New [4 + 3] Cycloaddition Approach to *Cis*-2,8-Disubstituted Oxocanes

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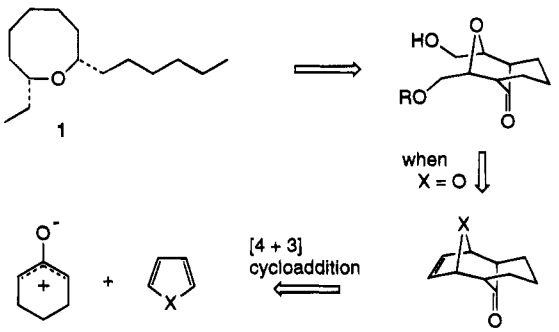
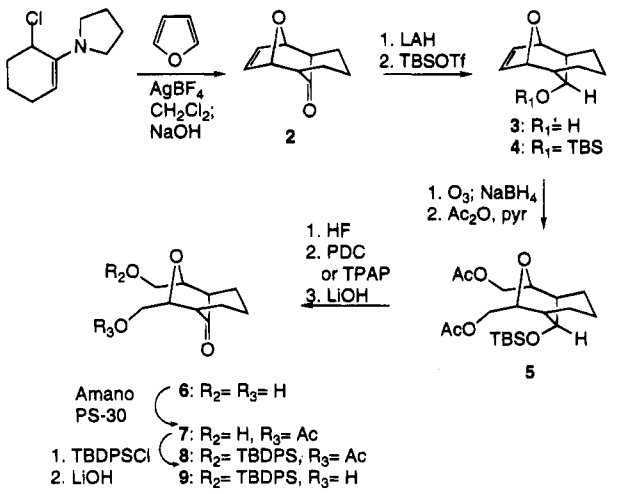
The wide occurrence of halogenated medium-sized cyclic ethers in several marine natural products isolated predominantly from a variety of *Laurencia* species has prompted the development of a number of elegant synthetic approaches.[1–3] Notwithstanding a few notable accomplishments of successful total syntheses,[4] however, there remains a paucity of general methods for the synthesis of medium-sized heterocycles and carbocycles. We have recently developed a new, general strategy for the stereoselective construction of functionalized medium-sized heterocycles and carbocycles by taking advantage of the [4 + 3] cycloaddition of *cyclic* oxyallyls and related allyls.[5] As a preliminary study in the area of the oxocane marine natural products, we report herein an enantioselective synthesis of (+)-*cis*-lauthisan (**1**).[6,7]



Our synthetic strategy utilizes the [4 + 3] cycloadduct **2** to generate the oxocane ring with the requisite *cis*-2,8-side chains (Scheme 1).[8,9] The known starting material

Scheme 1



2 is readily available (73–82%) from either the Schmid cycloaddition of 3-chloro-2-pyrrolidinocyclohexene or the Föhlisch cycloaddition of 2-chlorocyclohexanone with furan.[9–11] Cycloadduct **2** was first converted to diol **6** by standard transformations. Thus, LAH reduction of ketone **2** gave exclusively endo alcohol **3**, which was then protected as the TBS ether **4** in 97% overall yield. Subsequent ozonolysis, $NaBH_4$ reduction, and acetylation afforded diacetate **5** in 90% yield. After the keto group was restored at the bridge in a straightforward manner, hydrolysis gave rise to diol **6** in 89% overall yield.

At this juncture the enzymatic asymmetrization of the meso diol **6** was accomplished most conveniently by the use of crude Amano PS-30 lipase in isopropenyl acetate to give the mono acetate **7**, $[\alpha]^{25}_D$ −11.9° (*c* 9.5, $CHCl_3$), in 76% yield.[12] For determination of enantiomeric purity, **7** was converted by straightforward functional group manipulations (93% overall yield) to alcohol **9**, the ee of which was shown to be 85% by HPLC analysis (using a Daicel OD column). The assignment of the absolute

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(11) The term "cycloaddition" is used to indicate the overall bonding change rather than to imply a concerted mechanism.

(12) (a) The enantioselectivity by other lipases and esterases will be presented in a full paper. (b) Cf. Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414. (c) For an excellent overview of biotransformations in organic syntheses, see: Poppe, L.; Novák, L. *Selective Biocatalysis*; VCH: New York, 1992.

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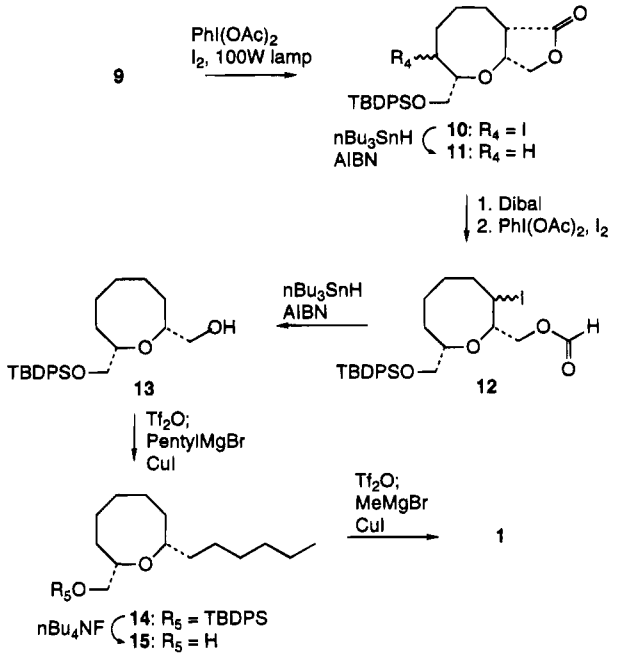
Scheme 2



configuration of **9** was tentatively made by analogy to structurally related examples[12c] and was ultimately confirmed by its conversion to (+)-*cis*-lauthisan (**1**).

Our attention was next focused on the oxidative cleavage of the keto bridge to unmask the 2,8-*cis*-disubstituted oxocane ring. Suárez cleavage by the action of $PhI(OAc)_2$ and I_2 in refluxing benzene resulted in a facile formation of iodo lactones **10**, as a 2:1 mixture of diastereomers, in 80–85% yield.[13] Treatment with *n*-Bu_3SnH smoothly gave lactone **11** in 76% yield (Scheme 2). Subsequent excision of the lactone functionality was then achieved by the iteration of Suárez cleavage on the corresponding lactol to furnish the diastereomeric iodoformates **12**. Upon concomitant deiodination–deformylation with neat *n*-Bu_3SnH, alcohol **13** was obtained in 63–75% overall yield and in 85% ee.[14]

The final leg of the synthesis of **1** was completed by the installation of the side chains employing the procedure of Kotsuki.[3e,15] Thus, treatment of **13** with Tf_2O, followed by pentylmagnesium bromide in the presence of CuI, furnished the desired compound **14** in 87% yield. Following desilylation (*n*-Bu_4NF) of **14**, the repetition of the Kotsuki protocol on alcohol **15** with MeMgBr afforded the target compound, (+)-**1**, in 79% yield. The physical and spectral data of synthetic (+)-**1** (85% ee) were in excellent agreement with literature values.

In summary, we have developed a new, efficient synthetic approach for the enantioselective preparation of medium-sized cyclic ethers. Our synthesis further underscores the potential of the hitherto little-explored [4 + 3] cycloaddition of cyclic oxyallyl or aminoallyl species. Further synthetic applications to structurally complex oxocene natural products are currently in progress.

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Supplementary Material Available: Experimental procedures and characterization data (^1H and ^{13}C NMR spectra) for **1**–**15** (46 pages).

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(14) (a) Determined by HPLC analysis using a Daicel OD column. (b) Enantiomeric purity of **13** was identical to that of **7**.

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