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Use of Allylic Strain To Enforce Stereochemistry. Direct Syntheses of 7,8-Dihydroxycalamenene and Mansonone C

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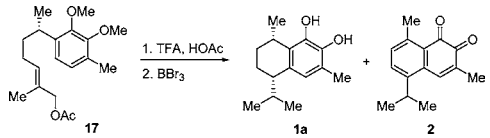
ABSTRACT



Direct syntheses of 7,8-dihydroxycalamenene and mansonone C were achieved. The *cis*-stereochemistry required for the synthesis of 7,8-dihydroxycalamenene was introduced by an intramolecular cyclization directed by allylic strain.

Allylic 1,3-strain has been used in acyclic systems to direct the introduction of new stereogenic centers.[1] Notable examples include the work of Kishi,[2] Adam,[3] and Giese.[4] We are not aware of any application of allylic strain to control the relative stereochemistry in disubstituted tetralins. Tetralins such as **1**, **3**, and **4** have attracted considerable synthetic attention (Figure 1).[5] 7,8-Dihydroxycalamenene (**1a)** exhibits

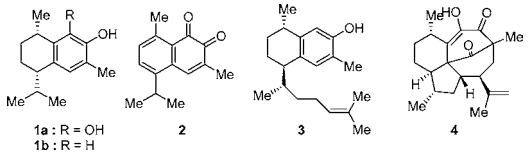


Figure 1. Tetralin-derived products and mansonone C.

useful anti-infective activity.[6] Hydroxycalamenene (**1b)** was isolated from *Hypericum elodeoides*.[7] Mansonone C (**2**), extracted from the heartwood of *Mansonia altissima*,[8] was found to possess promising antifungal, larvicidal, and antioxidant properties.[9] Schmalz recorded a synthesis of **1a** using arenechromium complexes to introduce the relative stereochemistry.[10]

Many synthetic approaches to these compounds begin with natural products such as menthone wherein the relative stereochemistry has already been established.[11]

Several researchers have noted that attempts to install stereochemistry by epimerization or by cyclization onto the aromatic ring have led to mixtures.[12,13] We report herein that a system such as **5**, wherein allylic strain between G and

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(5) Erogorgiaene (**3**): Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod.* **2001**, *64*, 100. Elisapterosin B (**4**): Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Barnes, C. L. *J. Org. Chem*. **2000**, *65*, 1390.
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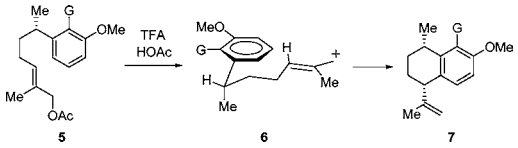
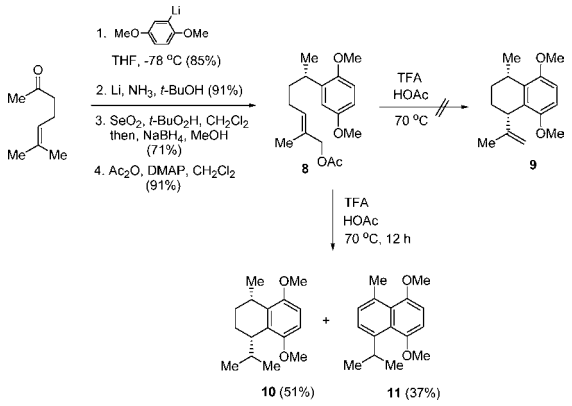
the methyl group forces the methyl group to be axial as the six-membered ring is being formed, affords exclusively the *cis*-stereoisomer **7** (Scheme 1).

Scheme 1



In order to evaluate the directing effect, we first synthesized allylic acetate **8** (Scheme 2). Allylic acetate **8** was synthesized starting from 6-methyl-5-hepten-2-one and the anion of 1,4-dimethoxybenzene. Dehydroxylation of the resulting benzylic alcohol using Li/NH_3 followed by allylic oxidation by the method of Sharpless[14] yielded an allylic alcohol which, upon acetylation, afforded **8**. Surprisingly, cyclization of allylic acetate **8** using the conditions of Ma and Zheng[15] afforded tetralin **10** and naphthalene **11** in 51% and 37% yields, respectively. Compound **9**, the expected product, was not isolated.

Scheme 2



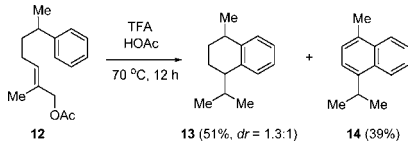
We believe that compounds **10** and **11** result from a novel cation-mediated disproportionation reaction. Comparison of the NMR spectrum of **10** with that of the literature compound[13] showed that the *cis*-stereoisomer was exclusively formed.

In support of this allylic strain assisted stereoselective cyclization, we have found that cyclization of allylic acetate **12**, which does not contain the directing group G, affords tetralin **13** as a 1.3:1 mixture of diastereomers (Scheme 3).

With the stereochemistry of **10** established, we began the synthesis of **1a** by the reaction of 5-methyl-4-hexen-1-al[16]

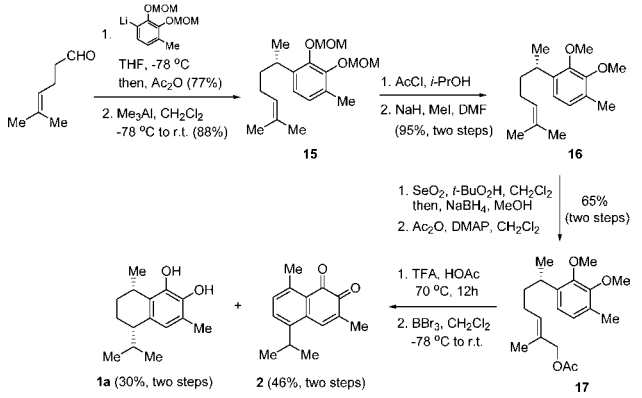
(14) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526

Scheme 3



with the anion of 1,2-bis(methoxymethoxy)-3-methylbenzene (Scheme 4). The resulting alkoxide was in situ acetylated by the addition of acetic anhydride. The displacement of the acetate to the corresponding methyl group was achieved using Me_3Al to afford **15**. In order to enhance the stability for the acid-mediated cyclization, MOM protecting groups were converted to the more stable methyl ether **16**. It was then oxidized and acetylated by the same methods used to generate **8**. Cyclization of **17** using trifluoroacetic acid in acetic acid at 70 °C for 12 h followed by deprotection by the use of BBr_3 generated 7,8-dihydroxycalamenene (**1a**) in two steps (30% yield). Interestingly enough, mansonone C (**2**) was also obtained from the same reaction in two steps (46% yield). The direct synthesis of 7,8-dihydroxycalamenene (**1a**) demonstrates the advantage of employing the concept of allylic strain in organic synthesis.

Scheme 4



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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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