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Nucleophilic Addition of Organozinc Reagents to 2-Sulfonyl Cyclic Ethers:

Stereoselective Synthesis of Manassantins A and B

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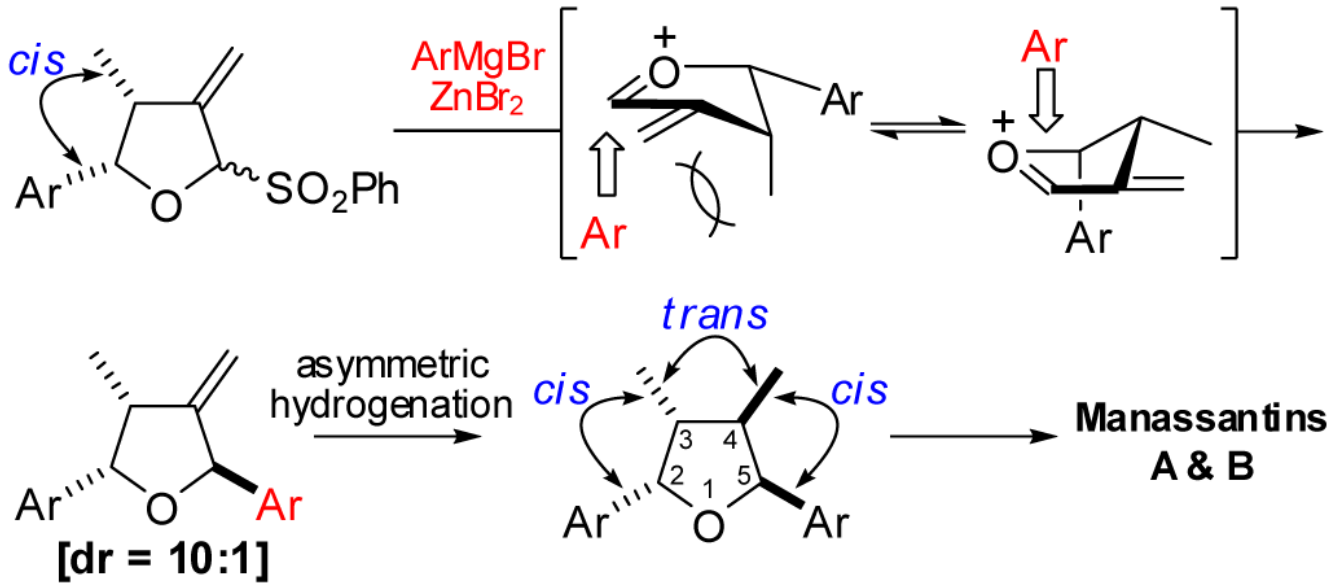
Abstract



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 carbonyl group without loss of activity.

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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.

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 over-expression 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. 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 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 $BF_3{\cdot}OEt_2$-promoted reductive deoxygenation of cyclic hemiketals.[8] The stereochemical outcome was rationalized based on 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 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 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 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 distereoselectivity (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 2 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) 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 equivalent of **17** to form the mono-alkylation 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** ((7S,7‴S)-epimer) revealed that **1**, **18**, and **22** exhibited similar levels of HIF-1 inhibitory activity (IC_{50} = 1–10 nM). The data 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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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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).

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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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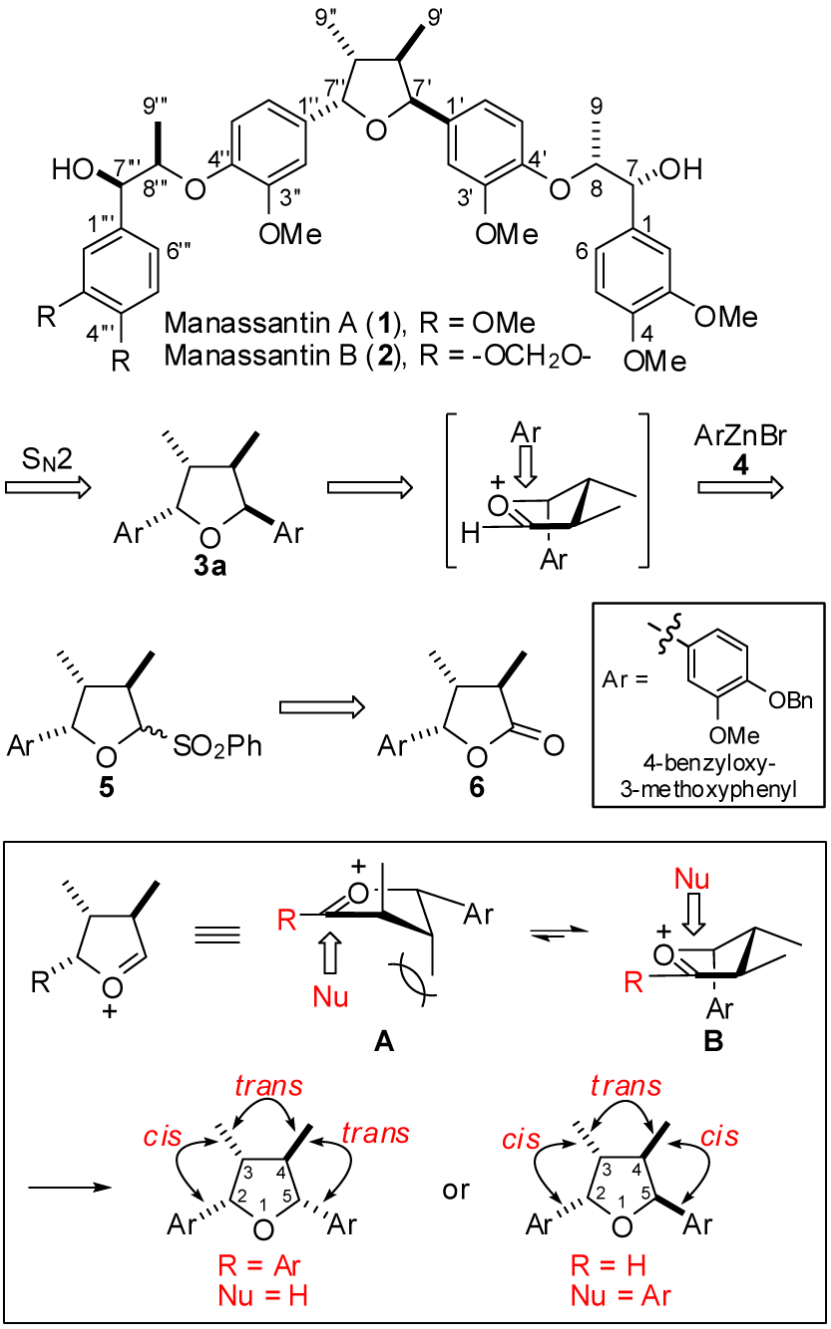
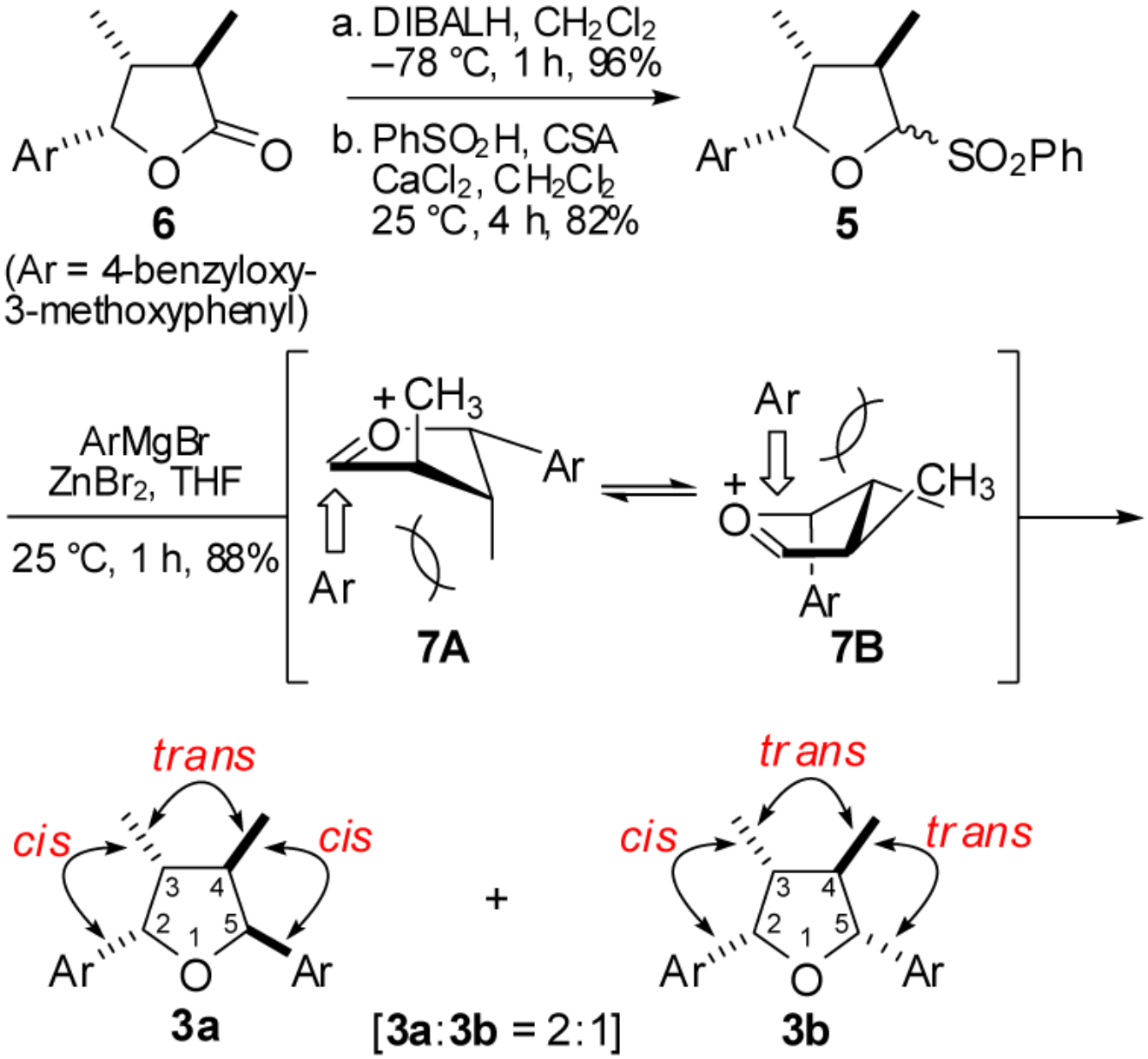
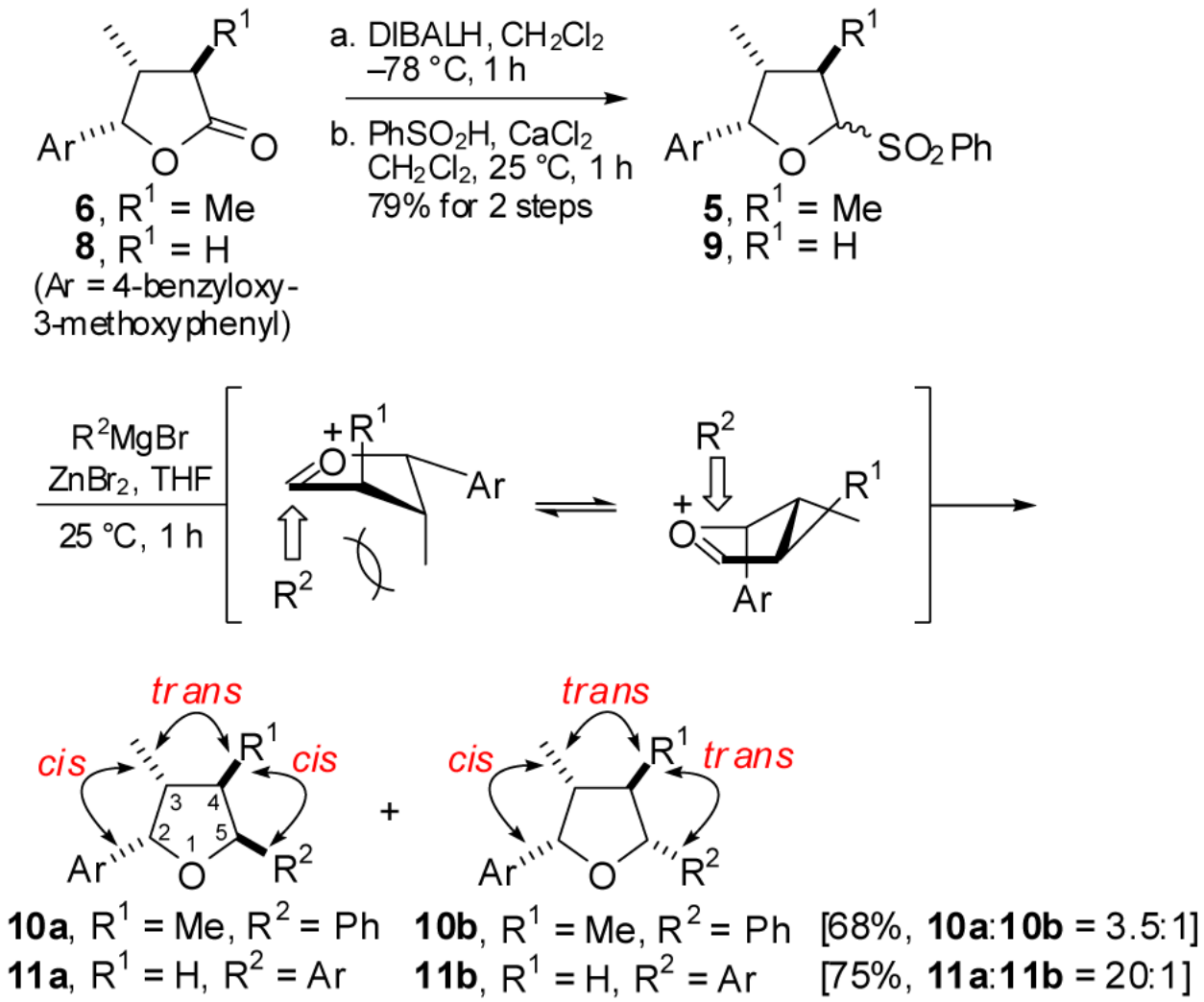


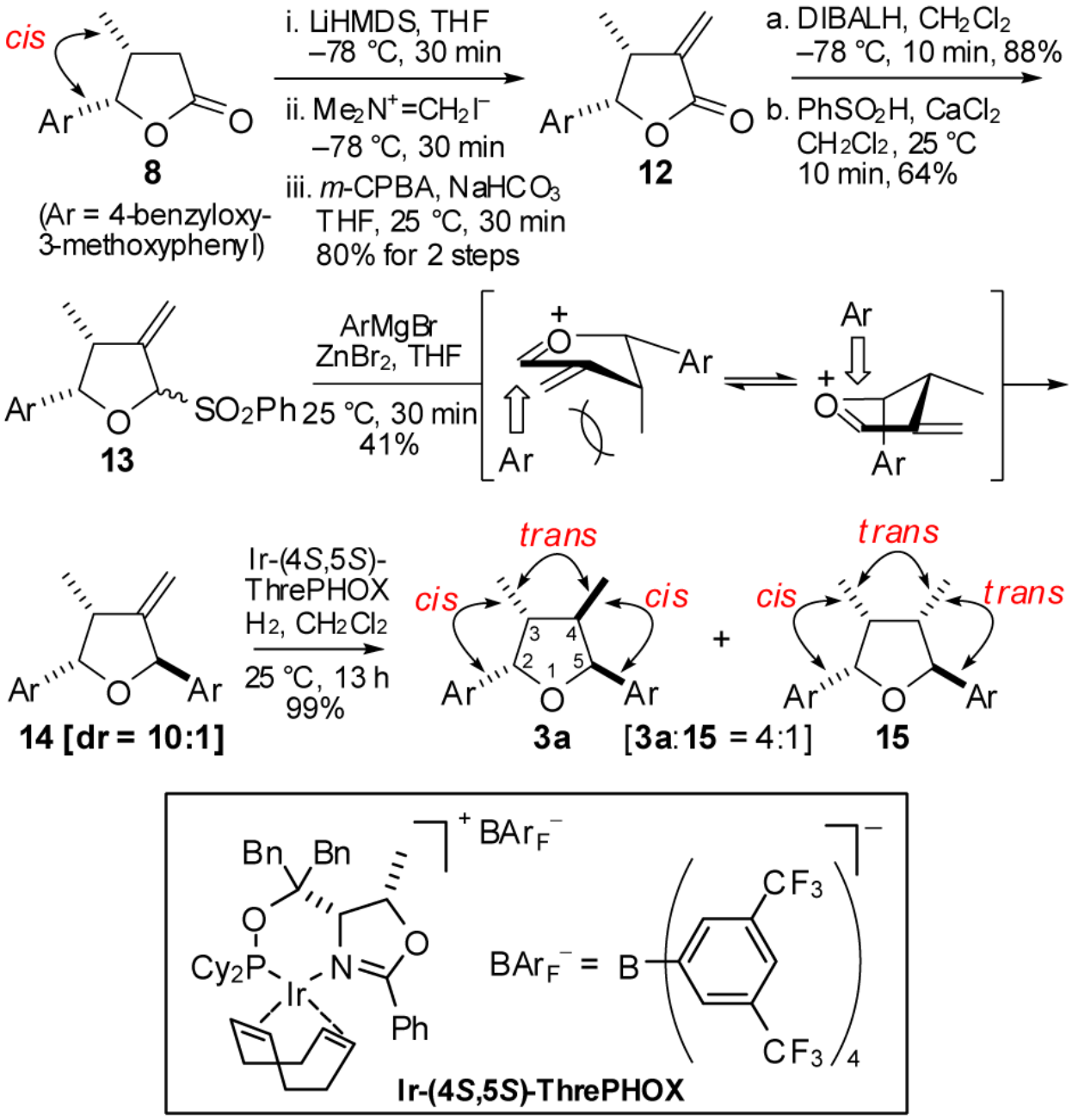
Figure 1.
Retrosynthetic plan for manassantins A (**1**) and B (**2**).



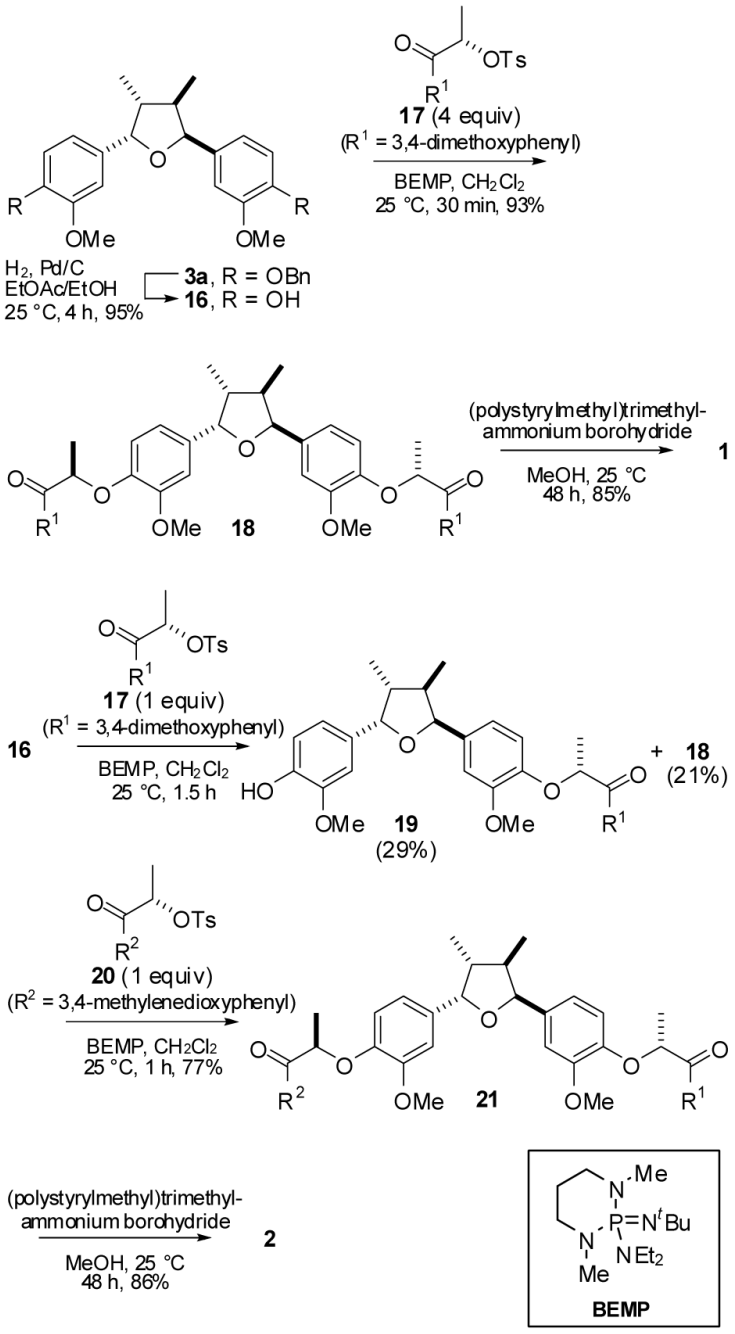
Scheme 1.
Nucleophilic addition of (4-benzyloxy-3-methoxyphenyl)zinc(II) bromide to 2-benzenesulfonyl cyclic ether



Scheme 2.
Model studies for nucleophilic addition reaction



Scheme 3.
Stereoselective synthesis of 2,3-*cis*-3,4-*trans*-4,5-*cis*-tetrahydrofuran



Scheme 4.

Completion of synthesis of manassantins A (**1**) and B (**2**)

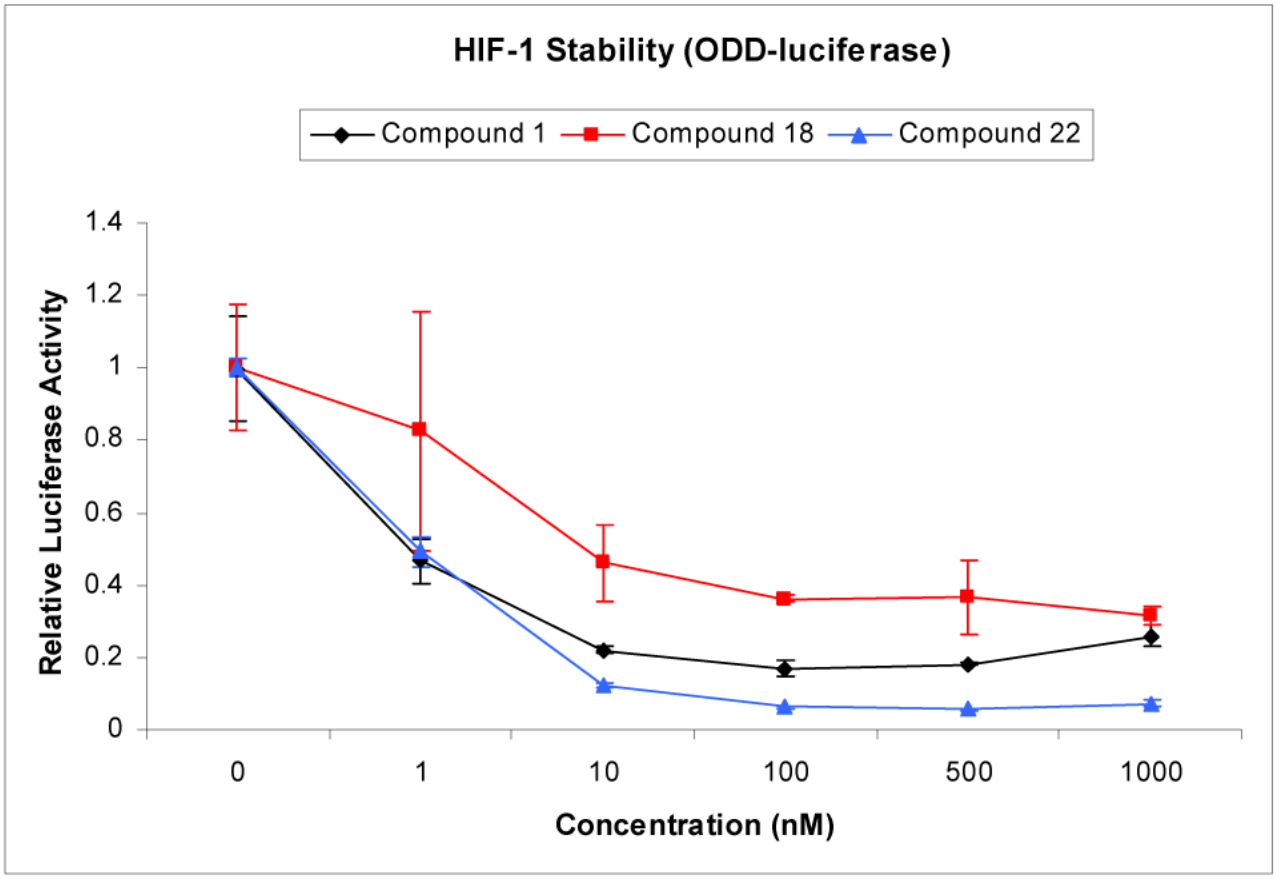


Figure 2.
Inhibition of HIF-1 by **1**, **18**, and **22**.