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Total Synthesis and Stereochemical Confirmation of Manassantin A, B, and B_1

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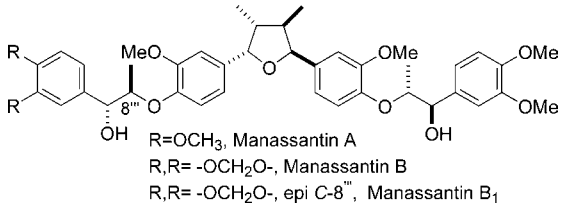
ABSTRACT



Stereocontrolled total syntheses of manassantins A, B, and B_1 and saucerneol are described for the first time based on a novel cycloetherification of end-differentiated benzylic alcohols as a common intermediate.

The manassantin group of structurally related and functionally unique dineolignans has been recently isolated from active root extracts of *Saururus cernuus* L. (Saururaceae), also referred to as "lizard tail". This fragrant aquatic plant is found in the eastern United States[1] as well as in parts of the orient (*Saururus chinensis*).[2] Although their structures and relative stereochemistries were only recently determined,[1c] the medicinal value of the plant has long been recognized by Native Americans, early colonists, and practitioners of Korean folk medicine for a host of diseases.[3] Many medically relevant activities have been associated with manassantin A (**1**) and B (**2**) in particular (Figure 1).[1−3] For example, manassantin B has been shown to be a potent inhibitor of the key transcription factor HIF-1 (hypoxia-inducible factor-1).[1c,d] Overexpression of HIF-1 in solid tumors is detrimental to tumor suppression and compromises anticancer treatment regimens.[4] Thus, selective inhibition of HIF-1 is an important objective in the quest for a chemotherapeutic agent against solid tumors.[4] Remarkably, manassantins A and B are also reported to inhibit PC-3 prostate cancer cell growth[5] and other cell lines with IC_{50} values superior to those for *cis*-platin and doxorubicin.[6] Inhibition of TNF-α in conjunction

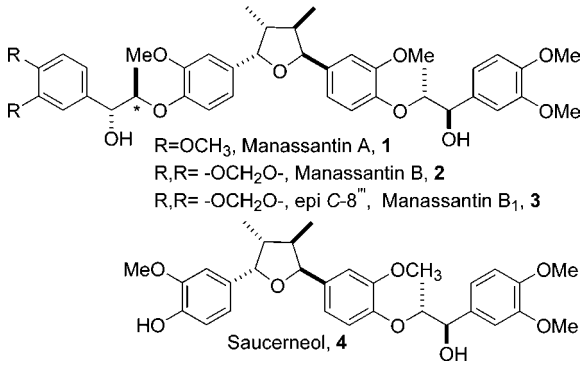


Figure 1. Structures of the manassantins and saucerneol.

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with *E*-selective expression may have relevance in the prevention of atherosclerosis and endothelial activation.[7] Manassantin A has also been associated with selective neuroleptic activity.[8] In their intial report, Rao and Alvarez[1a] revealed the gross structure and only partial relative configuration of **1** and **2**. They coined the name manassantin from the Sanskrit words "manas" or mind and "santi" or peace (i.e., peace of mind). The tranquilizing effect of a nitrogen-free natural product from an aquatic plant was unprecedented at the time.

Subsequently, Nagle and co-workers[1c] relied on the Mosher ester method to determine the configuration of the benzylic carbon in the quasi-C_2 symmetrical alcohols in the side chains and, by inference, the adjacent ether bearing carbon atoms. The absolute configuration of a *syn*−*anti*−*syn*-substituted central tetrahydrofuran ring was not determined. The Nagle group has recently isolated a previously unreported diastereomer B_1 (**3**) with an inverted configuration of one of the *C*-methyl groups in the side chain and also reported physical constants for manassantins A and B.[1d] Saucerneol (**4**) is a neolignan, also found in the *Saururus cernuus* L.[1a] Recently, the absolute configuration in the side chain was determined by Lee and co-workers using the Mosher ester method.[2a]

We undertook the total synthesis of the three manassantins (**1**−**3**) and saucerneol **4** (Figure 1) to confirm the previously assigned configurations and to provide viable synthetic methods that could supplement the relatively small quantities of products isolated by extraction. Visual analysis of the structure of manassantin A immediately reveals its exquisite C_2 symmetry. Except for the methylenedioxy group, manassantin B is also endowed with the same symmetry element unifying the disconnective analysis with a common intermediate (Figure 2). Thus, the core tetrasubstituted *syn*-*anti*−*syn*-tetrahydrofuran unit **A** can be derived from an intramolecular cycloetherification of a functionally differentiated acyclic precursor **B**. The intended stereochemistry of the ether-protected hydroxyl group in **B** would be generated from aldehyde **C**, already harboring three contiguous stereogenic centers. Sequential introduction of the requisite two *C*-methyl groups in a stereocontrolled manner would capitalize on 1,2-inductions of resident groups starting with γ-alkoxy-α,β-unsaturated ester **D**. Chirality would be derived from a catalytic asymmetric cyanohydrin formation of **E**, starting from the 3,4-dialkoxy benzaldehyde **F**. Thus, a major initial challenge resided in the introduction of vicinal syn-related *C*-methyl groups in an acyclic carbon chain harboring four contiguous stereogenic centers (**D**→**C**→**B**). The cycloetherification without racemization (**B**→**A**) of a para-activated benzylic position was another concern in the synthesis plan. Finally, steps to install the phenolic appendages (**A**→**1**, **2**, **3**) including two vicinal hydroxyethyl stereogenic centers would present the penultimate hurdle in the stereocontrolled projected assembly of manassantins A, B, and B_1.

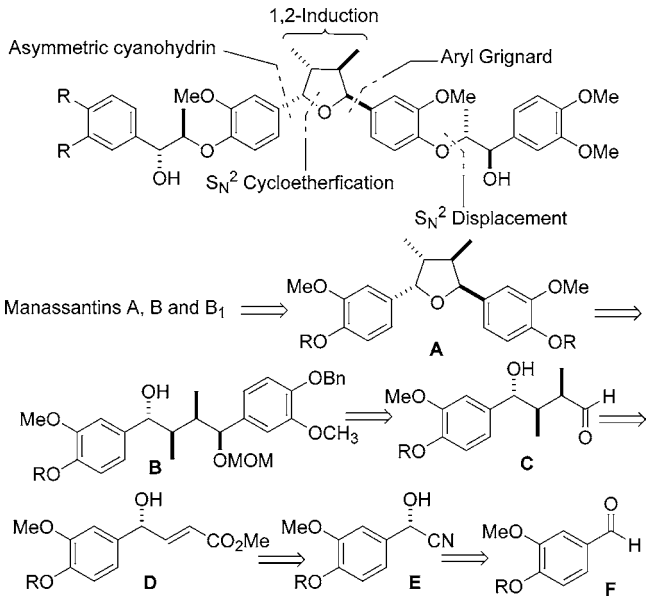

Figure 2. Disconnective analysis for the manassantins.

Cyanohydrin **5** (>99% ee after recrystallization), obtained from the corresponding aldehyde by a catalytic asymmetric protocol according to Belokon,[9] was converted to the ester **6** in excellent overall yield (Scheme 1). Treatment with Dibal-H gave an intermediate aldehyde, which was extended to the enoate **7** via a Wittig olefination in over 85% yield (for two steps). Treatment of **7** with lithium dimethylcuprate in the presence of TMSCl afforded the *anti*-*C*-methyl adduct as the major diastereomer in 87% yield, which was converted to the K-enolate and alkylated with MeI to give **8** in excellent diastereomeric ratio.[10] The ester group in **8** was first reduced to the corresponding alcohol, and the latter was back oxidized with the Dess−Martin periodinane reagent to afford aldehyde **9** in excellent overall yield. A critical step was to be tested at this juncture in the anticipated threo-controlled addition of the 3-methoxy-4-benzyloxyphenylmagnesium bromide to doubly sterically biased aldehyde **9**. After numerous trials,[11] efficient addition took place in the presence of $CeCl_3$ as an activator[12] to give a 2.5:1 mixture of epimeric alcohols **10a** and **10b** which could not be separated at this stage. Protection of the epimeric mixture of alcohols as the MOM ethers, followed by treatment with TBAF, and de-O-allylation gave a separable mixture of **11a** (55%) and **11b** (21% for three steps). The intended intramolecular etherification was best

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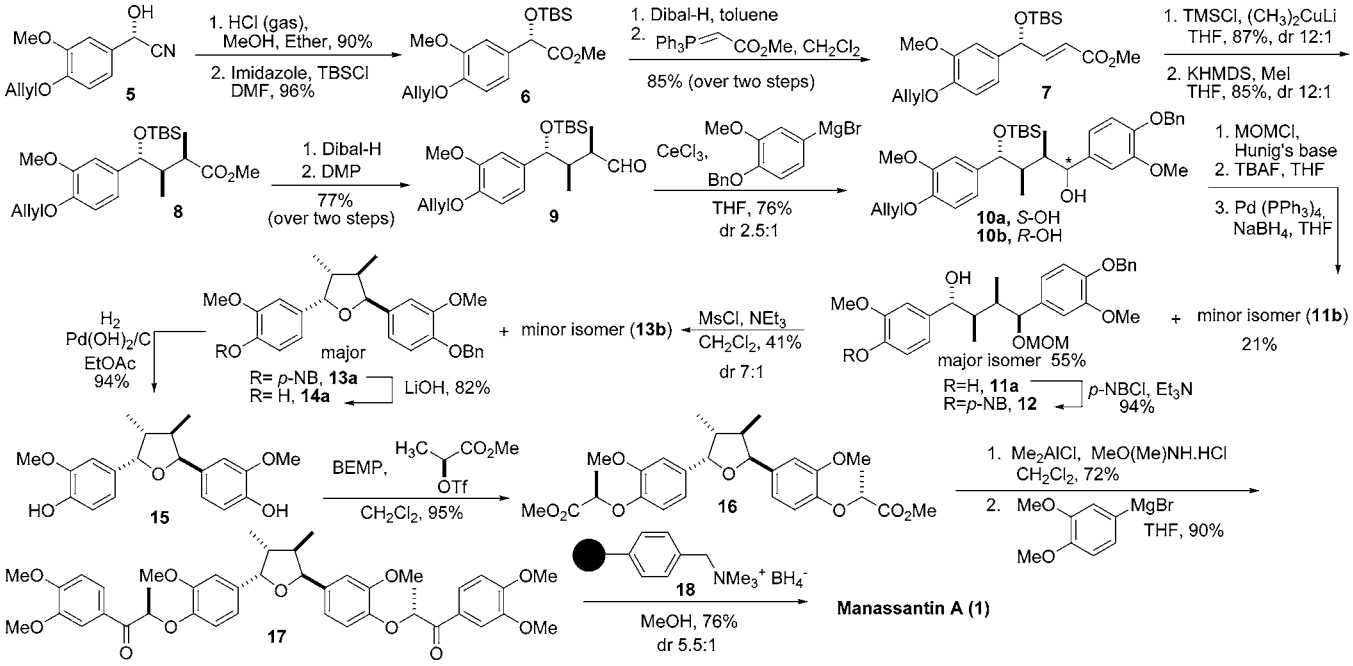
Scheme 1

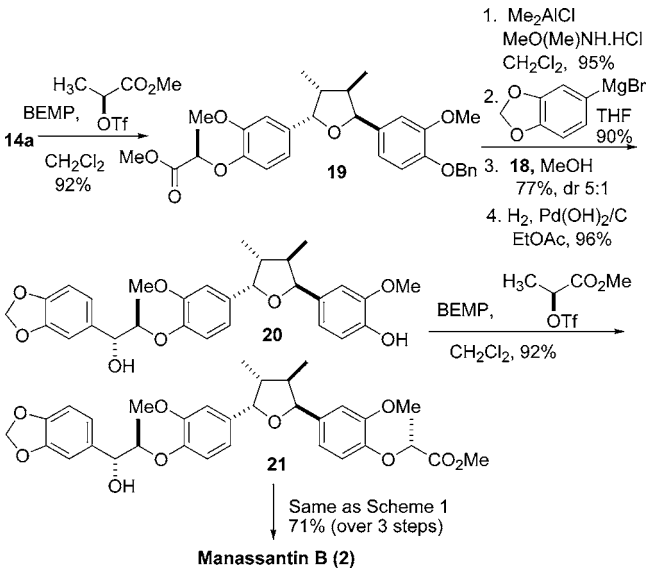


achieved using the *p*-nitrobenzoate ester **12** as a precursor. Treatment of **12** with mesyl chloride in CH_2Cl_2 (Scheme 1) in the presence of Et_3N gave the desired THF isomer **13a** as the major product (7:1). Cleavage of the *p*-nitrobenzoate ester in **13a** gave the C_2 symmetrical and end-differentiated core THF unit **14a**. Hydrogenolysis of the benzyl ether led to the known saucernetin diol **15**.[1b] The triflate ester of *S*-methyl lactate proved to be an excellent electrophilic partner in the double intermolecular S_N2 displacement with the phenolic hydroxyl group in **15**. Using a phosphazene base (BEMP),[13] reaction took place with complete inversion to give **16** in 95% yield. Conversion of **16** to the corresponding Weinreb amide[14] followed by treatment with the Grignard reagent prepared from 3,4-methylenedioxy-1-bromobenzene gave the ketone **17** in 90% yield. The selective reduction of the two carbonyl groups in **17** was best accomplished with a polymer supported borohydride **18**[15] to afford manassantin A (**1**) as the major product, easily separable from the minor *syn*-alcohol diastereomer (dr 5.5:1) in a total yield of 76%. The physical constants of **1** were in full accord with published data.[1a]

The synthesis of manassantin B (**2**) was achieved in the same manner starting from the enantiopure common intermediate **14a** (Scheme 2). An S_N2 displacement of the triflate ester of *S*-methyl lactate with **14a** as described above gave the ether **19** in excellent yield. Conversion to the Weinreb amide and treatment with 3,4-dimethoxy phenylmagnesium bromide gave a ketone, which was reduced with the polymer supported borohydride **18** to give the desired diastereomer (dr >5:1) as the major product. Cleavage of the benzyl ether gave **20**, and application of the same protocol as that described above first gave the bis-ether **21**, which was subjected to the three-step sequence to give manassantin B (**2**) as a major product (dr 6.5:1). Synthetic manassantin B was found to be identical, in all aspects, with an authentic sample kindly provided by Novartis (Basel).

The synthesis of manassantin B_1 presented a new challenge because it contains a *syn*-oriented hydroxylethyl ether linker in the methylenedioxyaryl portion of the molecule (Figure

Scheme 2



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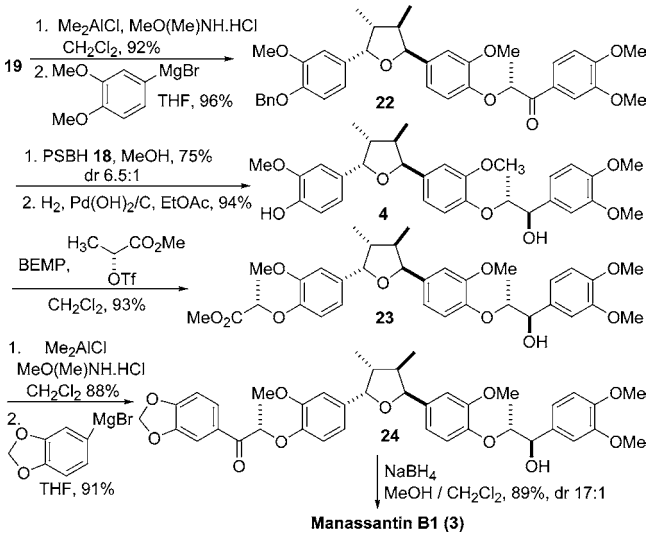
1). The common precursor **19** was first elaborated to the ketone **22** as described above in excellent yield (Scheme 3).

Scheme 3



Polymer supported borohydride reduction led, as expected, to the *anti*-alcohol (dr 6.5:1), which was converted to saucerneol **4** by hydrogenolysis. BEMP-mediated displacement of the triflate ester of *R*-methyl lactate with **4** proceeded smoothly to give **23** in 93% yield. Conversion to the Weinreb amide followed by reaction with the 3,4-methylenedioxy phenylmagnesium bromide led to the expected ketone **24**. Reduction with $NaBH_4$ in a mixture of MeOH and CH_2Cl_2 at low temperature gave manassantin B_1 (**3**) as the preponderant product (dr 17:1) in 89% yield. Comparison of physical constants provided definitive proof of its structure and absolute configuration.[1d]

The main challenge in the synthesis of the diversely substituted 2,5-diaryl-3,4-dimethyl tetrahydrofurans related to the manassantins is to control the relative and absolute stereochemistry of four contiguous stereogenic centers in the central ring and two in the side chains. Historically, expedient access to racemic 2,5-diaryl-3,4-dimethyl lignans has relied on the synthesis of 1,4-diaryl-2,3-dimethyl-1,4-diketones, followed by reduction to 1,4-diols and cyclization by treatment with MsCl and base.[16] This simple protocol produces diastereomeric mixtures of the racemic tetrasubstituted tetrahydrofurans. Cycloetherification can also be accompanied by unwanted Friedel−Crafts reaction on the benzylic mesylates.[17] Other methods have also been reported that rely on oxidative cyclization followed by functional group adjustments to give racemic lignans.[18] Recent methods relying on a chiral auxiliary mediated aldol reaction[19] and allylboration of aromatic aldehydes to α-methylene lactones are of interest.[20]

The successful application of the sequential cuprate addition and enolate *C*-methylation in our protocol is noteworthy in view of the paucity of methods for the stereocontrolled synthesis of vicinal carbon substitution in acyclic substrates.[10] The added practical advantage of our approach is the MOM-mediated S_N2 displacement of end-differentiated benzylic alcohols in the elaboration of the *syn*−*anti*−*syn*-tetrasubstituted THF core unit. This was best done with a *para*-nitrobenzoate phenolic ester.[21] The last stereochemical hurdle to overcome in the assembly of the manassantins consisted of the deployment of the phenolic ether side chain. An approach to this construct in relation to the synthesis of neolignans was reported by Lee and Ley.[15] Phenolic intermediates were used in S_N2 displacement reactions of α-keto tosylates, prepared in a three-step sequence employing an asymmetric dihydroxylation of *Z*-propenyl aromatics as a source of chirality.

An expedient method to prepare phenolic ethers of lactic acid consists of an S_N2-type displacement of the corresponding mesylates. Despite the simplicity of this method, there are only a few reports of documented examples.[22] Unfortunately in the case of Cs phenolate and the mesylate ester of L-ethyl lactate, a partially racemized product was observed.[22] We reasoned that the use of a hindered strong nitrogen base such as a phosphazene[13] in conjunction with an excellent leaving group such as a triflate would be a good combination. Indeed, smooth displacement took place to give the inverted ether in high yield. The reaction could also be successfully carried out in a bidirectional mode en route to manassantin A.

In conclusion, we have described an efficient and stereocontrolled route for the first total synthesis of manassantins A, B, and B_1 and the neolignan saucerneol. Definitive confirmation of the previously proposed absolute confirmation of these biologically important complex lignans has now been established through total synthesis.

Acknowledgment. We thank NSERC for financial assistance and Dr. Ying Wang (Novartis Pharma) for an authentic sample of manassantin B. We also acknowledge fruitful discussions with Dr. Silvio Roggo (Natural Products Unit, Novartis Institute for Biomedical Research, Basel).

Supporting Information Available: Full experimental procedures, compound characterizations, and selected ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The minor isomer **13b** had resulted from a face-selective attack of the distal benzylic alcohol via a quinonoid oxocarbenium ion with ejection of the OMOM group to giva an anti−anti−anti pattern. See Supporting Information (Scheme 1).

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