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A Synthesis of the Diazonamide Heteroaromatic Biaryl Macrocycle/ Hemiaminal Core

Matthew A. Zajac and Edwin Vedejs*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

edved@umich.edu

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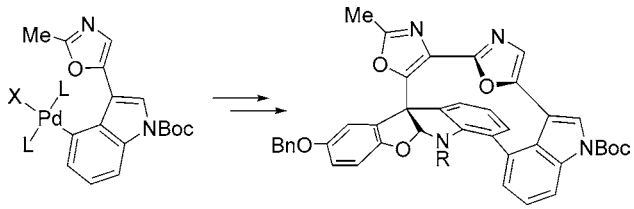
ABSTRACT



Stille coupling of an arylstannane aminal 19 with the palladium complex 23 leads to atropisomeric esters 28 and 29. Conversion to macrocycle 30 is demonstrated, a potential precursor of natural and unnatural diazonamides.

The structure of diazonamide A was recently revised from the originally proposed hemiacetal **1**[1] to the bicyclic aminal **2**.[2] Both of these structures have now been prepared by total synthesis,[2a,c,3,4] so there is no basis to doubt the identity of diazonamide A. Many questions remain to be addressed, however, including the structural features needed for biological activity, the prospects for efficient enantiocontrolled synthesis, and alternatives for assembly of the unique heteroaromatic core of diazonamides.

After the massive effort expended by many groups to prepare advanced intermediates targeting the incorrect structure **1**,[5,6] another important interim goal is to establish which of the original strategies is viable in the context of the revised structure. Here we describe our efforts to adapt a strategy that we had reported for the synthesis of the incorrect heteroaromatic core structure **3** in an earlier study. We had originally targeted a bicyclic acetal, as in **3**, based on the conjecture that an analogous acetal may be the biologically active form of diazonamide.[6a] Consequently, the revised structure of diazonamide A appeared to fit well with our approach, assuming that the bicyclic aminal would serve in the same beneficial role as had the bicyclic acetal in

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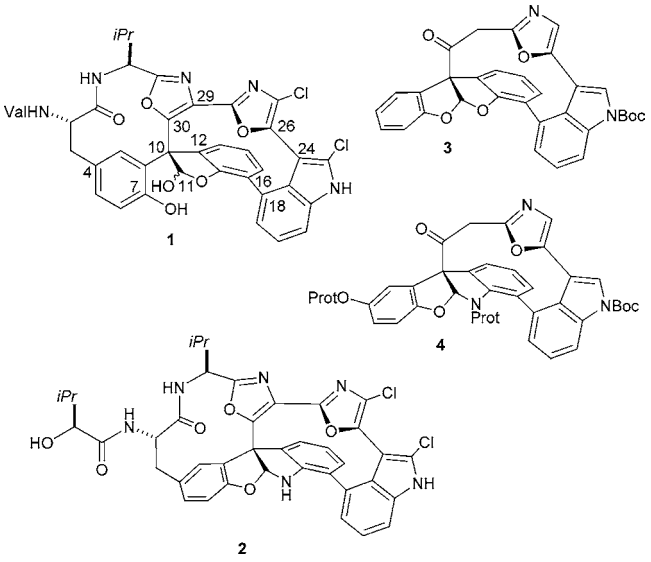
Scheme 1



precursors of **3**. Accordingly, we targeted heteroaromatic core structures **4** containing a protected bicyclic aminal, as well as a protected phenolic oxygen at C(4). The latter group is designed to serve as a versatile handle for varying the C(4) substituent with the eventual goal of introducing unnatural macrocycles in place of the peptide ring. This prospect offers a way to clarify the role of the peptide macrocycle on biological activity. As reported below, the key features of our macrocyclization approach have survived the change from **3** to **4**, but the means for implementing the seemingly small adjustment from bicyclic acetal to bicyclic aminal had to be extensively redesigned. We also describe the outcome of initial attempts to convert **4** into a bis-oxazole derivative.

Following a literature precedent,[7] the phenol **5**[8] was treated with *i*-PrMgCl to generate the alkoxide **6**. This was combined with the *N*-protected bromoisatin **8** (from **7**[9] and $ClCH_2$-OTBS[10]/NaH) to give adduct **9** (97%). After treatment with $SOCl_2$/NEt_3, the crude chloride **10** was deoxygenated to afford **11** (91% yield from **9**). The C(10) quaternary center was then installed by adding Mander's reagent ($CNCO_2Me$) and NaH to **11**, a procedure that provided clean conversion to **12** in 97% yield. A number of conventional fluoride sources failed to give deprotected oxindole **13**, but treatment of **12** with TAS-F[11] removed the siloxymethyl group to afford **13** (quant).

Reduction of **13** was explored en route to the C(11) aminal linkage (Scheme 3), the key functionality present in the corrected diazonamide structure **2** and in our target **4**. The plan was to activate the oxindole carbonyl for selective reduction by introduction of an easily removable *N*-allyl carbamate group. However, treatment of **13** with allyl

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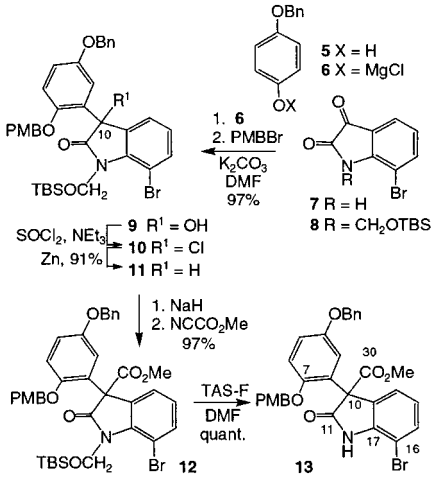
Scheme 2

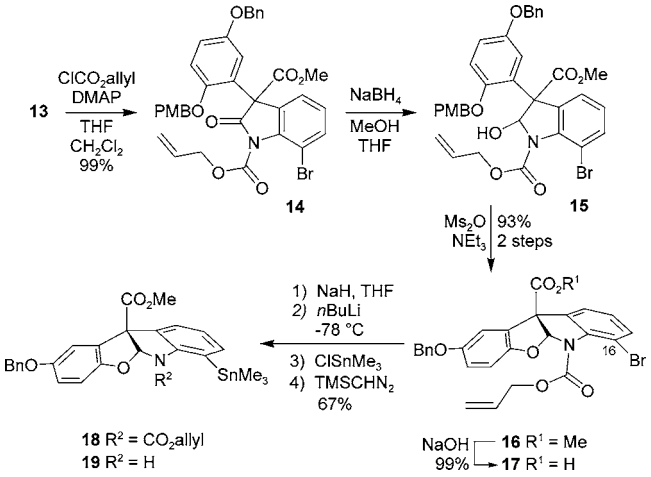


chloroformate and various bases gave a labile product that was not the desired **14**. Although decisive characterization of the initial product was not obtained, we suspect *O*-carboxylation of the oxindole based on the observation that reaction of **13** with allyl chloroformate and NaH in the presence of DMAP provides the *N*-carboxyl isomer **14** in nearly quantitative yield. Initial formation of the presumed *O*-carboxyl imidate intermediate is followed by a slower rearrangement to **14** catalyzed by DMAP.

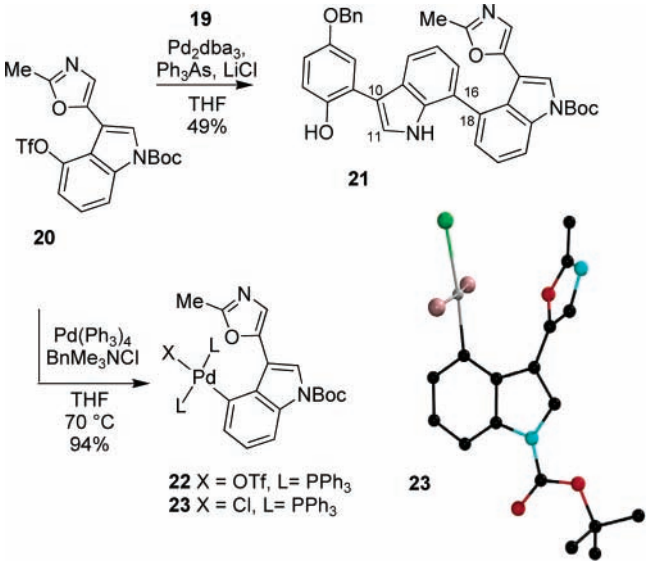
Reduction of **14** to **15** was straightforward with use of $NaBH_4$ in MeOH and THF. The crude reduction product was then treated with methanesulfonic anhydride and NEt_3 to form the C(11) aminal **16** in 95% yield from **14**. The NMR spectrum of **16** revealed a characteristic new singlet at δ 7.13 ppm corresponding to the C(11) aminal proton, and confirmed loss of the PMB group. This is a consequence of interaction between the benzylic ether oxygen with an intermediate *N*-carboxyl iminium ion.

With the aminal in place, the stage was now set to install the functionality at C(16) necessary for cross-coupling. In

Scheme 3



Scheme 4

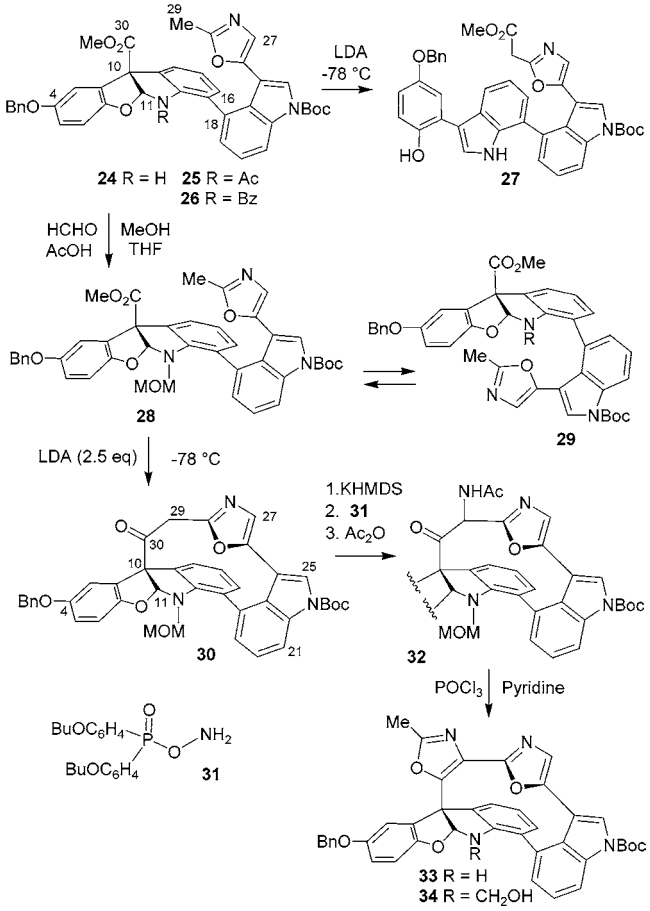


our earlier synthesis of the bicyclic acetal **3**, the analogous step was carried out with a crystalline C(16) boronic acid.[6a] However, the boronic acid derived from **15** could not be crystallized and the crude material was unstable. Fortunately, the trimethyltin derivative **18** needed for the analogous Stille coupling was better behaved. Thus, **16** was treated with NaOH to afford the acid **17** and temporary carboxyl protection was accomplished by deprotonation with NaH to give the sodium carboxylate in situ. Addition of *n*BuLi (10 min at −78 °C) followed by trimethyltin chloride, acidification, and $TMSCHN_2$ workup to re-esterify the acid then afforded stannane **18** (67% from **16**), and deprotection with catalytic $Pd(PPh_3)_4$ and 1,3-dimethylbarbituric acid produced **19**.[12]

Stannane **19** was then tested in Pd-catalyzed cross-coupling with oxazolyl indole **20**[6c] (Scheme 4), but numerous catalytic procedures were not successful. For example, Farina's Stille coupling conditions[13] formed the desired C(16)−C(18) bond, but with concomitant ring-opening of the C(11) aminal and decarboxylation of the C(10) ester to give a product tentatively assigned as indole **21** (49%), based on NMR and MS data.

In an attempt to obtain a faster reaction and suppress aminal ring opening, stoichiometric palladium sources were examined. After much experimentation it was found that heating **20** with $Pd(PPh_3)_4$ and benzyltrimethylammonium chloride ($BnMe_3NCl$) at 70 °C in THF provides an easily isolated, crystalline arylpalladium complex **23**, 94% after chromatography.[14] Without the chloride source, oxidative insertion of $Pd(PPh_3)_4$ occurred to form the palladium triflate **22**,[15] but **22** was less stable and could not be purified. The structure of **23** was confirmed by X-ray crystallography (Scheme 4; *P*-phenyls omitted for clarity).

Scheme 5



The palladium complex **23** was then used in the Stille coupling reaction with stannane **19** to assemble the crucial C(16)−C(18) bond (Scheme 5). The first try gave 31% of **24** simply by heating **23** with **19** (1:1 ratio, THF/65 °C).

A similar experiment in benzene produced **24** in 37% yield at partial conversion, but prolonged heating did not improve the yield. Better results were obtained by using a 1.8:1 ratio of **19**:**23** in benzene. This procedure afforded **24** in 54% yield (79% based on recovered **19**), and allowed practical recovery of both the excess **19** (55%) and the unreacted **23** (31%). The reaction was difficult to drive to completion, probably due to rate inhibition resulting from the PPh_3 released as palladium precipitates from the reaction mixture. However, good throughput was achieved by re-subjecting recovered **19** and **23** to the reaction conditions.

The ^1H NMR spectrum of **24** in benzene-d_6 provided evidence for two atropisomers that interconvert slowly on the NMR time scale at 20 °C. Two distinct signals were observed for the C(27) oxazole proton at δ 6.30 and 6.28 ppm in a ca. 2:1 ratio. This ratio was also reflected in the C(29) oxazole methyl signals at δ 1.98 and 1.53 ppm and the C(30) ester signals at δ 3.52 and 3.17 ppm.

Little change was seen in the NMR spectrum of **24** in toluene-d_8 from −20 to 40 °C, but line broadening became

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apparent at 60 °C. The first signs of coalescence were noted for the *N*-Boc signal (one broad singlet at δ 1.417 ppm compared to distinct singlets at δ 1.42 and 1.41 ppm at 20 °C). At 90 °C, coalescence was also observed for the C(27) oxazole proton (broad singlet at δ 6.22 ppm from two singlets at δ 6.25 and 6.20 ppm at room temperature), $\Delta G^* =$ ca. 19 kcal/mol for rotation about the C(16)−C(18) bond of **24**. This corresponds to half-lives for atropisomer interconversion of ca. 1.5 h at −23 °C and 3.5 min at 0 °C.

In an attempt to close the macrocycle, aminal **24** was treated with LDA under the same conditions that had produced **3** (acetal series; 0 °C, THF, 47% isolated).[6a] This experiment gave a complex mixture containing one substantial product, tentatively identified as the indole **27**. Formation of **27** suggests deprotonation at aminal nitrogen, followed by ring opening to the imine and nucleophilic attack at the C(30) ester to initiate carboxyl transfer. Lithium hexamethyldisilazide in place of LDA gave no improvement, and *N*-acetyl or benzoyl protection, as in **25** or **26**, did not survive LDA treatment. Clearly, a more base-resistant protecting group was needed.

An *N*-MOM group was introduced by treatment of **24** with formalin and AcOH in methanol/THF, giving a 2:1 mixture of atropisomeric products **28**/**29** in quantitative yield (Scheme 5). According to the ^{1}H NMR data, atropisomer interconversion was slower for **28**/**29** than for **24**, and signals remained sharp up to 60 °C. Further warming resulted in line broadening, but decomposition occurred prior to coalescence.

On the basis of the above observations, it was clear that Dieckmann-type macrocyclization of **28**/**29** would have to be conducted at temperatures below the threshold for atropisomer interconversion. Cyclization at room temperature had been tested in the synthesis of **3**, and had encountered side reactions including loss of the *N*-Boc protecting group. In the case of **28**/**29**, complications were already observed at −23 °C with use of LDA as the base. Thus, cyclization occurred within 2 min at −23 °C and **30** was formed in 37% yield. However, decomposition was apparent and recovery was modest. Better results were obtained at −78 °C. Although the yield of **30** was lower (29% isolated), 63% of the 2:1 mixture of **28**/**29** was recovered (92% material balance). The sample had reequilibrated in the course of workup and chromatography, and the atropisomer mixture could be used in further macrocyclization experiments. Attempts to assign atropisomer geometry for **28**/**29** with NOE methods were inconclusive. It is possible, but by no means clear, that the conversion to **30** is only 29% because the reactive atropisomer **28** is the minor component in the starting 2:1 mixture of **28**/**29**. If this is correct, then a 33% yield of **30** would be the limit (nonequilibrating conditions, −78 °C).

The ^{1}H NMR spectrum ($CDCl_3$) of macrocycle **30** is strikingly similar to that of the acetal macrocycle **3**. In stark contrast to **24** and **28**/**29**, the spectrum of **30** contains a single set of well-resolved ^{1}H signals at 20 °C. The C(27) oxazole proton of **30** appears as a singlet at δ 6.50 ppm (6.45 ppm in **3**) and the C(25) indole proton is a singlet at δ 7.72 ppm (7.78 ppm in **3**). More important, the C(29) methylene protons appear as an AB quartet at δ 4.07 ppm ($J = 15$ Hz) while the corresponding protons in **3** appear at δ 4.15 ppm ($J = 16$ Hz).

The C(30) ketone in **30** offers several alternatives for the eventual elaboration to the fused bisoxazole unit found in the diazonamides. One option has been investigated with the limited amount of racemic material at hand, starting with the enolate amination of **30**, using diarylphosphinyl-hydroxylamine reagent **31**[16] and KHMDS as the base. Conversion to the amino ketone was ca. 14%, based on isolation of the acetamide **32**, and 40% of **30** was recovered. Clearly, this step will have to be improved to validate the direct enolate amination approach. On the other hand, treatment of **32** under the same pyridine/$POCl_3$ conditions as used in Nicolaou's synthesis of diazonamide A[4] gave a mixture of the isolable bis-oxazoles **33** and **34** according to NMR and MS evidence. Upon standing in $CDCl_3$ for several hours, **34** decomposed to **33** (>80% combined). Although the scale was small, the finding is important because it shows that the key transformation to bis-oxazole **33** is possible with C(11) at the correct aminal oxidation state, and takes place without macrocycle fragmentation to an indole. The result indicates that the heteroaromatic biaryl macrocycle is not especially strained compared to **30**.

Further elaboration of **30** and **33** will be investigated after completion of an enantioselective route using a related strategy. Experiments are also under way to develop a better reagent for the enolate amination.

Acknowledgment. The authors thank Gorka Peris for helping to work out the conversion from **11** to **12**. This work was supported by NIH (CA17918).

Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Prepared by the method of Smulik and Vedejs (Smulik, J.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187), described for the less soluble bis-methoxyphenyl analogue.