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Nucleophilic Addition of Organozinc Reagents to 2-Sulfonyl Cyclic Ethers: Stereoselective Synthesis of Manassantins A and B

Hyoungsu Kim,[†] Amanda C. Kasper,[†] Eui Jung Moon,[‡] Yongho Park,[†] Ceshea M. Wooten,[†] Mark W. Dewhirst,*[,‡,§] and Jiyong Hong*[,†]

Department of Chemistry, Duke University, Durham, North Carolina 27708, Department of Pathology, Duke University Medical Center, Durham, North Carolina 27708, and Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina 27708

jiyong.hong@duke.edu; dewhi001@mc.duke.edu

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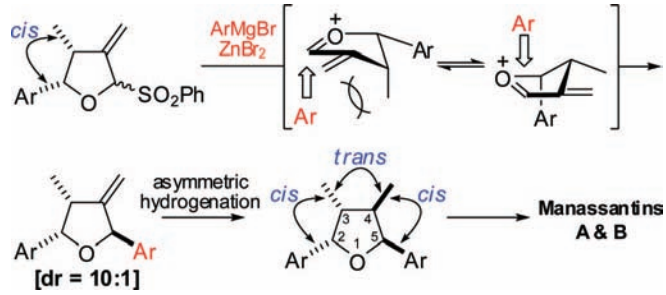
ABSTRACT



A convergent route to the synthesis of manassantins A and B, potent inhibitors of HIF-1, is described. Central to the synthesis is a stereoselective addition of an organozinc reagent to a 2-benzenesulfonyl cyclic ether to achieve the 2,3-*cis*-3,4-*trans*-4,5-*cis*-tetrahydrofuran of the natural products. Preliminary structure−activity relationships suggested that the (*R*)-configuration at C-7 and C-7‴ is not critical for HIF-1 inhibition. In addition, the hydroxyl group at C-7 and C-7‴ can be replaced with a carbonyl group without loss of activity.

Tumor cells function under a condition of low physiological oxygen levels known as hypoxia. To cope with this environment, tumor cells have developed a number of essential mechanisms to promote angiogenesis and cell survival.[1] Among these coping mechanisms is a response mediated by hypoxia-inducible factor 1 (HIF-1).[2] More than 60 target genes that HIF-1 regulates have been identified, and the products of these genes act at various steps in tumor progression.[3] In addition, tumor cells characterized by overexpression of HIF-1 have been shown to be more resistant to traditional cancer treatments such as radiation and chemotherapy.[4] Due to the importance of HIF-1 in tumor development and progression, a considerable amount of effort has been made to identify HIF-1 inhibitors for treatment of cancer. Several small molecules have been reported to inhibit the HIF-1 signaling pathway;[5] however, these compounds often exhibit biological activities other than HIF-1 inhibition.

[†] Department of Chemistry, Duke University.
[‡] Department of Pathology, Duke University Medical Center.
[§] Department of Radiation Oncology, Duke University Medical Center.

(1) Harris, A. L. *Nat. Rev. Cancer* **2002**, *2*, 38–47.
(2) Semenza, G. L. *Annu. Rev. Cell Dev. Biol.* **1999**, *15*, 551–578.
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(4) (a) Moon, E. J.; Brizel, D. M.; Chi, J. T.; Dewhirst, M. W. *Antioxid. Redox. Signal.* **2007**, *9*, 1237–1294. (b) Dewhirst, M. W.; Cao, Y.; Moeller, B. *Nat. Rev. Cancer* **2008**, *8*, 425–437.
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In addition, most of them lack the desired selectivity for the HIF-1 signaling pathway or toxicity profiles required for a useful therapeutic agent.

Interestingly, the dineolignans manassantins A (**1**) and B (**2**) (Figure 1), isolated from the aquatic plant *Saururus*

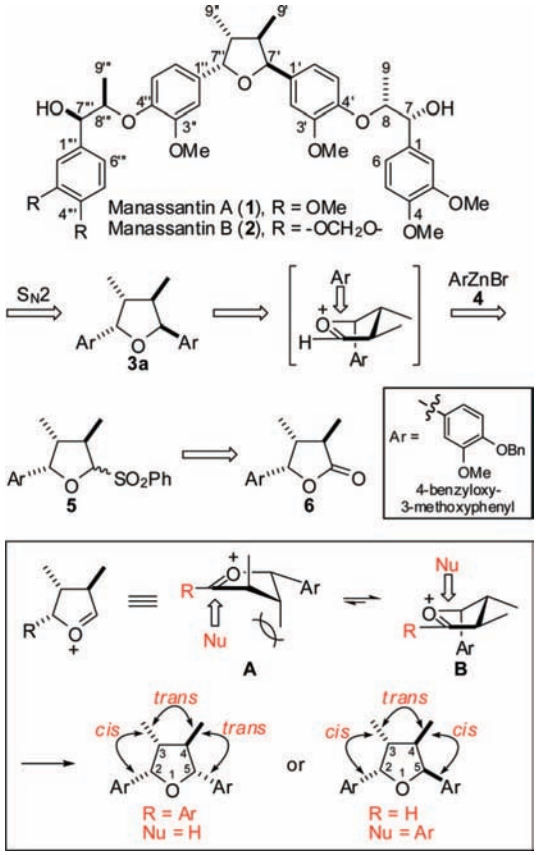


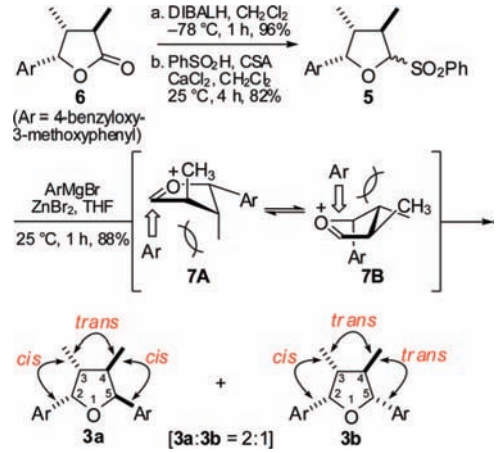
Figure 1. Retrosynthetic plan for manassantins A (**1**) and B (**2**).

cernuus L., have been shown to be potent inhibitors of HIF-1.[6] However, their molecular mechanisms of action have yet to be established. Hanessian and co-workers recently reported the first total synthesis of **1** and **2** as well as confirmed the absolute configuration of the natural products.[7] In broad connection with our interest in the stereoselective synthesis of tetrasubstituted tetrahydrofurans,[8] we undertook the synthesis of **1** and **2** to develop a synthetic route to the natural products that would be easily amenable to the development of analogues for biological studies. Herein, we report a synthesis of **1** and **2** through nucleophilic addition of an organozinc reagent to a 2-benzenesulfonyl cyclic ether to achieve the 2,3-*cis*-3,4-*trans*-4,5-*cis*-tetrahydrofuran moiety of the natural products and preliminary structure−activity relationships.

Figure 1 describes our approach to the synthesis of manassantins A (**1**) and B (**2**). Previously, we reported a stereoselective synthesis of 2,3-*cis*-3,4-*trans*-4,5-*trans*- and 2,3-*trans*-3,4-*trans*-4,5-*trans*-tetrahydrofurans via BF_3•OEt_2-promoted reductive deoxygenation of cyclic hemiketals.[8] The stereochemical outcome was rationalized on the basis of Woerpel's "inside attack" model.[9] Based on the same rationale, we envisioned that the organozinc reagent **4** would be added to the sterically more favorable conformation (**B**) of the 2-benzenesulfonyl cyclic ether **5** from the inside face of the envelope conformer to stereoselectively provide the 2,3-*cis*-3,4-*trans*-4,5-*cis*-tetrahydrofuran (**3a**). This core tetrahydrofuran unit **3a** could be coupled to the appropriate side arms via S_N2 reactions to complete the synthesis of **1** and **2**.

As shown in Scheme 1, reduction of **6**[8] with DIBALH

Scheme 1. Nucleophilic Addition of (4-Benzyloxy-3-methoxyphenyl)zinc(II) Bromide to 2-Benzenesulfonyl Cyclic Ether



followed by treatment with $PhSO_2H$ and camphorsulfonic acid provided the 2-benzenesulfonyl cyclic ether **5**.[10] Unfortunately, the key nucleophilic substitution reaction of **5** with (4-benzyloxy-3-methoxyphenyl)zinc(II) bromide **4**, derived in situ from (4-benzyloxy-3-methoxyphenyl)magnesium bromide and $ZnBr_2$,[10] provided a 2:1 diastereomeric mixture of 2,5-diaryl-3,4-dimethyl tetrahydrofurans. Careful analysis of ^1H NMR spectral data revealed that the major diastereomer had the desired 2,3-*cis*-3,4-*trans*-4,5-*cis*-configuration (**3a**) and the minor diastereomer had the 2,3-*cis*-3,4-*trans*-4,5-*trans*-configuration (**3b**). We reasoned that the

(6) (a) Rao, K. V.; Alvarez, F. M. *Tetrahedron Lett.* **1983**, *24*, 4947–4950. (b) Hodges, T. W.; Hossain, C. F.; Kim, Y.-P.; Zhou, Y.-D.; Nagle, D. G. *J. Nat. Prod.* **2004**, *67*, 767–771. (c) Hossain, C. F.; Kim, Y.-P.; Baerson, S. R.; Zhang, L.; Bruick, R. K.; Mohammed, K. A.; Agarwal, A. K.; Nagle, D. G.; Zhou, Y.-D. *Biochem. Biophys. Res. Commun.* **2005**, *333*, 1026–1033.

(7) Hanessian, S.; Reddy, G. J.; Chahal, N. *Org. Lett.* **2006**, *8*, 5477–5480.

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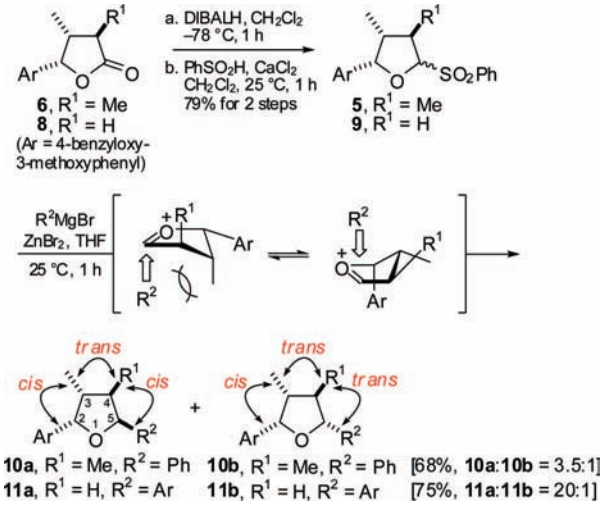
(9) (a) Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 6706–6707. (b) Larsen, C. H.; Riggway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209. (c) Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747–8756. (d) Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056–2064. (e) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063–2066.

(10) (a) Brown, D. S.; Ley, S. V. *Tetrahedron Lett.* **1988**, *29*, 4869–4872. (b) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293–4308.

poor diastereoselectivity of the reaction would stem from two competing factors. According to Woerpel's "inside attack" model, **4** would be delivered to **5** from the inside face of the envelope conformer (**7B**) to provide the desired tetrahydrofuran (**3a**). However, the addition of **4** to the oxocarbenium intermediate via **7B** also causes an unfavorable repulsive interaction with the C-4 methyl group leading to poor diastereoselectivity. We hypothesized that minimization of the steric repulsion between the incoming nucleophile and the C-4 methyl group would improve the disastereoselectivity.

To prove this hypothesis, we tested two model systems where the repulsive interaction was reduced by addition of a smaller nucleophile or removal of the C-4 methyl group (Scheme 2). As expected, addition of a sterically less

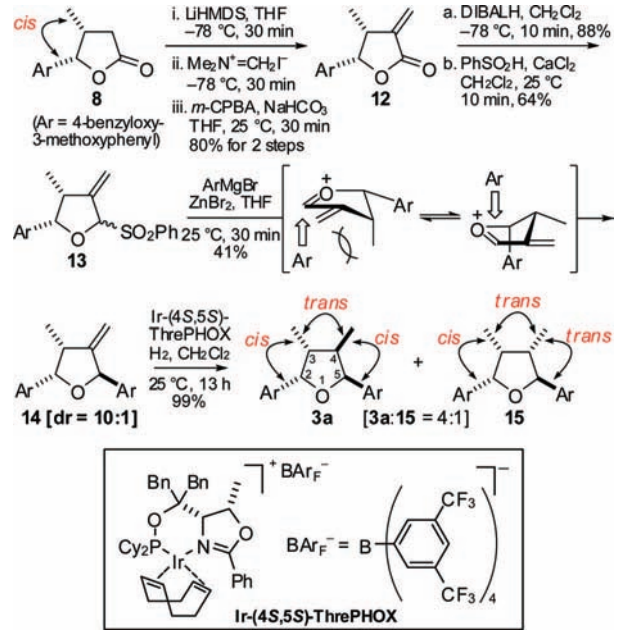
Scheme 2. Model Studies for Nucleophilic Addition Reaction



demanding PhZnBr to **5** gave a 3.5:1 diastereomeric mixture of **10a** and **10b**. In addition, when **4** was added to the cyclic ether **9**, the reaction proceeded with excellent diastereoselectivity (dr = 20:1). Based on the observations, we envisioned that the installation of a sterically less demanding *exo*-methylene group as a precursor to the C-4 methyl group and stereoselective reduction of the double bond would provide **3a** in good stereoselectivity.

As shown in Scheme 3, alkylation of **8** with Eschenmoser's salt and *m*-CPBA oxidation smoothly proceeded to afford **12** (80% for two steps).[11] Reduction of **12** with DIBALH followed by treatment with $PhSO_2H$ provided **13** in 64% yield. As expected, the *exo*-methylene group in **13** directed the addition of **4** via "inside attack" model to provide the desired 2,3-*cis*-2,5-*trans*-tetrahydrofuran **14** as a major diastereomer (dr = 10:1, 41%). However, catalytic hydrogenation under conventional conditions (e.g., Pd/C, PtO_2)

Scheme 3. Stereoselective Synthesis of 2,3-*cis*-3,4-*trans*-4,5-*cis*-Tetrahydrofuran



or diimide reduction of **14** only gave the desired 2,3-*cis*-3,4-*trans*-4,5-*cis*-tetrahydrofuran as a minor diastereomer (dr = 1:1−1:4). After extensive search of reaction conditions, we were delighted to find that asymmetric hydrogenation of **14** in the presence of Ir and (4*S*,5*S*)-ThrePHOX[12] provided **3a** in 99% yield (dr = 4:1).[13]

With the desired tetrahydrofuran **3a** in hand, we turned our attention to the installation of the side arms (Scheme 4). We anticipated that coupling of **16** and **17** by Mitsunobu coupling or oxidation−reduction condensation via alkoxydiphenylphosphines[14] would proceed to afford **18**. However, our efforts for coupling reactions were unsuccessful in all attempts and led us to adopt the procedures reported by Ley[15] and Hanessian.[7] A BEMP-mediated S_N2 reaction of **16** and **17**[16] followed by stereocontrolled reduction using polymer-supported BH_4 completed the synthesis of manassnatins A (**1**). In order to accomplish the synthesis of **2**, **16** was subjected to the BEMP-mediated S_N2 reaction with 1 equiv of **17** to form the monoalkylation product **19** (29%) in addition to **18** (21%). Compound **19** was then subjected to a second BEMP-mediated S_N2 reaction with **20**[16] to give **21** (77%). Reduction of **21** with polymer-supported BH_4 then afforded manassantin B (**2**).

ODD-Luc assay[17] to assess HIF-1 inhibitory activity of **1**, **18**, and *anti*-diol diastereomer **22** ((7*S*,7‴*S*)-epimer) revealed that **1**, **18**, and **22** exhibited similar levels of HIF-1 inhibitory activity (IC_{50} = 1−10 nM, Figure 2). The data

(11) (a) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330–331. (b) Mandal, M.; Yun, H.; Dudley, G. B.; Lin, S.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619–10637.

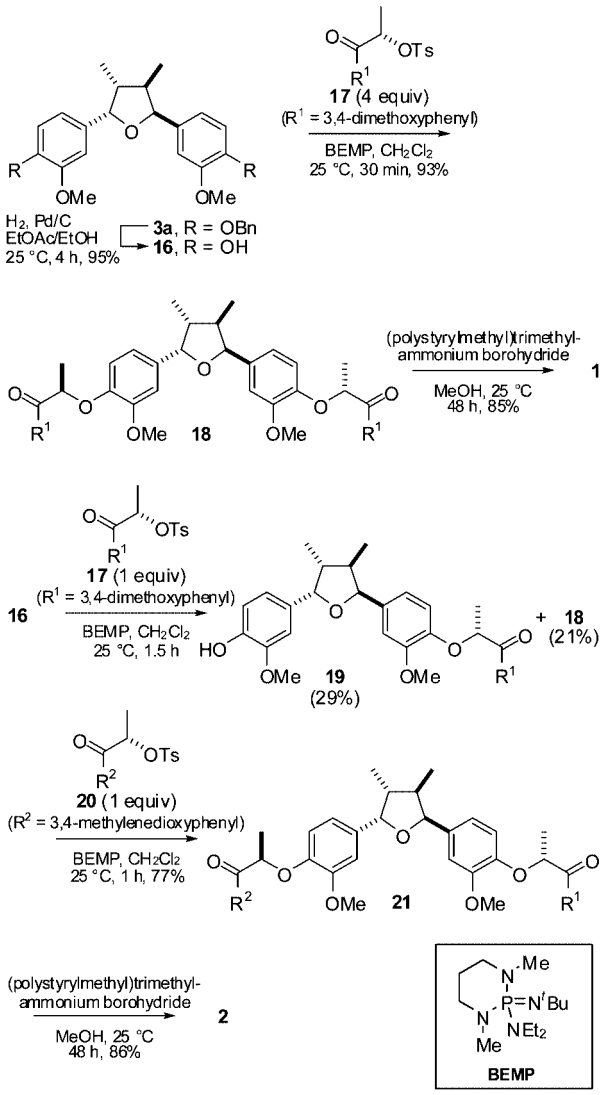
(12) McIntyre, S.; Hoermann, E.; Menges, F.; Smidt, P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282–288.

(13) Asymmetric hydrogenation of **14** in the presence of Ir and (4*R*,5*R*)-ThrePHOX provided **3a** as a minor diastereomer (dr = 1:2).

(14) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359–7367.

(15) Lee, A.-L.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 3957–3966.

Scheme 4. Completion of Synthesis of Manassantins A (**1**) and B (**2**)



suggested that the (*R*)-configuration at C-7 and C-7‴ is not critical for HIF-1 inhibition. In addition, the hydroxyl group at C-7 and C-7‴ can be replaced with carbonyl group without significant loss of activity.

(16) Following the procedures reported in ref 15, **17** and **20** were prepared from 1,2-dimethyl-4-(2-propen-1-yl)benzene and 5-(2-propen-1-yl)-1,3-benzodioxole, respectively.

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In summary, we applied a direct nucleophilic addition of the organozinc reagent **4** to the 2-benzenesulfonyl cyclic ether **5** followed by an asymmetric hydrogenation to synthesize the 2,3-*cis*-3,4-*trans*-4,5-*cis*-tetrahydrofuran moiety of **1** and **2**, potent inhibitors of HIF-1. The stereoselectivity of the nucleophilic addition reaction was improved by introduction of the sterically less demanding *exo*-methylene group as a surrogate for the C-9′ methyl group in **1** and **2**. The synthetic strategy would allow access to more potent and selective analogues of **1** and **2** for biological studies to identify their molecular mechanism of action.

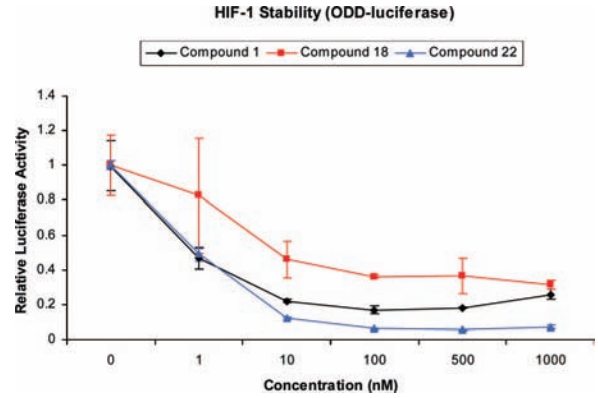

Figure 2. Inhibition of HIF-1 by **1**, **18**, and **22**.

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Supporting Information Available: General experimental procedures including spectroscopic and analytical data for **1**, **2**, **3a**, **3b**, **5**, **9**, **10a**, **10b**, **11a**, and **12**−**21** along with copies of ^{1}H and ^{13}C NMR spectra; detailed assay procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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