective reduction of the five-membered ring lactam of **25** with DIBAL-H initiated ring closure with participation of the adjacent phenolic hydroxy group to afford the desired cyclic aminal **26** in 55% overall yield. Finally, hydrogenolysis of the Cbz group with H_2 and Pearlman's catalyst followed by installation of the remaining peptide side chain with isovaleric acid ((*S*)-**3**) in the presence of EDC/HOBt furnished structure **2** in 82% overall yield. The ^1H NMR signals of synthetic **2** in [D_4]MeOH matched those reported for natural diazonamide A precisely, while those of the C37 epimer obtained by employing (*R*)-**3** in the final step were slightly, but diagnostically, different.[22] Based on this data, we confirm structure **2** for diazonamide A.



Scheme 4. Final stages and completion of the total synthesis of diazonamide A (**2**): a) $(Boc)_2O$ (30 equiv), sat. aq. $NaHCO_3$/dioxane (1:2), 25 °C, 24 h, 91% based on recovered starting material; b) IBX (3.0 equiv), DMSO, 25 °C, 2 h; c) $NaClO_2$ (5.0 equiv), NaH_2PO_4 (5.0 equiv), resorcinol (5.0 equiv), DMSO/H_2O (10:1), 0→25 °C, 2 h, 69% over two steps; d) **4** (3.0 equiv), EDC (5.0 equiv), HOBt (5.0 equiv), $NaHCO_3$ (15 equiv), DMF, 25 °C, 12 h, 65%; e) $POCl_3$/pyridine (1:4), 25 °C, 2 h, 52%; f) *hν* (200 nm), epichlorohydrin (3.0 equiv), LiOAc (2.0 equiv), MeCN/H_2O (3:1), 25 °C, 15 min, 30%—or Ph_3SnH (2.0 equiv), AIBN (0.1 equiv), C_6H_6, 80 °C, 3 h, 10%; g) NCS (4.0 equiv), CCl_4/THF (1:1), 60 °C, 2 h, 53%; h) TFA, 25 °C, 10 min, 98%; i) DIBAL-H (1.0 M in toluene, 100 equiv, added portionwise), THF, −78→25 °C, 3 h, 56%; j) H_2 (2.0 atm), $Pd(OH)_2$/C (20 wt%, catalytic), EtOH, 25 °C, 2 h; k) (*S*)-**3** (5.0 equiv), EDC (5.0 equiv), HOBt (5.0 equiv), $NaHCO_3$ (15 equiv), DMF, 25 °C, 12 h, 82% over two steps. IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one, py = pyridine, AIBN = 2,2′-azobisisobutyronitrile, NCS = *N*-chlorosuccinimide, DIBAL-H = diisobutylaluminum hydride.

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In conclusion, a path has now been chartered for the total synthesis of the long-sought diazonamide A which confirmed its structure as **2**, and through which this valuable, but scarce, natural substance is now rendered available for biological investigations.[23] Further synthetic work is expected to facilitate chemical biology studies and establish a clear structure–activity profile for this highly unusual molecular architecture.

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[14] 7-Bromoisatin (**8**) was prepared from 2-bromoaniline by a procedure similar to that reported for the synthesis of 7-iodoisatin: V. Lisowski, M. Robba, S. Rault, *J. Org. Chem.* **2000**, *65*, 4193 – 4194.

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[17] The use of NaHDMS was crucial in obtaining the desired benzylated product (**16**) in high yield. Other bases such as NaH or LiHMDS/HMPA led to significant amounts of bis-benzylated material by enabling engagement of the Boc-protected amine.

[18] MOM-protected 7-bromoisatin (**7**) was prepared from 7-bromoisatin (**8**) by treatment with LiHDMS and MOMCl. This protection was required to allow the use of stoichiometric amounts of the more precious oxazole species in the coupling reaction.

[19] In the conversion of **20** to **21**, partial cleavage of the phenolic MOM group was observed. The resulting material, however, was also serviceable for the subsequent steps leading to **22**.

[20] To the best of our knowledge, this particular reagent combination to generate an oxazole has not been reported previously, though simple dehydration with neat $POCl_3$ is known: R. L. Dow, *J. Org. Chem.* **1990**, *55*, 386 – 388. In our hands, this protocol provides a powerful method for oxazole construction in instances where more conventional dehydration procedures fail.

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[22] Especially revealing was the C37 proton signal (400 MHz, $[D_4]$MeOH) which, in the case of **2**, coincided precisely with the reported value for the natural product ($\delta = 3.88$ ppm), whereas in the case of its C37 epimer the signal for this proton appeared at $\delta = 3.92$ ppm. We should note that we were unable to obtain a sample of natural diazonamide A for direct comparison.

[23] Synthetic diazonamide A (**2**) exhibited potent cytotoxic activity at single digit nM concentrations against various human cancer cell lines of distinct origin, including ovarian carcinoma 1A9, lung carcinoma A549, prostate carcinoma PC-3, breast carcinoma MCS-7, and the taxol-resistant 1A9/PTX10 cell line. Its C37 epimer, although less active, also exhibited significant activity against the same cell lines. We thank Dr. Paraskevi Giannakakou and Aurora O'Brate of the Winship Cancer Institute, Emory University School of Medicine, for these biological assays.

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