ORGANIC LETTERS

2001
Vol. 3, No. 16
2451−2454

Synthesis of the Diazonamide A Macrocyclic Core via a Dieckmann-Type Cyclization

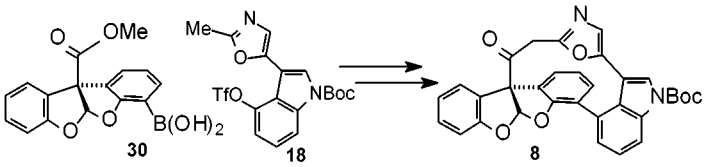
Edwin Vedejs* and Matthew A. Zajac

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

edved@umich.edu

Received May 10, 2001

ABSTRACT



Suzuki coupling of 18 and 30 affords 9 as an interconverting mixture of two atropisomers. Treatment with LDA at −23 °C affords the macrocyclic ketone 8 in 57% yield.

Diazonamides A and B (**1** and **2**, respectively) are cytotoxic marine natural products that contain an unprecedented macrocyclic ring consisting of oxazole, indole, and aryl subunits, as well as a connecting quaternary carbon, C(10).[1] The same macrocyclic subunit is present in **3**, a crystalline derivative prepared for X-ray studies. Since cyclization to the acetal **3** occurs readily from **2**, an analogous acetal **4** might be expected from **1**. One of the goals of the study reported below is to learn whether **4** or related structures may be involved in the cytotoxic acivity of **1**.

The unusual structural features and potent activity of the diazonamides have stimulated intensive synthetic efforts directed at **1**,[2−14] including palladium methodology to connect the aryl and indole rings at C(16)−C(18),[2−8] and coupling procedures using indoles that contain the C(24) oxazolyl ring.[3c,5,8] Enantiocontrolled assembly of the C(10) quaternary carbon has also been described,[3a,b,9,10] and reports of macrocycle synthesis have begun to appear.[8,9]

Earlier publications from this laboratory summarized the synthesis of the enantiomerically pure benzofuranone **5** and coupling of oxazolyl indole **6** with representative 2-alkoxyphenylboronic acids. A practical procedure was developed using Pd[dppf]Cl_2/K_3PO_4 in THF at 65 °C, resulting in conversion of **6** into **7** in 63% yield.[3c] The Pd[dppf]Cl_2 method provides access to a variety of potential macrocycle precursors, one of which is described later in this account

(1) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303−2304.

(2) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Veliz, E. A.; Yang, Z. C. *Synlett* **1996**, 609.

(3) (a) Vedejs, E.; Wang, J. *Abstracts of Papers*, 212th National Meeting of the American Chemical Society, Boston, August 1996; American Chemical Society: Washington, DC, 1996; ORGN 93. (b) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031. (c) Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033.

(4) (a) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2413. (b) Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901.

(5) (a) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223. (b) Wipf, P.; Methot, J. *Org. Lett.* **2001**, *3*, 1261.

(6) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167.

(7) Chan, F.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 835.

(8) Nicolaou, K. C.; Snyder, S. A.; Simonsen, K. B.; Koumbis, A. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 3473.

(9) (a) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640. (b) Chen, X.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 937.

(10) Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521.

(11) (a) Lach, F.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6893. (b) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897.

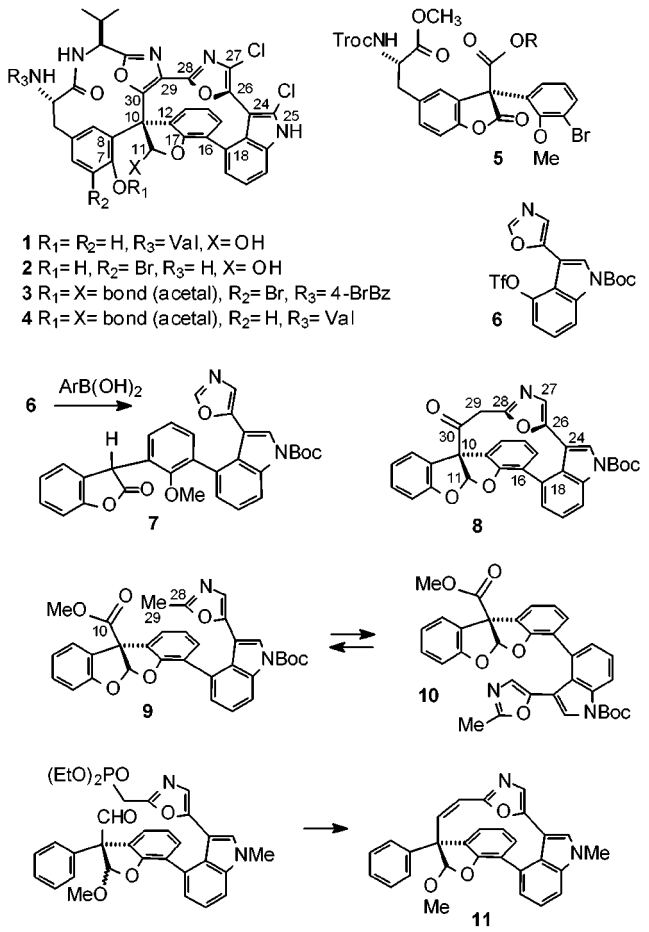
(12) (a) Magnus, P.; Kreisberg, J. D. *Tetrahedron Lett.* **1999**, *40*, 451. (b) Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831. (c) Kreisberg, J. D.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2001**, *42*, 627.

(13) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, *66*, 2107.

(14) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398.

10.1021/ol016097r CCC: $20.00 © 2001 American Chemical Society
Published on Web 07/12/2001

Scheme 1

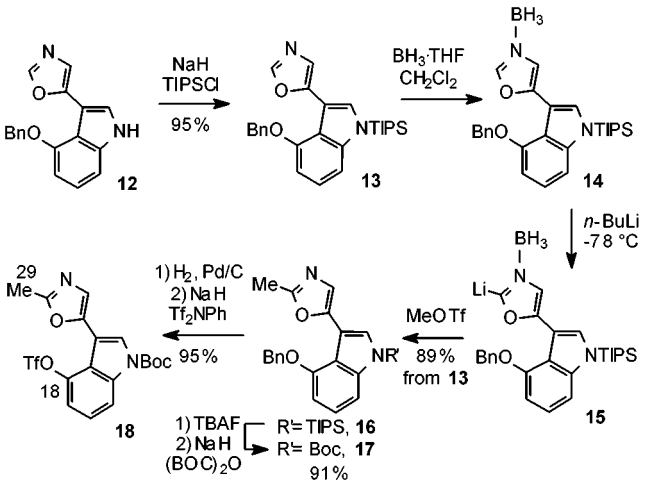


in a synthesis of the model macrocyclic ketone **8** (Scheme 1). This target was selected for the initial cyclization study because of its relationship with the hypothetical diazonamide acetal **4** and because of strategic considerations. Obvious disconnections relate **8** to the simple "imino-Dieckmann" cyclization precursor **9**, subject to the following assumptions: (1) the oxazole will act as an ester equivalent to activate the C(29) methyl group for "enolization" and cyclization, (2) the bicyclic acetal structure will favor the reactive "exo" atropisomer **9** over "endo" **10**, and (3) **9** and **10** will be in facile equilibrium.

Although Dieckmann-type cyclizations have not found much use in macrocycle synthesis,[15] we expected a favorable outcome because **9** has only three relevant free rotors. By comparison, the textbook synthesis of 2-carboethoxycyclohexanone involves restriction of five analogous rotor groups, suggesting that the entropic barrier from **9** to **8** should be favorable. According to our analysis, there is little enthalpic strain in **8** or in the derived stabilized (cisoid) enolate that may be needed to drive Dieckmann cyclization. However, concerns about the strain analysis and items (2) and (3), above, arose when Nicolaou et al. reported that Horner−Emmons cyclization from a related precursor occurs in 25% yield to give the *Z*-alkene **11** and that only one of the four precursor atropisomers and epimers undergoes cyclization.[8] An RCM strategy was also tested in this prior study, but no macrocyclic products were obtained. Fortunately, the Dieckmann approach has proved feasible using the methodology and strategy developed in our initial studies.

The initial goal of testing the macrocyclization necessitated the triflate subunit **18**, similar to oxazolyl indole **6**.[3c] Protection of the precursor indole **12**[3c] as the triisopropylsilyl (TIPS) derivative gave **13** in 95% yield (Scheme 2). The

Scheme 2



bulky TIPS group was used to block the indole C(2) position from deprotonation and to provide flexibility for the use of basic reagents in the next step. With the indole nitrogen and the 4-hydroxy substituent both protected, **13** could be methylated at C(28) via the lithiated oxazole borane complex **15**[16] (Scheme 2), a method that avoids electrocyclic lithiooxazole ring opening.[17]

The borane complex **14** was made by the addition of BH_3·THF to the indole **13** at room temperature. Treatment of **14** with *n*-BuLi at −78 °C produced **15**, and quenching with methyl triflate gave the C(28)-methylated oxazole **16** in 89% yield. Conversion to the N-Boc derivative **17** was then accomplished by removal of the TIPS group with TBAF followed by treatment with $(Boc)_2O$ (91% yield). Finally, the benzyl ether was cleaved (Pd/C, H_2) and the resulting phenol was treated with NaH and $(F_3CSO_2)_2NPh$ to give the desired triflate **18** in 95% yield.

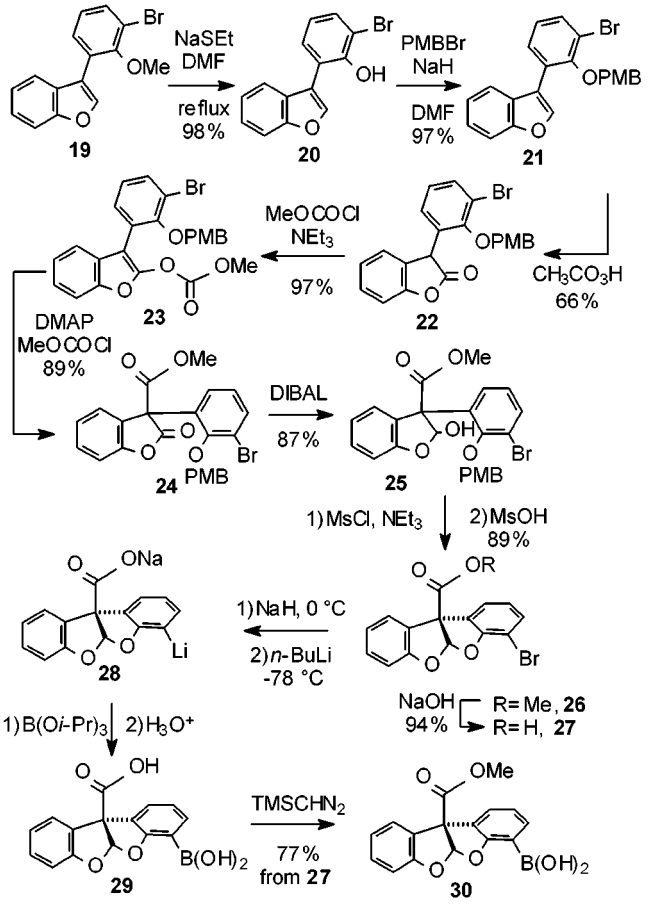
At this point, attention was turned to the preparation of the C(4)−C(17) subunit that contains the quaternary carbon C(10). Treatment of benzofuran **19**[3c] with NaSEt in refluxing DMF gave phenol **20** in 98% yield (Scheme 3). Subsequent protection of **20** as the *p*-methoxybenzyl ether (97% yield)

(15) (a) Stoll, M. *Chimia* **1948**, *2*, 217. (b) Leonard, N. J.; Schimelpfenig, C. W. *J. Org. Chem.* **1958**, *23*, 1708. (c) Tse, B. *J. Am. Chem. Soc.* **1996**, *118*, 7094.

(16) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192.

(17) Schröder, R.; Schöllkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533

Scheme 3



was followed by oxidative conversion to the lactone **22** using CH_3CO_3H.[3a,b,10,18]

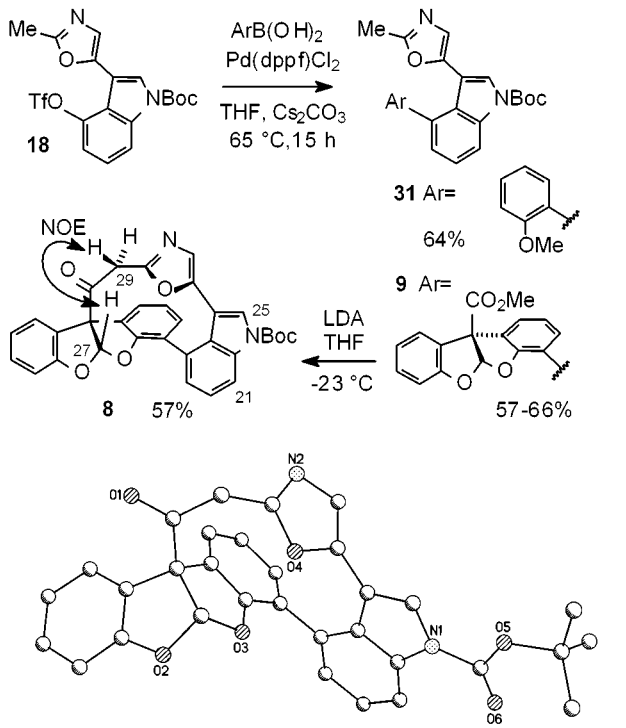
With the lactone in place, installation of the quaternary carbon was accomplished using Black's C-carboxylation method.[19] This procedure was used for the preparation of benzofuran **5** in our initial reports[3a,b] and also in a 1997 publication by Moody et al.[4a] The addition of methyl chloroformate and NEt_3 to lactone **22** resulted in the kinetically favored enol carbonate **23**. Further treatment with methyl chloroformate in THF, followed by 4-(dimethylamino)pyridine (DMAP),[19] produced the lactone **24** (89% isolated). The excess methyl chloroformate was necessary to avoid significant recovery of **22**.

Reduction of **24** with DIBAL afforded lactol **25**, having the C(11) oxidation state of naturally derived **1** or **4**. Next, conversion to the acetal **26** was desired to improve stability and to establish the relationship with acetal **4** (Scheme 1). Thus, the C(11) hydroxyl of **25** was converted to the mesylate ($MsCl/NEt_3$) and methanesulfonic acid was added at 0 °C. After NEt_3 workup, **26** was obtained in 89% yield. The NMR spectrum was simplified relative to that of **25** (removal of the PMB) and revealed a new singlet at δ 7.22 ppm, corresponding to the C(11) acetal proton.

According to the previous coupling procedure with the indolyl triflate **6**[3c] (Scheme 1), the C(16)-Br of acetal **26** would have to be transformed into an arylboronic acid in the presence of the carboxylate. Several attempts were made to directly convert **26** to **30**, including low-temperature magnesium− or lithium−halogen exchange and formation of the pinacolato boronic ester of **30** using Miyaura's conditions.[20] These procedures were partly successful (for example, the Miyaura method gave **30** in ca. 25% yield). However, better results were obtained via lithium−halogen exchange after saponification (NaOH) to the carboxylic acid **27** (94%). Temporary carboxyl protection by deprotonation of **27** with NaH gave the sodium carboxylate in situ, and treatment with *n*-BuLi produced the organolithium species **28** within 10 min at −78 °C. Subsequent quenching with triisopropyl borate resulted in boronic acid **29** after hydrolysis (aqueous HCl), but **29** was found to undergo protodeboronation over several hours at room temperature. To avoid this complication, **29** was methylated directly after workup with trimethylsilyldiazomethane to produce the stable methyl ester **30** in 77% yield.

With the coupling partners in hand, the reactivity of triflate **18** in the Suzuki reaction was investigated (Scheme 4). Initial

Scheme 4



evaluations were made for the coupling of 2-methoxyphenylboronic acid with **18** using the conditions previously optimized for triflate **6** ($Pd[dppf]Cl_2$, K_3PO_4, THF, 65 °C).[3c] The desired product (**31**) was obtained, but coupling was

(18) Adam, W.; Peters, K.; Sauter, M. *Synthesis* **1994**, 111.
(19) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Org. Chem.* **1987**, *52*, 5425.
(20) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.

slow. Fortunately, substituting Cs_2CO_3 for K_3PO_4 gave a faster reaction and a 64% yield of **31** after 15 h at 65 °C. When the modified procedure was applied to **18** and **30**, a single coupling product (**9**) was isolated in 57−65% yield, depending on the scale.

The NMR spectrum of **9** in $CDCl_3$ contained broad peaks indicative of atropisomers interconverting at room temperature.[3c] The broad C(27) oxazole proton signals at δ 6.20 and 6.37 ppm suggested two species in solution with a ratio of ca. 3:2. This ratio was also reflected in the C(29) methyl signals at δ 1.41 and 2.09 ppm, but a single N-Boc signal was present as a sharp singlet at δ 1.69 ppm. An NMR study was carried out in toluene-d_8 over a broad temperature range to estimate the energy barrier for atropisomer interconversion. This solvent altered the ratio of atropisomers to ca. 3:1 on the basis of the methyl ester and the C(29) methyl signals. A low-temperature spectrum at −20 °C clearly indicated the presence of two species with interconversion frozen out on the NMR time scale (methyl ester, δ 3.08 and 3.53 ppm; C(29) methyl, δ 1.30 and 1.96 ppm). Upon raising the temperature to 30 °C, the methyl ester and the C(29) methyl signals became broad, while heating the sample to >70 °C gave coalescence and one peak for both the C(29) methyl group and the methyl ester (δ 1.76 and 3.47 ppm, respectively). This behavior is characteristic of indoles containing the C(24) oxazole and a hindered aryl substituent at C(18) as described in an earlier publication from our laboratory.[3c] In the current study, a value for $\Delta G^* =$ ca. 15.5 kcal/mol was determined, corresponding to the barrier for rotation about the C(16)−C(18) bond. Thus, **9** exists as a mixture of atropisomers that interconvert on the laboratory time scale at temperatures well below 0 °C.[21]

With subunits **18** and **30** coupled, macrocycle precursor **9** contains the C(28)-methyl and C(10)-ester functionalities necessary to test the Dieckmann-type cyclization.[22] The first attempt by treatment of **9** with 3 equiv of lithium bis-(trimethylsilyl)amide at room temperature (8 min) gave macrocycle **8** in ca. 30% yield. Optimum conditions were reached by using 3 equiv of lithium diisopropylamide (LDA) at −23 °C (5 min), a procedure that afforded **8** in 57% yield. The structure and oxazole orientation corresponding to the macrocyclic biaryl subunit of naturally derived **3** were verified in detail by X-ray crystallography as shown in Scheme 4.

NMR analysis of **8** in $CDCl_3$ revealed a single set of well-resolved signals at room temperature, in contrast to **9**. However, cooling to −20 °C caused broadening of signals for the protons closest to indole nitrogen. At −45 °C, two sets of signals were frozen out in a 3:2 ratio: C(21)-H doublets at δ 8.42 ppm (major) and 8.07 ppm (minor); C(25)-H singlets at 7.97 ppm (minor) and 7.81 (major). The chemical shifts and coalescence temperatures correspond closely to those reported for *N*-alkoxycarbonyl indole rotamers.[23] Two sets of *N*-BOC singlets were also observed at −45 °C, δ 1.78 ppm (minor) and 1.68 ppm (major).

At rt, the C(27) oxazole proton was a sharp singlet at δ 6.45 ppm and the C(29) methylene protons appeared as an AB quartet (δ 4.15 ppm). A positive NOE interaction confirmed that one of these methylene protons is oriented as shown in macrocycle **8**, Scheme 4, proximal to the acetal proton. At −45 °C, the methylene signals were broadened and the oxazole C(27) proton was barely resolved into two partially overlapping singlets, suggesting small long-range effects on the chemical shifts due to *N*-BOC rotamers. Larger differences in these signals would be expected if the oxazole atropisomers had been frozen out. The NMR evidence is consistent with the presence **8** as the dominant atropisomer in solution, or with rapid interconversion of atropisomeric oxazoles.

In conclusion, the macrocyclic core (**8**) of diazonamide A was assembled in 11 linear steps from benzofuran **19** with an overall yield of 11%.[24] The C(16)−C(18) biaryl bond was made by Suzuki coupling following the analogy from the synthesis of **7**.[3c] The key macrocycle was formed by an imino-Dieckmann cyclization to close the C(29)−C(30) bond.[25] According to the X-ray and solution NMR evidence, the cyclization produced the correct oxazole atropisomer. High dilution conditions were not required for the cyclization, presumably due to the favorable conformational constraints present in the precursor **9**. The C(30) ketone in the resulting macrocycle **8** offers a number of options for the eventual elaboration to a fused oxazole as in the diazonamides **1**-**4**. Further studies toward the synthesis of relevant targets will be reported in due course.

Acknowledgment. This work was supported by NIH (CA17918). The authors thank Dr. D. A. Barda for working out the conversion from **19** to **20** and Dr. J. W. Kampf for the X-ray structure.

Supporting Information Available: Experimental details, spectroscopic characterization, and X-ray data tables for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

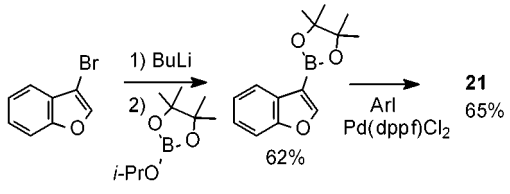
OL016097R

(21) For macrocyclization at −23 °C, $\Delta G^* = 15.5$ kcal/mol corresponds to a half-life of ca. 5 s for atropisomer interconversion.

(22) A similar cyclization has been considered by Moody et al.[4a]

(23) Oldroyd, D. L.; Weedon, A. C. *J. Org. Chem.* **1994**, *59*, 1333. Morales-Rios, M. S.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1987**, *25*, 911.

(24) In a preliminary study, intermediate **21** has also been made from benzofuran as shown below:



(25) For leading references to oxazole side chain lithiation, see: Lipshutz, B. H.; Hungate, R. W. *J. Org. Chem.* **1981**, *46*, 1410. Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.