

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

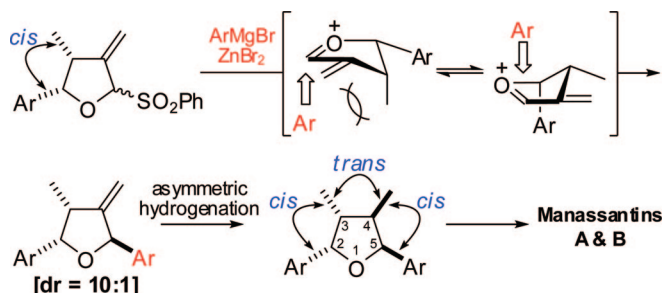
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Received October 24, 2008

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.

(3) Semenza, G. L. *Nat. Rev. Cancer* **2003**, 3, 721–732.

(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.

(5) (a) Giaccia, A.; Siim, B. G.; Johnson, R. S. *Nat. Rev. Drug Discov.* **2003**, 2, 803–811. (b) Semenza, G. L. *Drug Discovery Today* **2007**, 12, 853–859.

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(1) Harris, A. L. *Nat. Rev. Cancer* **2002**, 2, 38–47.

(2) Semenza, G. L. *Annu. Rev. Cell Dev. Biol.* **1999**, 15, 551–578.

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*

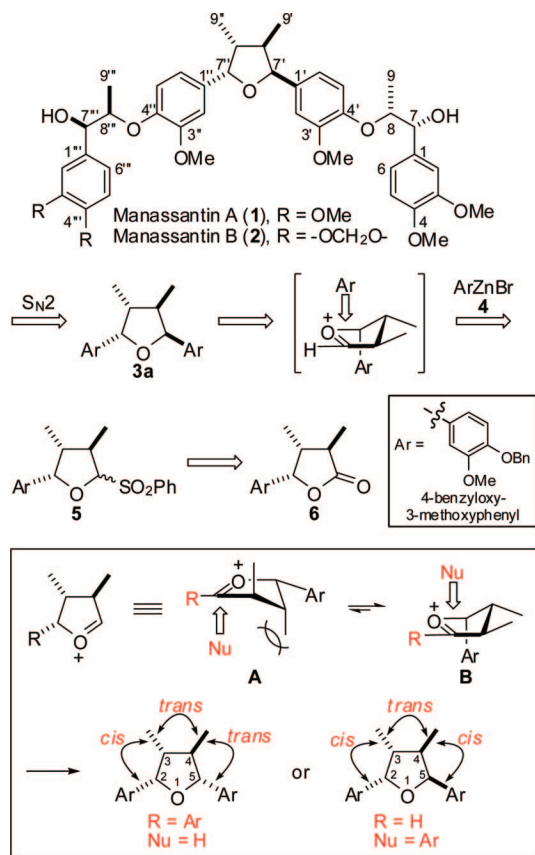


Figure 1. Retrosynthetic plan for manassantins A (**1**) and B (**2**).

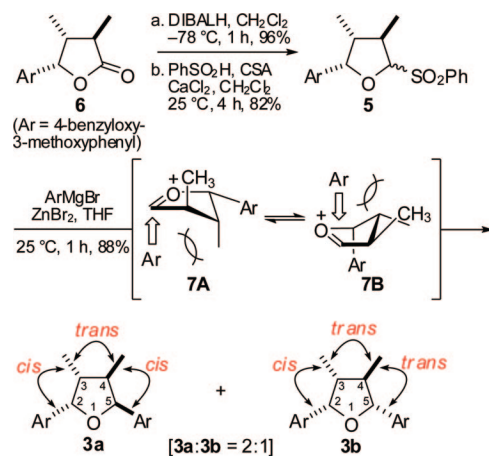
cernuus L., have been shown to be potent inhibitors of HIF-1.⁶ However, their molecular mechanisms of action have yet to be established. Hanessian and co-workers recently reported the first total synthesis of **1** and **2** as well as confirmed the absolute configuration of the natural products.⁷ In 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 $\text{BF}_3 \cdot \text{OEt}_2$ -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 unit **3a**. This core tetrahydrofuran unit **3a** could be coupled to the appropriate side arms via $\text{S}_\text{N}2$ 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.

(8) Kim, H.; Wooten, C. M.; Park, Y.; Hong, J. *Org. Lett.* **2007**, 9, 3965–3968.

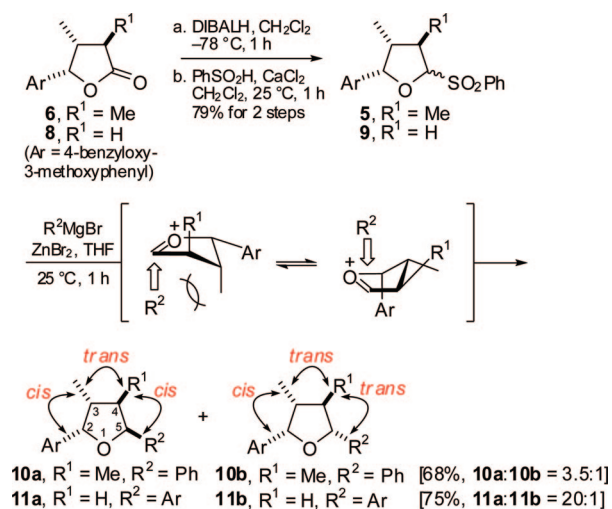
(9) (a) Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, 62, 6706–6707. (b) Larsen, C. H.; Riggway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, 121, 12208–12209. (c) Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, 55, 8747–8756. (d) Bear, T. J.; Shaw, J. T.; Woerpel, K. 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 diastereoselectivity.

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

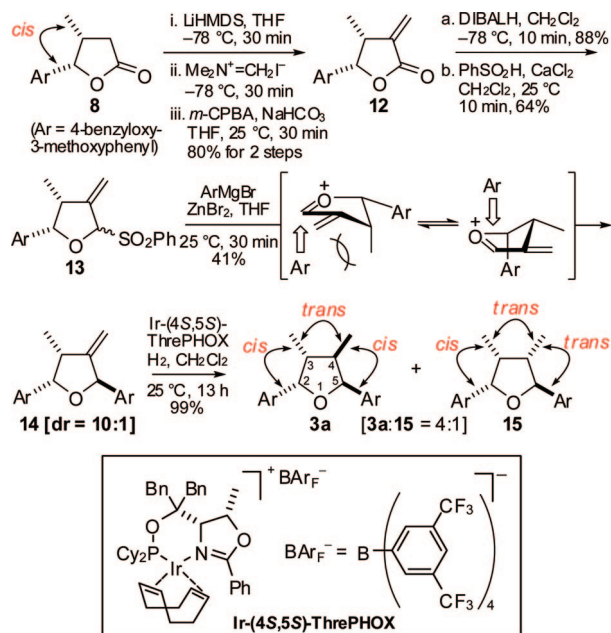
Scheme 2. Model Studies for Nucleophilic Addition Reaction



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 ($\text{dr} = 20:1$). 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 ($\text{dr} = 10:1$, 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 ($\text{dr} = 1:1$ –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*)-ThrePHOX¹² provided **3a** in 99% yield ($\text{dr} = 4:1$).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 alkoxydiphenylphosphines¹⁴ 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 Ley¹⁵ and Hanessian.⁷ A BEMP-mediated $\text{S}_\text{N}2$ reaction of **16** and **17**¹⁶ followed by stereocontrolled reduction using polymer-supported BH_4 completed the synthesis of manassnatin A (**1**). In order to accomplish the synthesis of **2**, **16** was subjected to the BEMP-mediated $\text{S}_\text{N}2$ 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 $\text{S}_\text{N}2$ reaction with **20**¹⁶ to give **21** (77%). Reduction of **21** with polymer-supported BH_4 then afforded manassantin B (**2**).

ODD-Luc assay¹⁷ 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 ($\text{IC}_{50} = 1$ –10 nM, Figure 2). The data

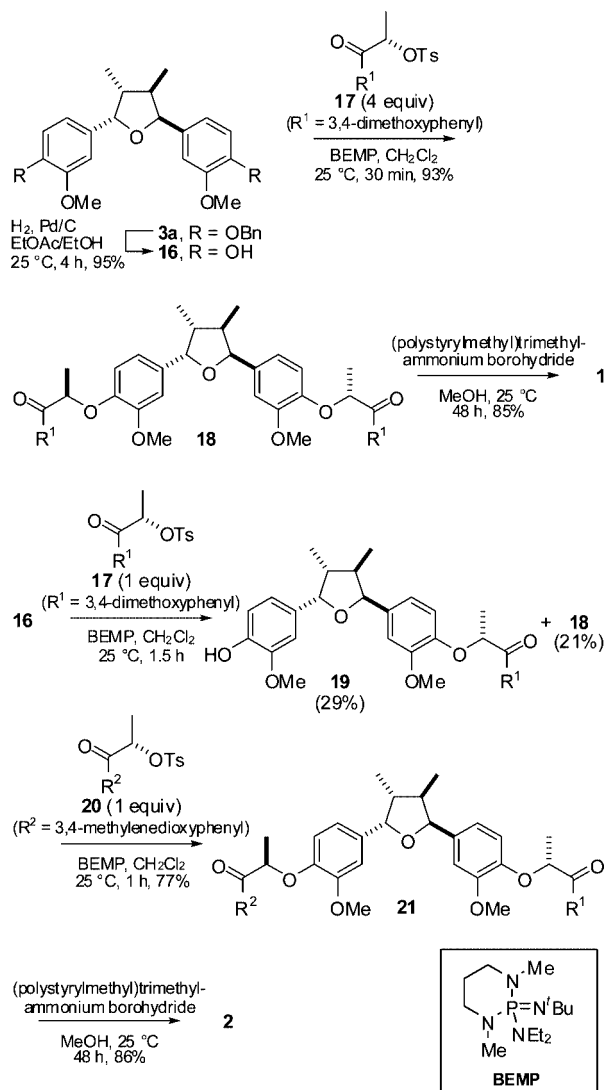
(12) McIntyre, S.; Hoermann, E.; Menges, F.; Smidt, P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282–288.

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

(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.

(17) Li, F.; Sonveaux, P.; Rabbani, Z. N.; Liu, S.; Yan, B.; Huang, Q.; Vujaskovic, Z.; Dewhirst, M. W.; Li, C. Y. *Mol. Cell* **2007**, 26, 63–74.

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.

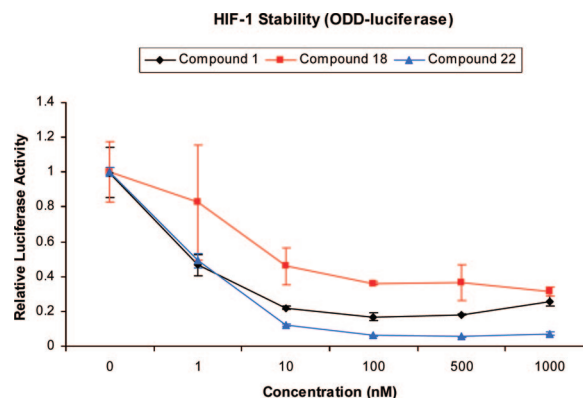


Figure 2. Inhibition of HIF-1 by **1**, **18**, and **22**.

Acknowledgment. We thank Dr. Chuan-Yuan Li (Department of Radiation Oncology, University of Colorado Health Sciences Center) for the 4T1-ODD-Luc. This work was supported by Duke University, Duke Chemistry Undergraduate Summer Research Program, NIH PO1 CA42745, and NIH/NCI CA40355. H.K. gratefully acknowledges the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2006-352-E00028) for a postdoctoral fellowship.

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 ¹H and ¹³C NMR spectra; detailed assay procedure. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL8024617