diffractometer. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145227 (**I**), CCDC-145228 (**II**), and CCDC-145229 (**III**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

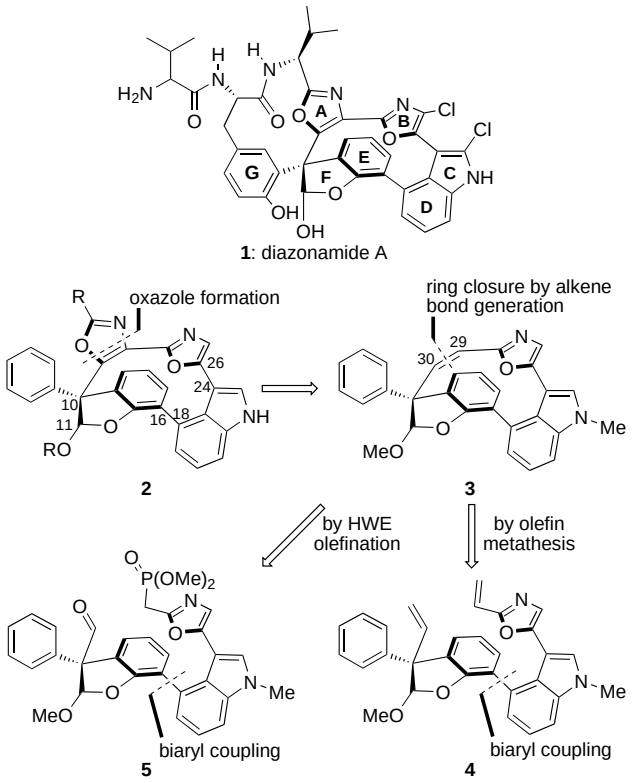
[12] G.Fèrey, *J. Solid. State Chem.* **2000**, *152*, 37.

[13] Crystal data for **II**: $[Cd(C_2O_4)]\cdot 2\,RbCl\cdot H_2O$, $M_r = 460.3$, crystal dimensions $0.06 \times 0.14 \times 0.18$mm, orthorhombic, space group, *Pbcm*, $a = 6.018(2)$, $b = 10.861(2)$, $c = 15.503(4)$ Å, $V = 1013.4(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 3.004$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 12.21$ mm^{-1}, $\lambda = 0.71073$ Å. The structure was solved by direct methods (SHELXTL-PLUS), 3866 reflections, 758 independent reflections. Full-matrix least-squares on $|F^2|$ (SHELXs-93, G. M. Sheldrick, Gottingen, **1993**) to $R_1 = 0.08$ and $wR_2 = 0.17$. Residual density, min./max.: $-2.72/2.03$ e Å^{-3}.[11b]]

[14] Crystal data for **III**: $K_2Cd(C_2O_4)_3\cdot 2\,KBr\cdot 2\,H_2O$, $M = 841.12$, crystal dimensions, $0.12 \times 0.12 \times 0.24$ mm, orthorhombic, space group, *Pbca*, $a = 11.898(6)$, $b = 10.963(1)$, $c = 15.203(6)$ Å, $V = 1983.2(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.817$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 7.077$ mm^{-1}, $\lambda = 0.71073$ Å. The structure was solved by direct methods (SHELXTL-PLUS), 7521 reflections, 1428 independent reflections. Full-matrix least-squares on $|F^2|$ (SHELXs-93, G. M. Sheldrick, Gottingen, **1993**) to $R_1 = 0.03$ and $wR_2 = 0.05$. Residual density, min./max.: $-0.593/0.369$ e Å^{-3}.[11b]]

[15] T. A. Kodenkandath, J. N. Lalena, W. I. Zhou, E. E. Carpenter, C. Sangregorio, A. U. Falster, J. R. Simmons, C. J. O'Connor, J. B. Wiley, *J. Am. Chem. Soc.* **1999**, *121*, 10743.

[16] Q. Huang, M. Ulutagay, P. A. Michener, S.-J. Hwu, *J. Am. Chem. Soc.* **1999**, *121*, 10323.



Scheme 1. Structure of diazonamide A (**1**) and retrosynthetic analysis of model system **2**.

Model Studies towards Diazonamide A: Synthesis of the Heterocyclic Core**

K. C. Nicolaou,* Scott A. Snyder, Klaus B. Simonsen, and Alexandros E. Koumbis

Diazonamide A (**1**, Scheme 1), a secondary metabolite isolated from the colonial ascidian *Diazona chinensis*, exemplifies an unprecedented molecular architecture encompassing a cyclic polypeptide backbone as well as an admirably complex and strained halogenated heterocyclic core trapped as a single atropisomer harboring a quaternary center at the epicenter.[1] Beyond the formidable synthetic challenge posed by such a daunting molecular framework, diazonamide A possesses potent in vitro cytotoxicity against human colon carcinoma and B-16 murine melanoma cell lines with IC_{50} values in the nanomolar range. These biological actions, however, are exerted through an unknown mode of action. Unfortunately, more extensive bioassays have been hampered by an inability to harvest additional material from the original source. As such, diazonamide A represents one of the most enticing natural products isolated in recent years and a serious challenge to synthetic chemists. Although several groups have reported progress on particular structural subunits of diazonamide A,[2] no one has yet successfully prepared the fully unsaturated 12-membered polycycle. Herein we report the first synthesis of this heteroaromatic macrocyclic core by a concise and novel strategy which proceeds to provide atropisomerically pure product.

Since we envisioned from the outset that the heterocyclic core would pose the greatest synthetic challenge for a total synthesis of diazonamide A, we focused our efforts primarily on the preparation of model system **3** (Scheme 1) as a means to address key synthetic issues such as potential atropisomerism along the $C_{16}-C_{18}$ and $C_{24}-C_{26}$ biaryl linkages. As shown in Scheme 1, our synthetic rationale was based on two fairly obvious but strategic bond disconnections. Because numerous methods are currently available to generate macrocycles by alkene bond formation, we felt that disconnection of the $C_{29}-C_{30}$ alkene would be prudent and could potentially arise in the

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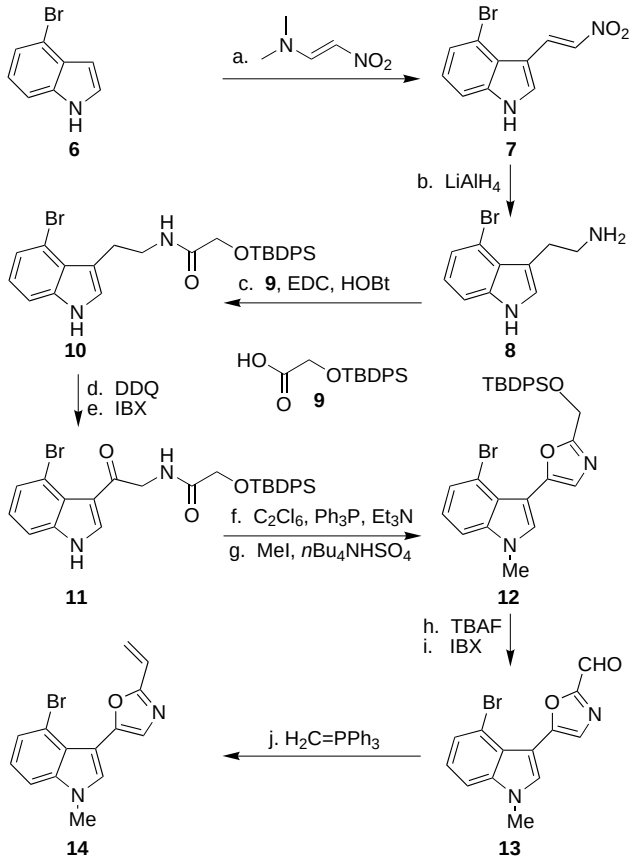
[**] We thank Dr. D. H. Huang, Dr. G. Suizdak, and Dr. R. Chadha for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. We also thank Professor R. H. Grubbs for a generous gift of catalyst **30**. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), a predoctoral fellowship from the National Science Foundation (S.A.S.), postdoctoral fellowships from the Alfred Benzons Foundation and the Danish Natural Science Research Council (K.B.S.), and grants from Abbott, Amgen, Array-Biopharma, Boehringer–Ingelheim, GlaxoWellcome, Hoffmann–LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

forward direction either by metathesis of the olefinic groups in **4** or by an intramolecular Horner–Wadsworth–Emmons (HWE) reaction between the phosphonate and aldehyde residues in **5**; the resultant $C_{29}-C_{30}$ alkene could then serve as a scaffold upon which to construct the A-ring oxazole, thereby completing the ABCDEF polycycle **2**. From either **4** or **5**, our second key disconnection rupturing the $C_{16}-C_{18}$ biaryl linkage revealed, by a retro Suzuki or Stille type coupling, two fragments of roughly equal molecular complexity, thereby affording a highly convergent retrosynthetic blueprint.

Due to the power of the olefin metathesis reaction in macrocycle formation, particularly with regard to complex natural product total synthesis,[3] we initially sought to test this method as a means to generate the $C_{29}-C_{30}$ alkene. Toward this end, our synthetic endeavors commenced with preparation of the BCD indole–oxazole fragment **14** as shown in Scheme 2. Starting from 4-bromoindole (**6**),[4] condensation



Scheme 2. Preparation of indole–oxazole fragment **14**: a) Dimethylamino-2-nitroethylene (1.1 equiv), TFA, 25 °C, 30 min; b) $LiAlH_4$ (1.0 M in THF, 6.0 equiv), THF, 25 °C → 65 °C, 4 h, 87% over two steps; c) **9** (1.0 equiv), EDC (1.0 equiv), HOBt (1.0 equiv), CH_2Cl_2, 25 °C, 2 h, 79%; d) DDQ (3.0 equiv), THF/H_2O (9/1), 0 °C, 3 h; e) IBX (3.0 equiv), THF/DMSO (1/1), 25 °C, 3 h, 90% over two steps; f) Cl_3CCCl_3 (2.0 equiv), Ph_3P (2.0 equiv), Et_3N (4.0 equiv), 25 °C, 15 min; g) MeI (4.0 equiv), nBu_4NHSO_4 (1.1 equiv), C_6H_6, 10% aq. NaOH, 25 °C, 20 min, 88% over two steps; h) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 15 min, 92%; i) IBX (3.0 equiv), THF/DMSO (1/1), 25 °C, 3 h, 90%; j) methylene triphenylphosphonium bromide (1.5 equiv), *n*BuLi (1.6 M in hexanes, 1.3 equiv), THF, 0 → 25 °C, 15 min, 89%. TFA = trifluoroacetic acid, EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, TBDPS = *tert*-butyldiphenylsilyl, HOBt = 1-hydroxy-1*H*-benzotriazole, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF = tetrabutylammonium fluoride, IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide.

with dimethylamino-2-nitroethylene[5] followed by $LiAlH_4$-mediated reduction readily afforded 4-bromotryptamine (**8**) in 87% overall yield. Subsequent coupling of **8** with TBDPS-protected glycolic acid derivative **9**[6] in the presence of EDC and HOBt smoothly provided intermediate **10** (for abbreviations of reagents and protecting groups, see legends in schemes). Although the conversion of **10** to **11** upon treatment with DDQ is known,[7] we found that far superior yields of **11** could be obtained by reverting to a two-step procedure in which initial exposure of **10** to DDQ in THF/H_2O (9/1) at 0 °C resulted in formation of the desired benzylic hydroxy group which was then readily oxidized by using IBX (90% overall yield).[8] Notably, protection of the indole nitrogen was unnecessary during this synthetic sequence and exposure to IBX did not afford any N-oxidized products. The synthesis of **14** was then completed through the following five-step protocol: 1) formation of the oxazole ring using a modified variant of the Gabriel–Robinson cyclodehydration reaction;[9] 2) *N*-methyl protection of the indole nucleus employing phase-transfer conditions (88% over two steps); 3) TBAF-mediated cleavage of the terminal TBDPS group (92%); 4) oxidation of the resultant hydroxyl group with IBX (90%); and 5) generation of the desired alkene upon Wittig reaction of **13** with $Ph_3P{=}CH_2$ (89%).

Our next task was to synthesize the requisite EFG fragment **26**, as delineated in Scheme 3. Although numerous methods to access such benzofuranone fragments in racemic form are known, we sought to develop a novel route to this type of system with the hope of generating the C_{10} quaternary center of diazonamide A stereoselectively. As such, our approach began with aldehyde **15**.[10] After initial treatment of **15** with PhMgBr, the hydroxy group of the resultant bisbenzylic compound was smoothly oxidized by utilizing IBX, and the newly generated ketone was treated with $Ph_3P{=}CH_2$ to afford olefin **16** in 80% overall yield over these three steps. Acid-catalyzed removal of the methoxymethyl (MOM) protecting group was then followed by alkylation of the resultant phenolic residue with chloroacetonitrile in acetone to afford **17** in 75% yield. Subsequent *m*CPBA-mediated epoxidation of the olefin provided key intermediate **18**. As shown in Scheme 4, we envisaged that upon exposure of **18** to base, deprotonation of the methylene group adjacent to the cyanide followed by selective 5-*exo*-tet opening of the epoxide ring would lead to the desired quaternary system **21** via intermediate **20**.[11] Gratifyingly, treatment of **18** with KO*t*Bu in DMF at −57 °C followed by immediate quenching with 10% aqueous HCl at that temperature afforded **21** in 54% yield. The only other product observed in this novel cyclization step was 3-phenylbenzofuran **22**, which resulted from a previously reported cyclofragmentation reaction.[12] With **21** in hand, subsequent TBS protection afforded crystalline intermediate **23**, which when subjected to X-ray analysis[13] revealed that the cyclization reaction proceeded to give a racemic mixture of compounds possessing only the relative *trans* stereochemistry as indicated for **21** and **23**. As such, stereoselective generation of the epoxide in **18** followed by our cyclization protocol would provide an enantioselective route to the C_{10} quaternary center of diazonamide A.

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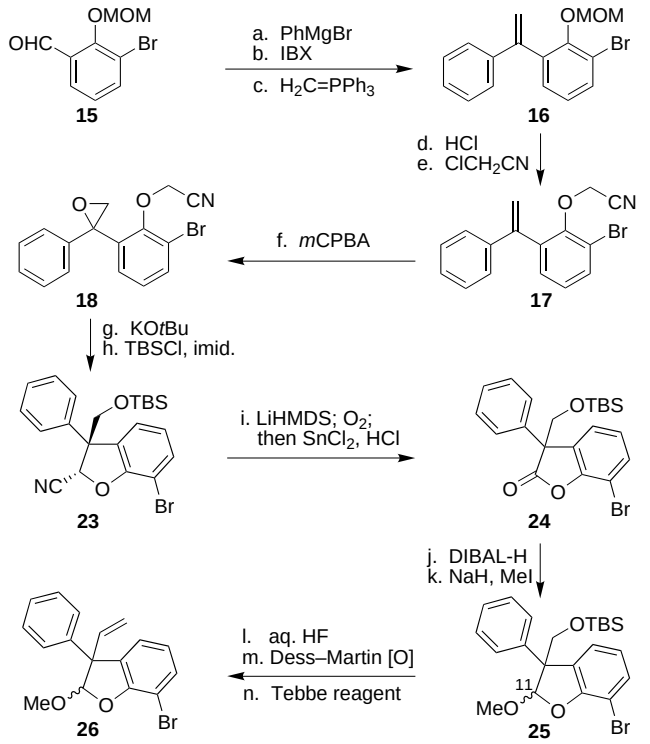
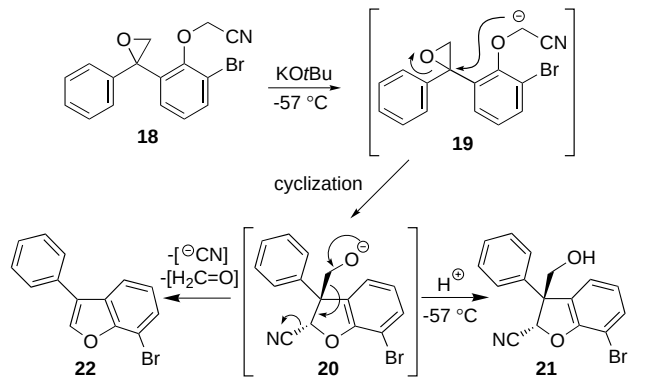


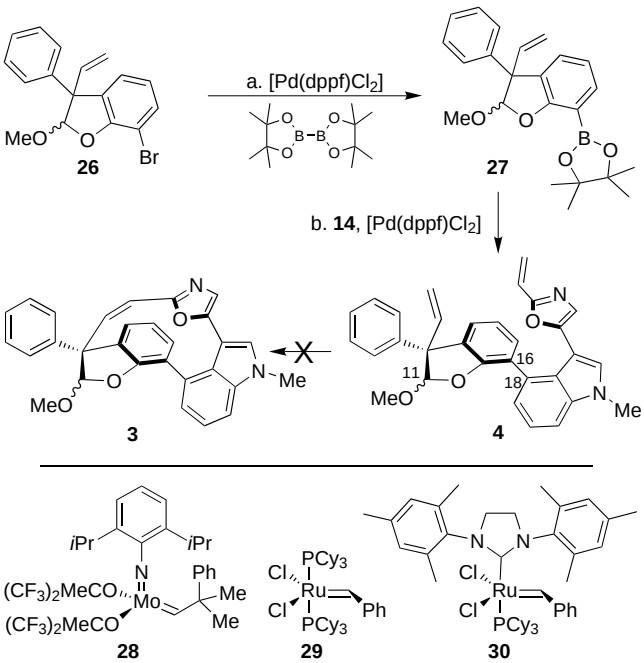
Scheme 3. Preparation of quaternary center fragment **26**: a) PhMgBr (1.0 M in THF, 1.3 equiv), THF, $-78\rightarrow25\,^{\circ}C$, 2 h, 100%; b) IBX (2.0 equiv), THF/DMSO (1/1), 25 °C, 1 h, 93%; c) methylene triphenylphosphonium bromide (1.4 equiv), *n*BuLi (1.6 M in hexanes, 1.2 equiv), THF, 0 °C, 12 h, 86%; d) conc. HCl, EtOH/CH_2Cl_2 (2/1), 40 °C, 12 h, 100%; e) $ClCH_2CN$ (3.0 equiv), K_2CO_3 (2.0 equiv), acetone, 56 °C, 2 h, 75%; f) *m*CPBA (3.0 equiv), CH_2Cl_2, 25 °C, 6 h, 91%; g) KO*t*Bu (1.0 M in THF, 1.5 equiv), DMF, $-57\,^{\circ}C$, 2 min; then 10% HCl (excess), $-57\,^{\circ}C$, 54%; h) TBSCl (1.5 equiv), imidazole (2.0 equiv), DMF, 25 °C, 12 h, 99%; i) LiHMDS (1.0 M in THF, 2.0 equiv), THF, $-78\,^{\circ}C$, 15 min; O_2, 15 min, $-78\,^{\circ}C$; 1 M $SnCl_2$ in 10% aq. HCl, $-78\rightarrow0\,^{\circ}C$, 30 min, 94%; j) DIBAL-H (1.0 M in toluene, 1.5 equiv), toluene, $-78\,^{\circ}C$, 1 h, 92%; k) NaH (60% dispersion in mineral oil, 3.0 equiv), MeI (5.0 equiv), THF, 25 °C, 24 h, 91%; l) aq. HF, MeCN, 0 °C, 1 h, 99%; m) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, $0\rightarrow25\,^{\circ}C$, 2 h, 96%; n) Tebbe reagent (0.5 M in toluene, 1.5 equiv), THF, 0 °C, 10 min, 74%. MOM = methoxymethyl, imid. = imidazole, *m*CPBA = *m*-chloroperoxybenzoic acid, TBS = *tert*-butyldimethylsilyl, LiHMDS = lithium salt of 1,1,1,3,3,3-hexamethyldisilazane, DIBAL-H = diisobutylaluminum hydride.



Scheme 4. Novel cyclization reaction to generate **21**.

The synthesis of **26** from **23** was then completed in six additional transformations. First, **23** was readily converted to benzofuranone **24** upon treatment with LiHMDS followed by exposure to O_2 and $SnCl_2$.[14] Next, the lactone moiety was partially reduced with DIBAL-H to the corresponding lactol with subsequent protection of the hydroxy group as a methyl ether using NaH and MeI to afford **25** in 79% overall yield from **23**. Although the reduction proceeded stereoselectively, the methylation step resulted in epimerization of the C_{11} center. The TBS ether was then easily cleaved upon exposure to aqueous HF in MeCN, and the resultant primary alcohol was oxidized to the corresponding aldehyde using Dess–Martin periodinane. Finally, the desired terminal alkene group of **26** was generated upon treatment with Tebbe reagent (70% yield from **25**). Significantly, attempts to synthesize the final alkene through Wittig homologation utilizing $Ph_3P=CH_2$ led solely to 3-phenylbenzofuran **22** (Scheme 4). We postulate that a betaine intermediate (unobserved in the reaction with Tebbe reagent presumably due to the high oxophilicity of titanium) potentially provides a species capable of undergoing a cyclofragmentation reaction to **22**.

With **14** and **26** in hand, the stage was now set to attempt biaryl coupling of the two fragments and, subsequently, the key olefin metathesis-based macrocyclization. Efforts to prepare the boronic acid of either **14** or **26** under standard conditions (*n*BuLi, $B(OMe)_3$) failed in numerous attempts. However, as shown in Scheme 5, the boronate ester of **26** was

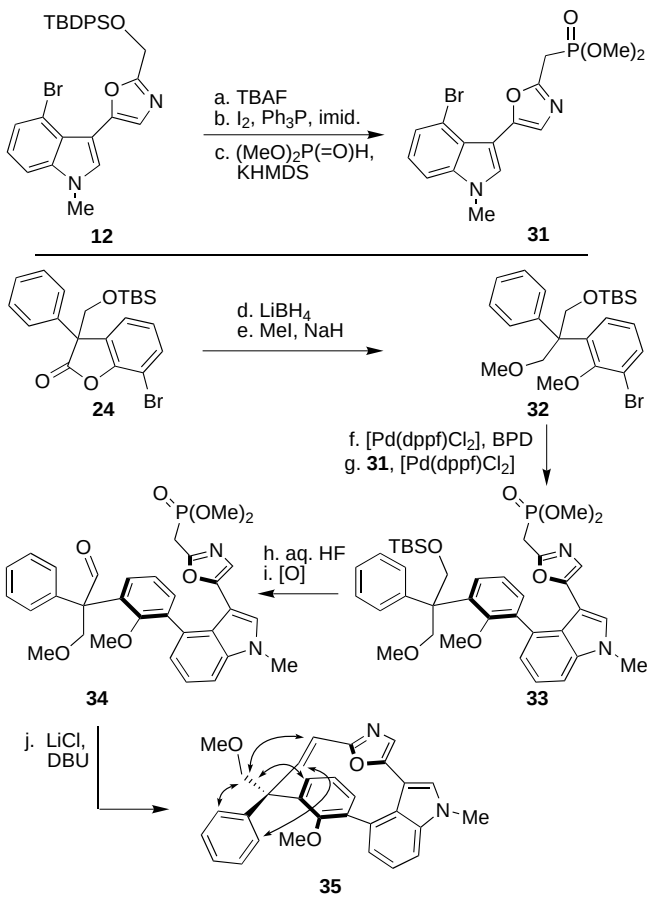


Scheme 5. Biaryl coupling to generate **4** and attempted olefin metatheses with catalysts **28**–**30** to provide **3**: a) Bis(pinacolato)diboron (1.2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0.15 equiv), KOAc (3.0 equiv), DMSO, 90 °C, 6 h, 42%; b) **14** (1.0 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0.15 equiv), K_2CO_3 (5.0 equiv), DME, 85 °C, 2 h, 62%. dppf = diphenylphosphanylferrocene, Cy = cyclohexyl.

generated in modest yield (42%) using the conditions described by Ishiyama et al.[15] and, gratifyingly, **27** could readily be coupled with **14** using $[Pd(dppf)Cl_2]$ and K_2CO_3 in DME at 85 °C to afford **4** in 62% yield. As expected, ^1H NMR analysis of **4** indicated a diastereomeric mixture of four compounds due to the mixture of C_{11} epimers and atropisom-

ers around the newly formed $C_{16}-C_{18}$ biaryl linkage, confirming a result observed earlier in a related system.[2c] Unfortunately, although we were extremely pleased to have prepared **4** in only 16 linear steps from known starting materials, our excitement was quickly dashed when attempted olefin metatheses (toluene, 70 °C, several days) in the presence of catalysts **28**, **29**, or **30**[16] failed to result in **3** and led only to recovered starting material or decomposition. Although we recognized from the outset that olefin metathesis in this system would prove challenging, with potential difficulties arising from the presence of heterocycles containing basic nitrogen atoms and the fact that styrene derivatives are less favorable substrates for the reaction,[17] we believe that steric hindrance close to the double bonds is the overriding factor which prevents successful formation of **3**.[18]

Despite these discouraging results, we felt that our overall synthetic plan could be resurrected, with little alteration of the previously developed chemistry, by utilizing an intramolecular variant of the HWE reaction, an extremely powerful and mild C–C bond-forming process which has been widely employed in organic synthesis.[19] Although we desired to construct an intermediate such as **5** (see Scheme 1) possessing the requisite aldehyde and phosphonate functionalities necessary for condensation, based on our failure to generate alkene **26** from **25** using $Ph_3P{=}CH_2$ we felt that the carefully constructed lactol system would have to be opened prior to the key HWE reaction to prevent similar formation of a 3-arylbenzofuran product. As such, we initiated efforts to prepare key intermediate **34**, as delineated in Scheme 6. The indole phosphonate **31** was readily generated in 74% overall yield from the previously synthesized indole–oxazole **12** by initial removal of the TBDPS group upon exposure to TBAF, halogen exchange of the resultant hydroxy group, and mild formation of the phosphonate residue by S_N2 displacement of the primary iodide using the anion generated from dimethyl phosphite. The other key building block, compound **32**, was synthesized in two steps from **24** in 63% overall yield utilizing $LiBH_4$ to fully reduce the lactone, followed by methylation of both the phenolic and the primary hydroxy groups. As before, the boronate ester of **32** was synthesized in 49% yield using bis(pinacolato)diboron in the presence of $[Pd(dppf)Cl_2]$ and KOAc, and this intermediate could then be directly coupled to phosphonate **31** in 52% yield utilizing the Suzuki reaction protocol employed earlier.[20] Subsequent cleavage of the TBS ether followed by Dess–Martin oxidation provided the key aldehyde phosphonate **34** in 85% yield over the two steps. Despite the failure of initial attempts to effect macrocyclization under mildly basic conditions (K_2CO_3, [18]crown-6),[19b,c] use of LiCl and DBU[21] smoothly led to the formation of a new product in just 6 h at ambient temperature in 45% yield. Although NMR analysis of this HWE product confirmed that macrocyclization did indeed occur, NOE studies verified that only a single diastereomer of **34** reacted, providing **35** with the indicated undesired stereochemistry. As such, this particular pathway does not represent a viable method to prepare model system **3** since the previously opened F ring is inaccessible from **35**. However, the power of the HWE reaction to effect macrocyclization and install such a *trans* alkene in this highly strained system was encouraging. As such, we felt that we had to test whether our earlier reservations about employing aldehyde phosphonate **5** for an intramolecular HWE reaction were warranted.



Scheme 6. Formation of macrocyclic alkene **35**: a) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 15 min, 92%; b) Ph_3P (1.7 equiv), imidazole (2.0 equiv), I_2 (1.5 equiv), CH_2Cl_2, 0 °C, 10 min, 94%; c) $(MeO)_2P(=O)H$ (2.0 equiv), KHMDS (0.5 M in toluene, 1.5 equiv), THF, 0 °C, 10 min, 86%; d) $LiBH_4$ (2.0 M in THF, 2.0 equiv), Et_2O, 0 °C, 2 h, 90%; e) NaH (60% dispersion in mineral oil, 5.0 equiv), MeI (10.0 equiv), THF, 25 °C, 12 h, 70%; f) bis(pinacolato)diboron (1.2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0.15 equiv), KOAc (3.0 equiv), DMSO, 90 °C, 4 h, 49%; g) **31** (1.0 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0.30 equiv), K_2CO_3 (5.0 equiv), DME, 85 °C, 2 h, 52%; h) aq. HF, MeCN, 0 °C, 15 min; i) Dess–Martin periodinane (2.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 0→25 °C, 1 h, 85% over two steps; j) DBU (5.0 equiv), LiCl (5.0 equiv), MeCN, 25 °C, 6 h, 45%. BPD = bis(pinacolato)diboron, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, KHMDS = potassium salt of 1,1,1,3,3,3-hexamethyldisilazane. Selected NOE interactions shown for **35** confirm the indicated stereochemistry.

Towards this end, **5** (see Scheme 7) was easily synthesized in four steps from **25** and **31** utilizing chemistry described earlier and, most gratifyingly, subsequent treatment of **5** with NaH in THF at 0 °C resulted in the formation of macrocycle **3** in 25% yield with none of the previously feared cyclofragmentation observed. Although NMR analysis of all intermediates from

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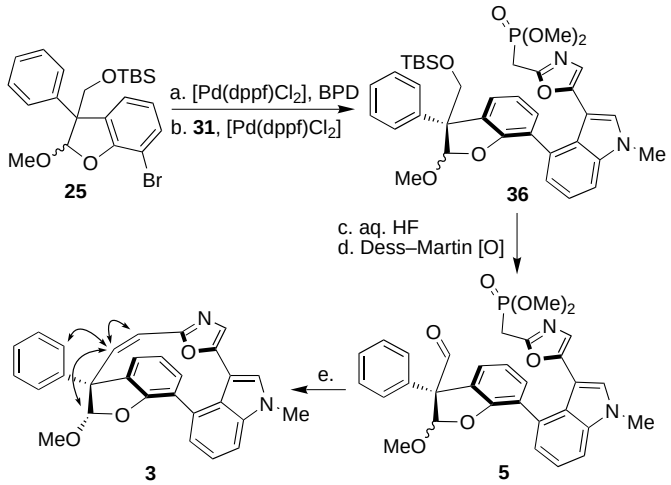
Table 1. Selected physical properties for compounds **35** and **3**.

35: $R_f = 0.12$ (silica gel, ethyl acetate/hexane 1/1); IR (film): $\tilde{\nu}_{max} = 2912$, 2851, 1590, 1487, 1451, 1410, 1371, 1226, 1108, 1010, 795, 703 cm^{-1}; ^1H NMR (600 MHz, CD_3CN): $\delta = 7.98$ (d, $J = 17.5$ Hz, 1H), 7.46 (s, 1H), 7.44 (dd, $J = 8.3$, 0.8 Hz, 1H), 7.42 (dd, $J = 8.3$, 1.3 Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.25–7.23 (m, 2H), 7.15 (dd, $J = 8.1$, 1.5 Hz, 1H), 6.98 (t, $J = 7.7$ Hz, 1H), 6.98 (dd, $J = 7.4$, 0.9 Hz, 1H), 6.85 (s, 1H), 6.82 (dd, $J = 7.4$, 1.7 Hz, 1H), 5.87 (d, $J = 17.5$ Hz, 1H), 4.26 (AB, $J = 9.2$ Hz, $\nu_{ab} = 64.7$ Hz, 2H), 3.81 (s, 3H), 3.31 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 162.0$, 157.6, 149.3, 148.2, 146.1, 141.1, 139.4, 139.2, 134.0, 130.4, 130.3, 129.0, 128.8, 127.1, 125.5, 125.4, 123.9, 122.3, 122.3, 117.9, 114.5, 110.8, 104.3, 75.3, 60.3, 60.2, 59.5, 33.7; HR-MS (matrix-assisted laser desorption/ionization) for $C_{30}H_{27}N_2O_3^+$ [$M+H^+$]: calcd: 463.2016, found: 463.2005.

3: $R_f = 0.18$ (silica gel, ethyl acetate/hexane 1/1); IR (film): $\tilde{\nu}_{max} = 2925$, 1591, 1492, 1446, 1373, 1225, 1190, 1115, 928, 747 cm^{-1}; ^1H NMR (600 MHz, CD_3CN): $\delta = 7.53$ (dd, $J = 8.3$, 0.8 Hz, 1H), 7.46 (s, 1H), 7.42–7.38 (m, 5H), 7.33–7.29 (m, 1H), 7.20 (dd, $J = 7.0$, 0.9 Hz, 1H), 6.97 (dd, $J = 8.5$, 1.3 Hz, 1H), 6.95 (dd, $J = 8.3$, 1.3 Hz, 1H), 6.90 (d, $J = 12.7$ Hz, 1H), 6.86 (s, 1H), 6.81 (t, $J = 7.4$ Hz, 1H), 6.46 (d, $J = 12.7$ Hz, 1H), 5.99 (s, 1H), 3.88 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN): $\delta = 159.0$, 146.0, 143.0, 138.5, 132.5, 131.9, 131.0, 130.9, 130.2, 129.4, 128.7, 127.9, 127.8, 126.4, 126.3, 124.5, 124.0, 123.3, 123.0, 122.0, 121.6, 119.1, 116.7, 110.9, 61.0, 57.9, 33.7; HR-MS (matrix-assisted laser desorption/ionization) for $C_{29}H_{23}N_2O_3^+$ [$M+H^+$]: calcd: 447.1703, found: 447.1707.



Scheme 7. Synthesis of heterocyclic macrocycle **3**: a) Bis(pinacolato)diboron (1.2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0.15 equiv), KOAc (3.0 equiv), DMSO, 90 °C, 4 h, 50%; b) **31** (1.0 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0.30 equiv), K_2CO_3 (3.0 equiv), DME, 85 °C, 2 h, 60%; c) aq. HF, MeCN, 0 °C, 15 min; d) Dess–Martin periodinane (2.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 8 h, 85% over two steps; e) NaH (2.0 equiv), THF, 0 °C, 1 h, 25%. Selected NOE interactions shown for **3** confirm the indicated stereochemistry.

36 onward indicated a diastereomeric mixture of four compounds (due to a mixture of C_{11} epimers and atropisomerism around the $C_{16}-C_{18}$ linkage), similar examination of **3** indicated that only a single diastereomer, which possesses the stereochemistry shown, resulted from this final transformation. Theoretically, one would expect a 50% yield from this HWE reaction since the atropisomers cannot interconvert at the reaction temperatures employed and only half of the material would have both the aldehyde and phosphonate groups on the same side of the molecule. Although this expectation was met, surprisingly only one of the C_{11} epimers underwent the condensation reaction. Despite this unexpected outcome, the HWE reaction still served as an excellent means by which to separate the $C_{16}-C_{18}$ atropisomers which resulted from the Suzuki coupling, providing **3** in atropisomerically pure form.

In conclusion, although the synthesis of the heterocyclic core of diazonamide A initially seemed elusive after numerous failed approaches, both as illustrated here as well as in several attempts whose description will have to await the full account of this work, the power of the Suzuki and HWE reactions to effect C–C bond formation has ultimately provided a highly convergent solution for the preparation of model system **3** in just 17 linear steps from known starting materials. As such, multigram quantities of both **25** and **31** are available, and analogues of both fragments for future biological studies can readily be incorporated into the existing synthetic pathway. Additionally, the chemistry described for the preparation of **25** has already been employed[22] to synthesize a tyrosine-derived benzofuranone fragment possessing the requisite functionality necessary to complete diazonamide A. Continuing studies aim at the total synthesis of diazonamide A and further investigations of the chemical biology of this important new class of antitumor agents.

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Triplet Di(9-anthryl)carbene Undergoes Trimerization**

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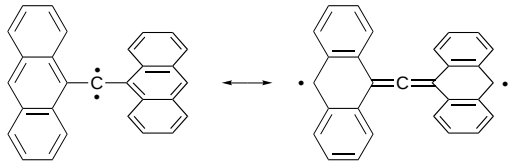
A large number of triplet carbenes have been characterized by electron paramagnetic resonance (EPR) spectroscopy.[1, 2] The principal information extracted from EPR spectra of triplet carbenes in randomly oriented matrices are the zero-field splitting (ZFS) parameters D and *E*, where *D* is a measure of the number of the unpaired electrons and thus allows the amount of delocalization in a carbene with conjugated π systems to be determined, while *E* measures the difference in the magnetic dipole interaction and, when weighted by *D*, allows one to estimate the bond angle at the carbene center.

Among the many triplet carbenes known, triplet di(9-anthryl)carbene (**1**) is unique as it shows the smallest *D* (0.113 cm^{-1}) and *E* (0.0011 cm^{-1}) values ever reported. This



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means that the carbene has almost linear and perpendicular geometry with extensive delocalization of the unpaired electrons into the anthryl portions of the molecule.[3]

Although these spectroscopic results suggest that the carbene should exhibit a reactivity that is substantially different from that observed for other diarylcarbenes, its chemistry has not been studied extensively. Herein we report that the carbene undergoes an unusual trimerization reaction, one that has never been observed before for any other carbenes.[4]

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