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Synthetic Studies toward Diazonamide A. A Novel Approach for Polyoxazole Synthesis

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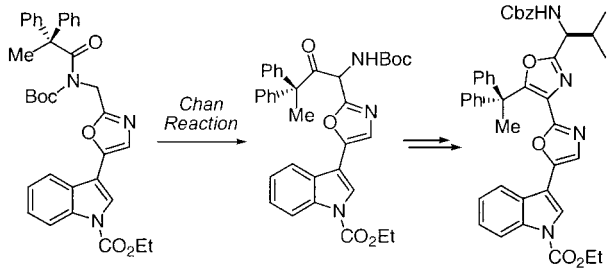
ABSTRACT



The indole–bisoxazole fragment of diazonamide A was prepared by a Chan-type rearrangement of a tertiary amide. This approach represents a remarkably direct strategy for polyoxazole synthesis.

The architectural complexity of the cytotoxic marine metabolite diazonamide A (**1**) presents a daunting challenge to the synthetic chemist. Isolated in 1991 from the colonial ascidian *Diazona chinensis*, this halogenated cyclic peptide demonstrated impressive in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines (IC_{50} < 15 ng/mL).[1] Unfortunately, a shortage of the natural material is preventing further biological study.

The unique structure of diazonamide A, a complex macrocyclic arrangement of heteroaromatic rings linked through biaryl linkages and a deeply embedded quaternary center, was established by an X-ray crystal structure.[1] Several academic groups have reported progress toward the total synthesis of this formidable target.[2]

Previously, we reported a sequence leading to benzofuranone−indolyloxazole fragment **4** featuring a Heck annulation to set the quaternary center (Figure 1).[2e] We envisioned that cyclization of a hydroxy acid or amino acid to form a lactone or lactam, followed by Chan ring contraction, might be an efficient strategy for closure of the 12-membered **B**-ring (**3** → **2**) and for positioning the functionality necessary for annulation of the **a2**-oxazole.

Although quite attractive from a retrosynthetic perspective the original Chan rearrangement[3] of α-acyloxyacetates

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

(2) (a) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, *66*, 2107−2110. (b) Konopelski, J. P.; Hottenroth, J. M.; Oltra, H. M.; Veliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609−611. (c) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2413−2419. (d) Jamison, T. F. Ph.D. Dissertation, Harvard University, Cambridge, MA, 1997. (e) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223−2226. (f) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167−8170. (g) Jeong, S.; Chen, X.; Harran, P. G.; *J. Org. Chem.* **1998**, *63*, 8640−8641. (h) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, *3*, 398−400. (i) Magnus, P.; Kreisberg, J. D. *Tetrahedron Lett.* **1999**, *40*, 451−454. (j) Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831−834. (k) Chan, F.; Magnus, P.; McIver, E. *Tetrahedron Lett.* **2000**, *41*, 835−838. (l) Chen, X.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 937−940. (m) Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031−1032. (n) Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033−1035. (o) Lach, F.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6893−6896. (p) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897−6900. (q) Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901−6904. (r) Nicolaou, K. C.; Snyder, S. A.; Simonsen, K. B.; Koumbis, A. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 3473−3478. (s) Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521−3523.

(3) Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.* **1984**, *25*, 3399−3402.

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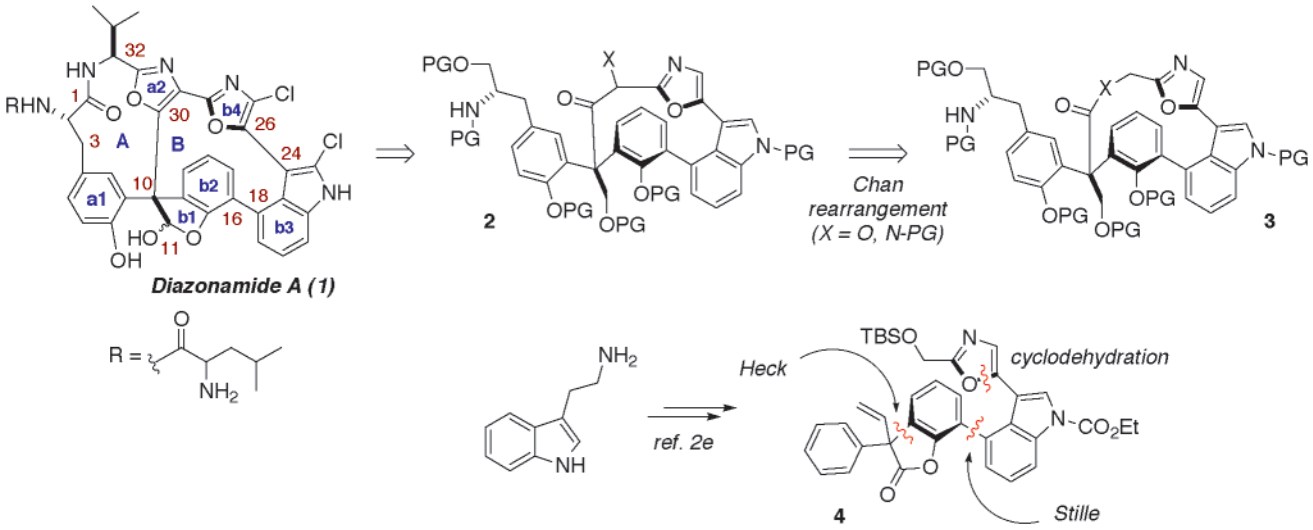
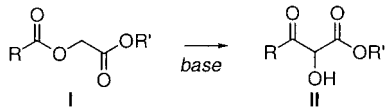


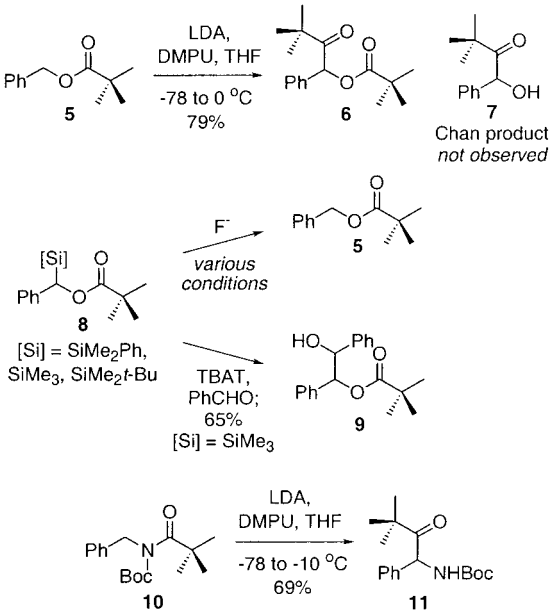
Figure 1. Retrosynthetic analysis of diazonamide A.

(**I**) into 2-hydroxy-3-ketoesters (**II**) has received only moderate attention in natural product synthesis.[4]



Since it was not clear if the acidity of a benzylic methylene group was sufficient to allow for a Chan reaction, we initiated model studies with benzyl pivaloate (Scheme 1). However, attempts to rearrange **5** with LDA led only to the intermolecular Claisen product **6**, with no trace of the desired Chan product **7**.

Scheme 1. Preliminary Model Studies



We reasoned that a more rapid benzylic anion formation might prevent the Claisen side reaction. Thus a series of α-silyl benzyl pivaloates (**8**) were prepared[5] and subjected to anhydrous fluoride sources such as CsF and tetrabutylammonium triphenyldifluorosilicate (TBAT).[6] Even under forcing conditions (e.g., heat in the presence of molecular sieves), only protodesilylation was observed. In contrast, addition of benzaldehyde led to monoacylated hydrobenzoin **9**.[7]

Since we were unable to achieve the synthesis of hydroxy ketones of type **7**, we turned our attention to a report by Hamada and co-workers on N → C acyl migrations of acyclic imides.[8] Upon warming of imide **10** to −10 °C, we obtained indeed a 69% yield of the desired α-amino ketone **11**. One explanation for the success of this model is the relative population of *s*-cis and *s*-trans conformations of the ester and tertiary amide, since only the *s*-cis conformation is likely to undergo the rearrangement.[9]

As an extension of this strategy, we tested the feasibility of oxazole-substituted imides to undergo selective Chan

(4) (a) White, J. D.; Vedananda, T. R.; Kang, M.; Choudhry, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 8105−8107. (b) White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Gray, B. D.; Kang, M.; Kuo, S.; Whittle, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 790−792. (c) Holton, R. A.; Somoza, C.; Kim, H.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597−1598. (d) White, J. D.; Jeffrey, S. C. *J. Org. Chem.* **1996**, *61*, 2600−2601.

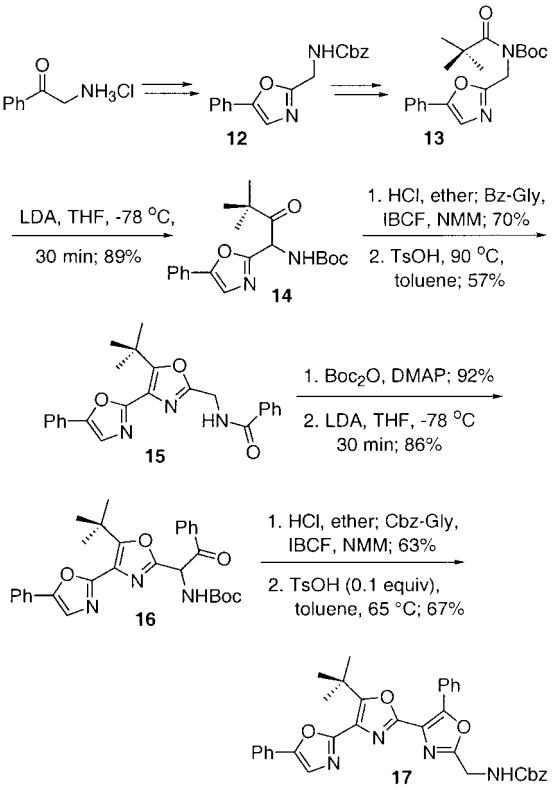
(5) The dimethylphenylsilyl derivative was prepared by addition of $PhMe_2SiLi$ to benzaldehyde followed by acylation, while the TMS and TBS derivatives were prepared by a retro-Brook rearrangement (Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392−2398) on the α-tributylstannyl silyl-protected benzyl alcohol followed by acylation.

(6) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901−6905.

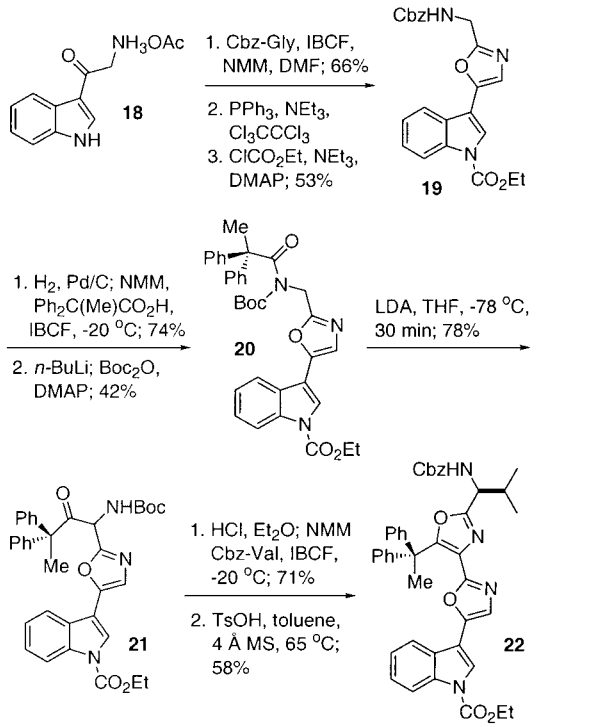
(7) A 1:1 mixture of stereoisomers was obtained.

(8) Hara, O.; Ito, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537−5540.

Scheme 2. Polyoxazoles via Sequential Chan Reactions



Scheme 3. Synthesis of the Indolyl Bisoxazole Fragment of Diazonamide A



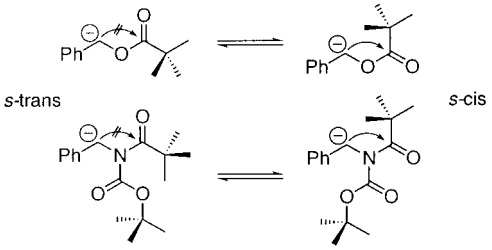
rearrangements (Scheme 2). Imide **13** was prepared in four steps from 2-aminoacetophenone hydrochloride. The Chan rearrangement on this substrate was even more facile, and C(5)-deprotonation or arene metalation did not interfere, giving the desired amino ketone **14** in 89% yield after 30 min at −78 °C.

The sequential Chan reaction represents a general method for polyoxazole synthesis. Thus, HCl-mediated cleavage of the Boc group followed by coupling to *N*-benzoylglycine and TsOH-mediated cyclodehydration afforded bisoxazole **15**. Boc-protection and another Chan rearrangement (LDA, −78 °C, 85% yield) furnished aryl ketone **16**. Finally, elaboration to trisoxazole **17** was achieved by coupling of the unmasked amine to *N*-Cbz-glycine with isobutyl chloroformate (IBCF) and cyclodehydration. The four-step sequence from **15** to **17** represents one cycle for polyoxazole synthesis. Polyoxazoles and other polyazoles are noteworthy structural features of many bioactive natural products.[10]

A more representative model **20** for our planned total synthesis of diazonamide A contains the indole nucleus and a more crowded quaternary center (Scheme 3).

Amino ketone **18** was prepared in two steps from indole via the acyl cyanide as described by Horne et al.[11] Coupling to *N*-Cbz-glycine, cyclodehydration,[12] and protection of the indole provided indolyloxazole **19**. Hydrogenolysis and coupling to $Ph_2(Me)CCO_2H$ followed by amide protection yielded imide **20**. $Ph_2(Me)CCO_2H$ was selected as the acyl component because it provides an adequate substitute for the **a1/b2** ring system at C(10) of diazonamide A. The key LDA-mediated Chan rearrangement proceeded smoothly on this model, giving amino ketone **21** in 78% yield. For the completion of the indole−bisoxazole fragment of the natural product, the Boc group of **21** was cleaved and the resulting amine coupled to *N*-Cbz-valine. Acid-mediated cyclodehydration then introduced bisoxazole **22** in >90% enantiomeric purity.[13] The straightforward conversion of **21** to **22** is a further demonstration of how tightly the imide Chan reaction integrates with oxazole synthesis.

(9) Calculations (6-31G*) suggest little ground-state energy preference for the *s*-trans conformation over the *s*-cis (1.4 kcal/mol) for the imide. In the case of the ester, this preference is considerable (>16 kcal/mol).



(10) Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1−10.
(11) Miyaka, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121−2123.
(12) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.
(13) Determined by analysis of the Mosher amide derivatives of **22** with both (*R*)- and (*S*)-MTPA. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

In conclusion, a new modification of the Chan rearrangement has been developed that serves as the basis of a versatile and direct strategy for iterative polyoxazole synthesis. As α-amino ketone **21** demonstrates, products of this Chan reaction are potentially well suited for annulation of oxazole **a2** onto the **B**-macrocycle of the complex natural product diazonamide A. Further progress along this retrosynthetic plan will be reported in due course.

Acknowledgment. We are grateful to the National Institutes of Health (GM 55433) for support of this research.

Supporting Information Available: Experimental procedures and spectral data for compounds **12**−**17** and **19**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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