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The Shortest (Four-Step) Total Synthesis of the Eight-Membered Cyclic Ether (*rac*)- and (–)-*cis*-Lauthisan

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Access to the eight-membered cyclic ether (*rac*)- and (–)-*cis*-lauthisan was achieved in two complementary ways in only four steps for the longest linear sequence by starting from commercially available materials. The sequence features a *cis*-stereoselective reductive cyclization as the key step.

Introduction

Medium-ring ethers are present in a number of biologically active marine natural products, particularly from Laurencia red algae.[1] Some compounds of this class contain an eight-membered oxocane or oxocene ring, usually with *cis* stereochemistry in the alkyl substituents at C-2 and C-8. Among them, (+)-laurencin (**1**; Figure 1), isolated from the extracts of *Laurencia glandulifera*,[2] is the most representative example and has been the subject of significant synthetic effort over the past years.[3] Regardless, the formation of medium-sized rings remains a challenge because of their relative thermodynamic instability and the unfavorable entropic factors contributing to difficult ring formation.[4] Consequently, there continues to be a huge interest in developing efficient and general processes that allow access to such naturally occurring systems.

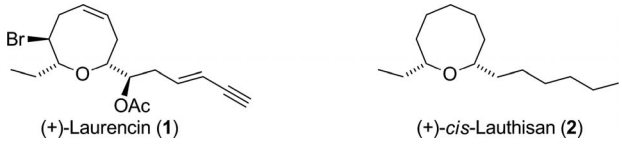
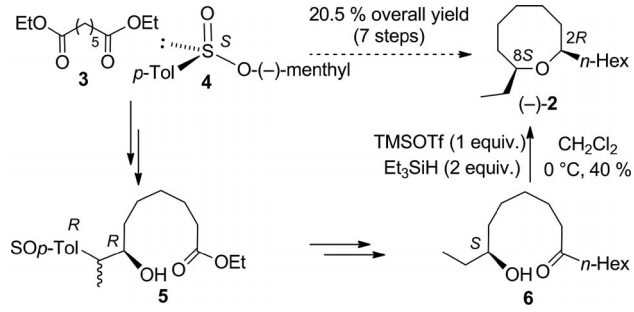


Figure 1. Structures of eight-membered cyclic ethers (+)-laurencin (**1**) and (+)-*cis*-lauthisan (**2**).

(+)-*cis*-Lauthisan (**2**; Figure 1) is the fully saturated core of natural derivative **1** and has been often used as a target to check the validity of a particular synthetic methodology for efficient oxocane construction. Although several strategies have been employed for the stereoselective preparation of racemic[5] and enantioenriched[6] *cis*-lauthisan, most of them require multistep syntheses or take place with moderate *cis* selectivities.

In recent years, we have described the syntheses of differently sized cyclic ethers based on the Et_3SiH/TMSOTf-promoted (Tf = trifluoromethanesulfonyl) reductive cyclization of the corresponding hydroxy ketone.[7] The synthesis of (–)-*cis*-**2** we had previously reported[8] was accomplished in seven steps and 20.5% overall yield by starting from commercially available diethyl pimelate (**3**) and enantiopure (–)-(*S*)-menthyl *p*-toluenesulfinate (**4**; Scheme 1). Key β-hydroxy sulfoxide intermediate (*S*)-**5** in this synthesis was later transformed into enantiopure hydroxy ketone (*S*)-**6**, the reductive cyclization of which led to a 40% yield of (–)-**2** in a stereoselective manner.



Scheme 1. Previous seven-step total synthesis of (–)-*cis*-lauthisan (**2**) from diethyl pimelate (**3**) and (–)-menthyl *p*-toluenesulfinate (**4**).

To improve the yield of the cyclization step, we reasoned to introduce a (*Z*)-substituted double bond in acyclic saturated hydroxy ketone **6** to restrict its conformational mobility, which would thus entropically favor the intramolecular process. We initially focused on (*rac*)-*cis*-**2**, as depicted in the retrosynthesis (Scheme 2), via unsaturated hydroxy ketone **8**, with the hexyl and ethyl substituents exchanged with respect to intermediate **6**, as a complementary way to access the *cis*-disubstituted eight-membered cyclic ether framework.

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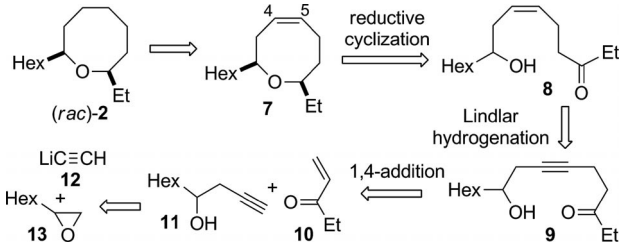


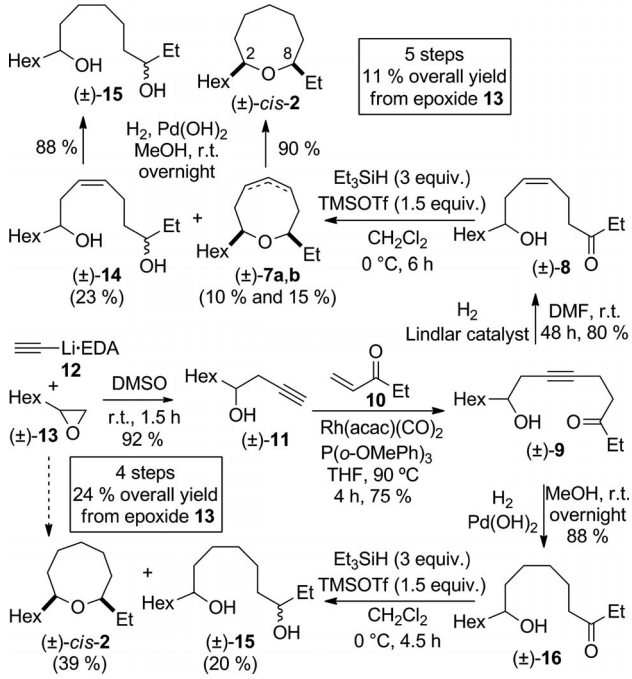
Scheme 2. Retrosynthesis towards (±)-*cis*-lauthisan (**2**) from vinyl ketone (**10**) and (±)-1,2-epoxyoctane (**13**) through unsaturated intermediate **8**.

Thus, (*rac*)-*cis*-**2** could be synthesized from cyclic alkene **7** having a double bond at C4–C5 by proceeding from the reductive cyclization of unsaturated hydroxy ketone **8**, which in turn could arise, in a controlled reduction, from alkyne **9** (Scheme 2). This intermediate would be formed from commercially available ethyl vinyl ketone (**10**) and homopropargylic alcohol **11**, which could proceed from the opening of commercially available racemic 1,2-epoxyoctane (**13**) with lithium acetylide **12**.

Results and Discussion

The synthesis of key unsaturated hydroxy ketone **8** began with ring opening[9] of oxirane (±)-**13** with the lithium acetylide–ethylenediamine (EDA) complex (**12**) to provide carbinol (±)-**11** in 92% yield (Scheme 3). Conjugate addition of homopropargylic alcohol **11** to ethyl vinyl ketone (**10**) was accomplished by using $Rh(acac)(CO)_2$ (acac = acetylacetonate) as the catalyst and tri(*o*-methoxyphenyl)phosphane as the ligand[10] (THF, 90 °C, 4 h) to give alkyne (±)-**9** containing the entire carbon skeleton of (±)-*cis*-lauthisan in 75% yield. Partial controlled hydrogenation of the triple bond of **9** with Lindlar catalyst (DMF, r.t., 48 h) provided desired hydroxy (*Z*)-alkenyl ketone (±)-**8** in 80% yield. Reductive cyclization of (±)-(*Z*)-**8** was performed with Et_3SiH (3 equiv.) and TMSOTf (1.5 equiv.) in CH_2Cl_2 at 0 °C. Under these conditions, a mixture of four compounds was formed. Separation by flash chromatography allowed cyclized alkene isomers (±)-**7a**,**b** with the double bond at the C-4 or C-5 position to be isolated in 15 and 10% yield, respectively, in addition to open-chain diastereoisomeric diols (±)-**14**, resulting from the direct reduction of the C=O group of (±)-**8**, in 23% yield.

We confirmed the cyclic structures of (±)-**7a** and (±)-**7b** and the acyclic structure of (±)-**14** by hydrogenation of each mixture in the presence of $Pd(OH)_2$ (Scheme 3). Under these conditions, isomers (±)-**7a**,**b** converged to (±)-*cis*-**2** (90% yield), whereas compounds (±)-**14** led to the corresponding open-chain saturated diastereoisomeric diols (±)-**15** in 88% yield. The relative *cis* stereochemistry between the substituents at C-2 and C-8 in cyclic unsaturated ethers (±)-**7a**,**b** was determined by NOESY experiments on hydrogenation product (±)-(**2**). Thus, the total synthesis of (±)-*cis*-**2** could be completed in five steps in 11% yield overall. Although this synthesis of *cis*-lauthisan is shorter than our



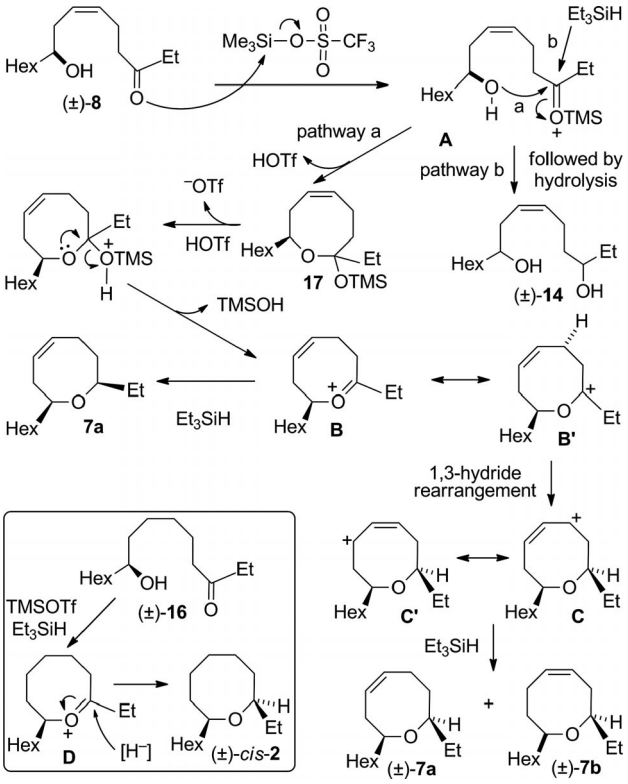
Scheme 3. Four-step total synthesis of (±)-*cis*-lauthisan (**2**) from ethyl vinyl ketone (**10**) and (±)-1,2-epoxyoctane (**13**) through saturated intermediate (±)-**16**.

previous one[8] (seven steps, 20.5% yield), the overall yield is not competitive owing to the low efficiency of the reductive cyclization step of (*Z*)-unsaturated hydroxy ketone (±)-**8**, which afforded the cyclized skeleton in only 25% yield.

Given that the presence of the double bond in (±)-**8** did not improve this yield, we decided to focus again on the reductive cyclization of saturated acyclic precursor (±)-**16** (Scheme 3). Thus, hydroxy ketone (±)-**16** was easily available (88% isolated yield) by full hydrogenation of the triple bond in alkyne (±)-**9** (Scheme 3). Upon treatment with Et_3SiH and TMSOTf, (±)-**9** evolved into a mixture of (±)-*cis*-**2** and diastereomeric diols (±)-**15**, which were isolated in 39 and 20% yield, respectively. The stereochemical course of the reductive cyclization of (±)-**16** was identical to that previously observed for isomeric derivative (*S*)-**6** (Scheme 1).[8] Thus, (±)-*cis*-**2** was prepared in four steps in 24% yield overall, which is the shortest total synthesis described to date.

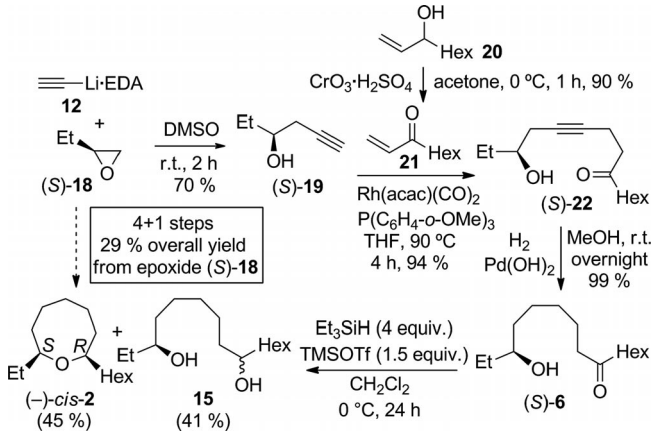
In agreement with the mechanism proposed for these reactions,[11,12] the formation of isomeric cyclic unsaturated ethers (±)-**7a**,**b** could be explained as shown in Scheme 4. Initially, the Lewis acid (TMSOTf) must activate the carbonyl group of hydroxy ketone (±)-**8** to give a species such as **A**. Intramolecular nucleophilic attack of OH to the activated carbonyl group gives rise to unisolated mixed ketal **17** (pathway a), precursor of cyclic oxocarbenium ion **B**, the formation of which is favored by the triflic acid present in the reaction medium. The stereoselective reaction of Et_3SiH with oxocarbenium ion **B** explains the formation of cyclic ether (±)-**7a**. A 1,3-hydride rearrangement of intermediate **B**, which situates the deficiency at the carbon atom (i.e., **B′**), would lead to allylic carbenium ion **C**. Two resonance

forms, **C** and **C′**, can be written to stabilize the charge in the allylic carbenium ion. Attack of Et_3SiH to both **C** and **C′** justifies the observed formation of regioisomeric cyclic ethers (±)-**7a**,**b** with the rearranged double bond. Taking into account the stereochemistry of hydrogenated product (±)-**2**, which results from the mixture of unsaturated cyclic ethers (±)-**7a**,**b**, the hydride rearrangement must be *syn*-facial from the pseudoaxial position. Direct attack of Et_3SiH to the activated CO group of intermediate **A** (pathway b) would explain the formation of open-chain diols (±)-**14**.



Scheme 4. Mechanism of the TMSOTf/Et_3SiH-promoted reaction of (±)-**8** and (±)-**16** leading to cyclic regioisomers (±)-**7** and (±)-*cis*-lauthisan (**2**), respectively.

Considering these results and with the aim to shorten our previously reported synthesis of (–)-*cis*-**2** on the basis of the reductive cyclization of hydroxy ketone (*S*)-**6** (Scheme 1), we decided to synthesize this precursor, in a shorter way, from the chiral pool by following a retrosynthetic approach similar to that shown in Scheme 2 for *rac*-**2** and by using commercially available enantiopure (*S*)-1,2-epoxybutane (**18**) as the starting material. Thus, as shown in Scheme 5, ring opening of oxirane (*S*)-**18** with lithium acetylide–EDA gave homopropargylic alcohol (*S*)-**19** in 70% yield. 1-Nonen-3-one (**21**), needed to complete the carbon skeleton present in (–)-**2**, was obtained in 90% yield after oxidation of commercially available 1-nonen-3-ol (**20**) with Jones reagent, as described in the literature.[13] Rh-catalyzed conjugate addition of terminal alkyne (*S*)-**19** to enone **21** afforded enantiopure (*S*)-**22** in 94% yield, after chromatographic purification. Full hydrogenation of the triple bond in (*S*)-**22** in the presence of $Pd(OH)_2$ gave required hydroxy ketone (*S*)-**6** in 99% yield. Reductive cyclization of (*S*)-**6** under conditions similar to those shown in Scheme 3 [Et_3SiH (4 equiv.), TMSOTf (1.5 equiv.), CH_2Cl_2, 0 °C] afforded a mixture of (–)-*cis*-**2** and diastereoisomeric diols **15**, from which the former could be isolated in 45% yield. Thus, the shortest total synthesis of (–)-*cis*-**2** reported to date was accomplished in 4+1 steps in 29% yield overall starting from commercially available precursors.



Scheme 5. (4+1)-Step total synthesis of (–)-*cis*-lauthisan (**2**) from commercially available epoxide (*S*)-**18** and allylic alcohol **20**.

Conclusions

We have described two complementary ways to achieve the shortest total syntheses of (*rac*)-*cis*-lauthisan (**2**) in 4 steps and 24% yield overall from commercially available ethyl vinyl ketone and racemic 1,2-epoxyoctane and (–)-**2** in 4+1 steps and 29% yield overall from commercially available 1-nonen-3-ol and enantiopure (*S*)-1,2-epoxybutane. The heterocyclic system was formed from the stereoselective Lewis acid catalyzed reductive cyclization of saturated isomeric hydroxy ketone (*rac*)-**16** and (*S*)-**6**, respectively. The exchange of the position of the ethyl and hexyl substituents in these open-chain precursors did not affect the stereoselectivity of the reductive cyclization step. We observed that this process is not applicable to unsaturated hydroxy ketones such as **8**, as the formation of intermediate carbenium ions triggers undesired rearrangements, which decrease the efficiency of the process.

Supporting Information (see footnote on the first page of this article): Experimental procedures and copies of the NMR spectra.

Acknowledgments

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