ORGANIC LETTERS

2000
Vol. 2, No. 22
3521−3523

Synthesis of C(3) Benzofuran-Derived Bisaryl Quaternary Centers: Approaches to Diazonamide A

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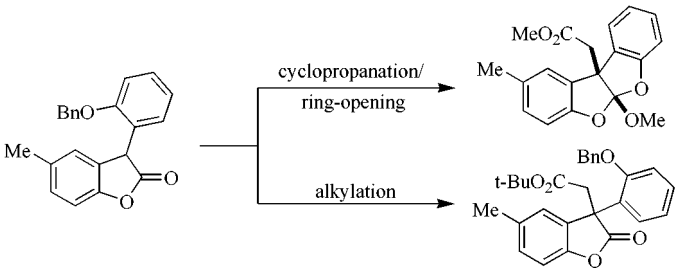
Received September 11, 2000

ABSTRACT



Two complementary strategies for the synthesis of the diazonamide A bisaryl quaternary center are described. The first strategy relies upon an extremely facile tandem cyclopropanation/ring-opening sequence, which has proven amenable to chiral catalysis to provide enantioenriched material. The second strategy relies upon a more concise alkylation route ideal for material advancement.

Diazonamide A (**1**, Figure 1) is a secondary metabolite of the colonial ascidian *Diazona chinensis* isolated off the coast of the Philippines.[1] In vitro, **1** exhibits potent activity against human colorectal carcinoma and murine melanoma cancer cell lines (IC_{50} < 15 ng/mL against HCT-116 and B-16). Advanced testing and biological screening of **1**, however, have been limited by a lack of the natural material. Thus, total synthesis is the only means available to access quantities necessary for further testing.

Upon examination, **1** presents a number of interesting and challenging structural features that include: the bisoxazole-indole moiety, the bisaryl-substituted asymmetric quaternary center C(10), and the rigid heterocyclic skeleton that holds the molecule into a configuration possessing two atropisomeric axes (about the C(16)−C(18) and C(24)−C(29) bonds). As a result of its unique structure and promising biological activity, diazonamide A has generated significant interest in recent years among the synthetic community.[2] In planning our synthesis of diazonamide A, we believed that the three asymmetric sp^3 centers on the left-hand macrocycle (i.e., C(32), C(2), and C(10)) could be used to solve the more difficult problem of controlling the axial chirality on the right side of the molecule. This disconnection led us to focus our attention on the preparation of esters **2a**,**b**. Central to the problem of constructing **2** is the introduction of the bisaryl quaternary center, which represents C(10) in the natural product. Herein we disclose the development of two complementary strategies for the construction of this challenging carbon center in a diazonamide A model system.

Work commenced with commercially available hydroxycinnamate **3**, which was converted to allylic alcohol **4** via

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

(2) (a) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, *66*, 2107. (b) Konopelski, J. P.; Hottenroth, J. M.; Altra, H. M.; Veliz, E. A.; Yang, Z. C. *Synlett* **1996**, 609. (c) Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2413. (d) Jamison, T. F. Ph.D. Dissertation, Harvard University, Cambridge, MA, 1997. (e) Boto, A.; Ling M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 2223. (f) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223. (g) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640. (h) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398. (i) Magnus, P.; Kreisberg, J. D. *Tetrahedron Lett.* **1999**, *40*, 451. (j) Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831. (k) Chan, F.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 835. (l) Chen, X.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 937. (m) Vedejs, E.; Wang. J. *Org. Lett.* **2000**, *2*, 1031. (n) Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033.

10.1021/ol006578v CCC: $19.00
Published on Web 10/04/2000

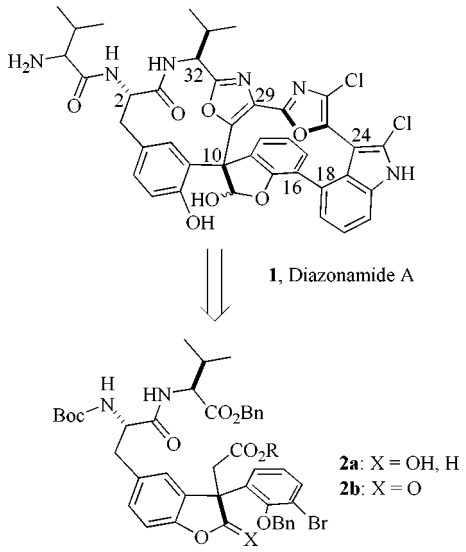
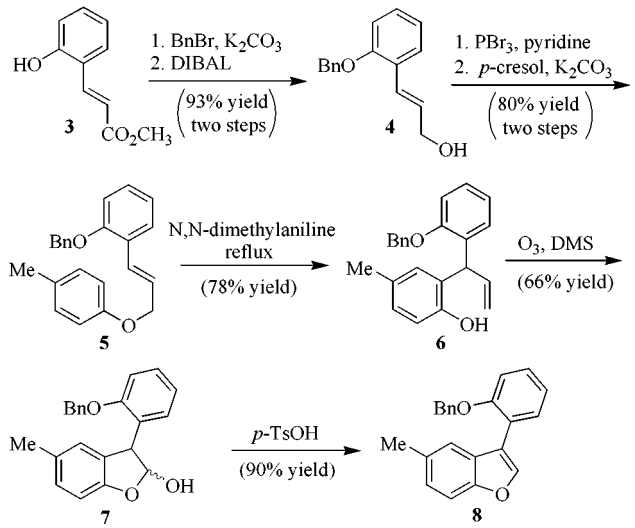


Figure 1. Retrosynthetic analysis.

formation of the benzyl ether and DIBAL reduction (Scheme 1).[3] Subsequent bromination and alkylation of *p*-cresol

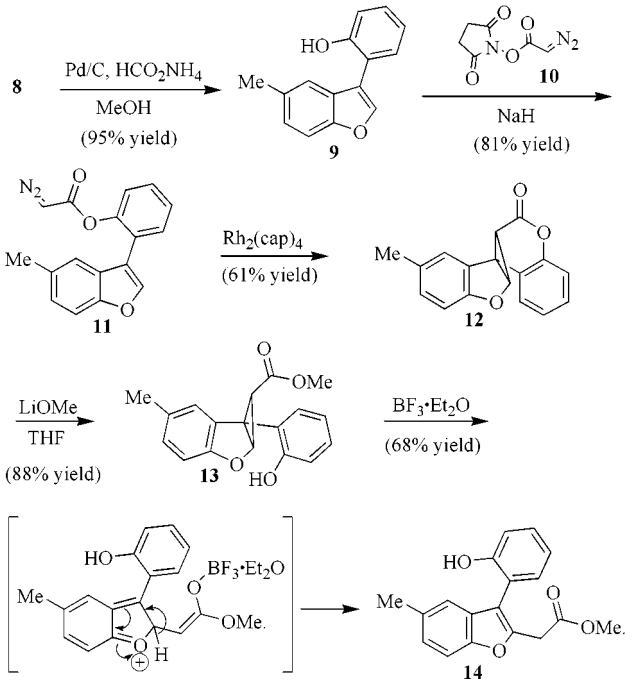
Scheme 1



furnished allyl ether **5**, which underwent smooth *ortho*-Claisen rearrangement to olefin **6**.[4] Reductive ozonolysis followed by dehydration of the resulting hemiacetal **7** afforded benzofuran **8**, a very versatile intermediate.

With **8** in hand we set out to explore formation of the quaternary center via a cyclopropanation/ring-opening approach (Scheme 2).[5] To this end, benzyl deprotection of **8**

Scheme 2



under transfer hydrogenation conditions proceeded in excellent yield to deliver phenol **9**. Treatment of **9** with the *N*-hydroxysuccinimide ester **10** and NaH afforded α-diazo ester **11**.[6] After much experimentation it was found that cyclopropanation of **11** occurred with dirhodium(II) caprolactamate ($Rh_2(cap)_4$) in refluxing CH_2Cl_2 to give cyclopropane **12**.[7] Unfortunately, conversion of **12** to ester **13** followed by treatment with $BF_3{\cdot}Et_2O$ resulted in cleavage of the undesired cyclopropane bond to furnish benzofuran **14**. We believe this reaction proceeds by through-ring scission of the cyclopropane followed by rearomatization.

In an effort to redirect the ring opening, we turned to a substrate containing an alkoxy group at the C(2) position of the benzofuran. To this end, benzofuran **8** was oxidized to lactone **15** with peracetic acid (Scheme 3).[2m] After considerable experimentation it was found that **15** could be methylated in high yield to furnish a 1.7:1 ratio of the desired *O*-alkylated benzofuran **17** and *C*-alkylated lactone **16**, respectively. Deprotection of the former to **18** followed by acylation furnishes α-diazo ester **19**. Decomposition of **19** with $Rh_2(cap)_4$ gave rise to the desired cyclopropane **20** in excellent yield. With **20** in hand, attention focused on the development of suitable conditions for cyclopropane ring opening. To our delight, treatment of **20** with 3 equiv of LiOMe led directly to ortho ester **22**.[8] This remarkable cascade reaction, which unmasks the desired quaternary center, likely proceeds via initial formation of ester **21** followed by opening of the cyclopropane.[9] Overall, installation of the alkoxy group proved to be advantageous by both improving the yield of the cyclopropanation reaction and directing the rupture of the correct cyclopropane bond.

(3) The structure assigned to each to new compound is in accord with its infrared and high-field ^1H and ^{13}C spectra, as well as appropiate parent ion identification by high-resolution mass spectrometry.

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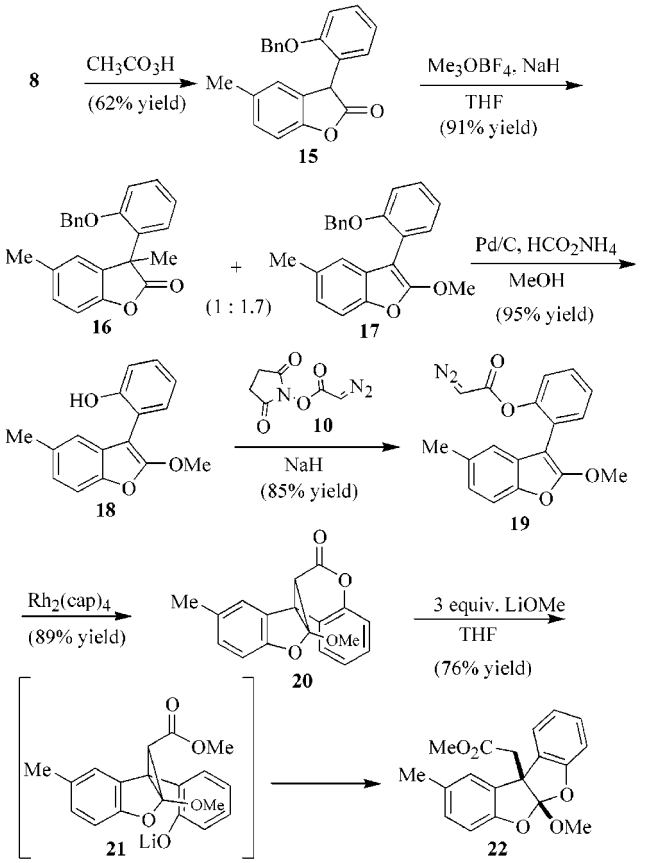
(5) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299.

(6) Ouihia, A.; Rene, L.; Guilhelm, J.; Pascard, C.; Badet, B. *J. Org. Chem.* **1993**, *58*, 1641.

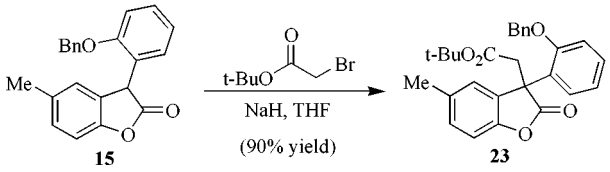
(7) A second compound that appears to be the product of aryl C−H insertion can also be isolated from the reaction mixture in 15% yield.

Scheme 3



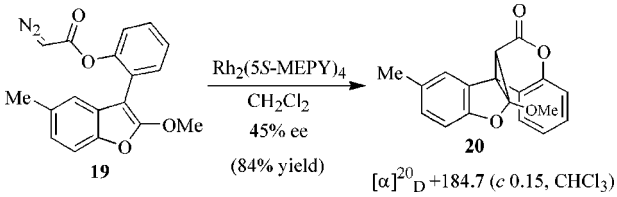
Central to the success of the aforementioned cyclopropanation/ring-opening sequence was our recognition that the C(2) position of the benzofuran must be in the acid oxidation state. While not desired in the natural product, this increase in oxidation levels led us to consider a complementary alkylation approach to the quaternary center (Scheme 4). To

Scheme 4



this end, the enolate of lactone **15** was prepared as previously described and treated with *tert*-butyl bromoacetate to afford C(3)-alkylated lactone **23** in excellent yield. Importantly, this product contains the same carbon−carbon connectivity and oxidation states found in ortho ester **22**. The convergent nature of both approaches described herein to the quaternary center should prove valuable in further studies directed toward diazonamide A. Whereas the alkylation approach is ideally suited for the advancement of material (four fewer steps), the cyclopropanation/ring-opening sequence provides a means of introducing asymmetry into the synthesis (Scheme 5). Preliminary work in this area has met with some success.

Scheme 5



Treatment of α-diazo ester **19** with commercially available Doyle's catalyst under a single set of reaction conditions gave rise to optically active cyclopropanated product **20** in 45% ee.[10,11]

In summary, we have developed complementary cyclopropanation/ring-opening and alkylation strategies for the construction of the bisaryl quaternary center present in diazonamide A. Essential to both approaches was the realization that the C(2) position of the ring system must be in the acid oxidation state. Further efforts directed at the total synthesis of diazonamide A in a fully functionalized system are currently underway and will be reported in due course.

Acknowledgment. We are pleased to acknowledge the support of this investigation by Bristol-Myers Squibb, Yamanouchi, Pfizer, and Merck. J.L.W. is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available: Experimental and spectral data pertaining to all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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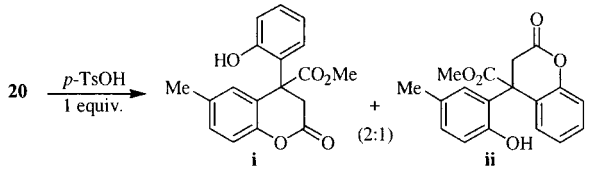
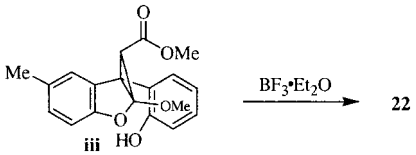
(8) Cyclopropane **20** can also be opened under acidic conditions (*p*-TsOH, 1 equiv) to give a 2:1 mixture of **i** and **ii**, respectively.



(9) The intermediacy of compound **21** is supported by the isolation of **iii** and its conversion to **22** upon treatment with $BF_3 \cdot Et_2O$. The formation and conversion of **21** can also be monitored by TLC analysis of the reaction mixture.



(10) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(11) The enantioselectivty of this reaction was determined using the chiral shift reagent Eu(hfc)$_3$. At this time the absolute stereochemistry of **20** is not known; **20** is only drawn as shown for illustrative purposes. For further details see the Supporting Information.