A Concise Total Synthesis of Enantiomerically Pure (+)-*cis*- and (+)-*trans*-Lauthisan

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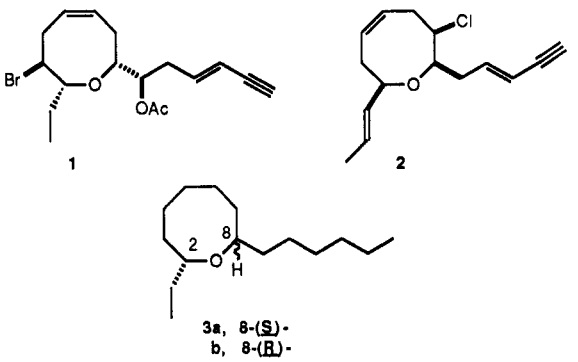
Summary: A general synthetic strategy based upon thermally induced Claisen ring expansion as the pivotal step allows for rapid elaboration of the lauthisans in enantiomerically pure condition and proper absolute configuration.

The red algal metabolites laurencin (**1**)[2] and laurenyne (**2**)[3] are illustrative of many biologically active marine natural products that possess medium-ring cyclic ether frameworks.[4] While oxocenes and oxocanes have been derived through a variety of synthetic strategies,[5-13] none can be categorized as entirely flexible. A general protocol for the preparation of enantiomerically pure eight-membered cyclic ethers from simple allylic alcohols is described herein in the form of a concise synthesis of *cis*-lauthisan (**3a**) and *trans*-lathisan (**3b**).[14] These targets have often served as the testing ground for the efficacy of oxocane construction.[6a,8,11b]

The synthetic advantages offered by the present approach stem from initial reliance on the Sharpless epoxidation to set *R* or *S* configuration at C-2.[15] Excellent control of the extent and nature of the pendant substituents is subsequently made possible because structural complexity is developed from three readily available building blocks. The combination of these features with facile ring expansion of the 1,4-dioxanone ring system[16] to 3-oxocen-7-ones via the Kinney variant[17] of the Claisen rearrangement results in considerable simplification of the requisite molecular construction. Finally, the double bond and carbonyl group in these isomerization products provide for highly desirable chemical flexibility.



Exploration of the above plan began with kinetic resolution of commercially available (±)-1-penten-3-ol. Through use of diisopropyl L-tartrate and interruption of the epoxidation after 70% conversion,[18] the unreacted *R* isomer **4** could be recovered in enantiomerically pure condition.[19] The sodium hydride mediated condensation of (*R*)-**4** with (±)-2-bromooctanoic acid[20] in refluxing tetrahydrofuran provided **5** (90%, Scheme I). The configuration at the alkoxy carbon was not affected when proper care was exercised during the subsequent ozonolysis to give **6** (93%), and this aldehyde was reacted without undue delay with vinylmagnesium bromide.

Spectral analysis of **5** showed the substance to be an epimeric mixture at the position α to the carboxylic acid as expected. Although the introduction of a third stereogenic center during 1,2-addition to the aldehyde group in **6** was more stereocontrolled, acid-catalyzed cyclization of the resulting hydroxy acids delivered **7** (63% for two steps) in the form of two major and two minor diastereomers. As will be demonstrated, neither of the two new stereochemical markers in **7** ultimately impact on the chiral integrity of the target molecules or the efficiency with which they are produced. For these reasons, no attempt was made to establish with certainty the prevailing con-

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(19) Rigorous characterization of **4** with regard to configurational homogeneity was achieved by preparation of the Mosher ester and ^{19}F NMR analysis. The racemic alcohol was comparably dealt with.

(20) Purchased from the Aldrich Chemical Co.

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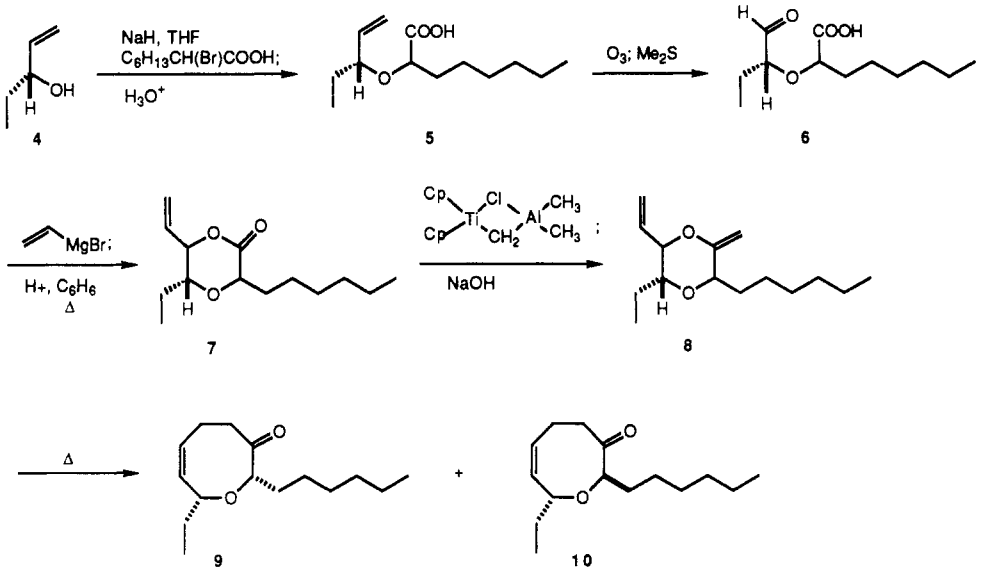
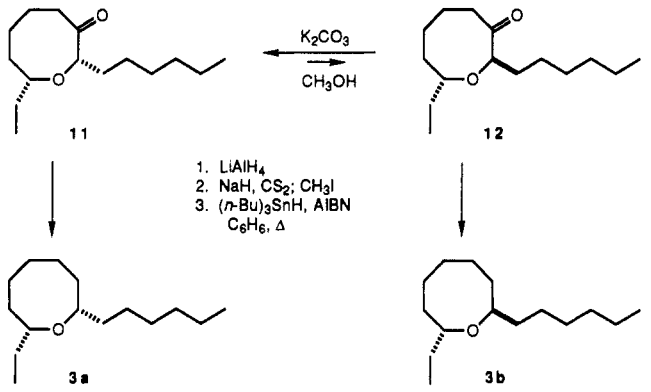
Scheme I



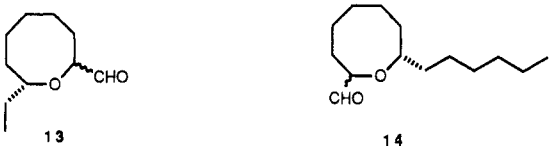
Scheme II



figurational relationships at this stage.

The mixture of 1,4-dioxanones was treated with the Tebbe reagent[21] (room temperature, 90 min) and quenched with 15% sodium hydroxide solution. The resultant vinyl ethers **8** were twice chromatographed through basic alumina to guarantee complete removal of organometallic impurities.[22] The yield of **8** purified in this manner was 65%. With the carbonyl oxygen replaced by CH_2, [3,3]-sigmatropy[23] could be performed smoothly in base-washed heavy-walled glass tubes[17] at 185 °C for 36 h. The oxocenones **9** and **10** were isolated with 86% efficiency in a ratio approximating 1:1.4.

The **9**/**10** mixture was directly hydrogenated over 5% Pd/C to provide **11** and **12** (95%, Scheme II). The cis and trans isomers were separated by preparative GC at 160 °C and individually subjected to base-catalyzed equilibration. Cis stereoisomer **11** was anticipated to prevail because both pendant groups are equatorial in a favored boat–chair conformer.[5b,24] Experimentally, the **11**/**12** equilibrium ratio was determined to be 5.6:1. This observation compares favorably with earlier results uncovered for **13** (cis/trans, 8:1)[11a] and **14** (cis/trans, 5:1).[11b]



Completion of the synthesis proved to be straightforward, removal of the C-7 oxygen being accomplished by sequential lithium aluminum hydride reduction of both **11** and **12**, conversion of each oxocanol to its xanthate, and free-radical deoxygenation with tri-*n*-butyltin hydride and AIBN in hot benzene.[25] The overall efficiency of both sequences was 82%. Whereas **3b** exhibited $[\alpha]^{22}_D$ +13.7° (*c* 0.18, $CHCl_3$), the specific rotation of **3a** [+14.4° (*c* 0.09, $CHCl_3$)] was virtually identical to the value reported recently by Kotsuki et al. [+13.9° (*c* 0.15, $CHCl_3$)].[8]

In summary, this study marks a fundamentally new approach to the preparation of chiral medium-ring cyclic ethers from simple allylic alcohol precursors in either enantiomeric series and with numerous points of possible chemical divergence.

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