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Medium-Sized Cyclic Ethers via Stevens [1,2]-Shift of Mixed Monothioacetal-Derived Sulfonium Ylides: Application to Formal Synthesis of (+)-Laurencin

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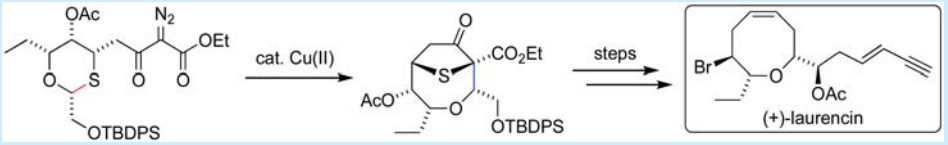
Supporting Information



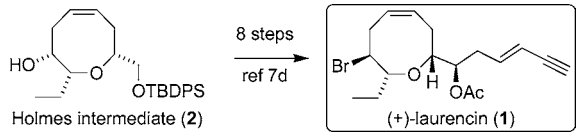
ABSTRACT: A novel approach to medium-sized cyclic ethers was devised using a Stevens [1,2]-shift of a sulfonium ylide derived from a readily accessible six-membered mixed-monothioacetal precursor. The concise and efficient transformation offers a surprising degree of chirality transfer with observed retention of stereochemical configuration on the anomeric migrating carbon and has been applied as the key step in an enantioselective formal synthesis of (+)-laurencin.

Medium-sized cyclic ether moieties occur frequently in marine natural products,[1,2a,b] some of which exhibit important biological activities.[2a−c] Medium-sized cyclic ethers are generally difficult to construct by standard cyclization methods.[3] The synthetic challenge is attributed to the inherent difficulties of the formation of medium-sized rings from acyclic precursors due to enthalpic and entropic factors, with the eight-membered rings at the nadir on the plot of reaction rate versus ring size for the example of lactone formation.[4] Because of the inherent challenges, tremendous synthetic effort has been devoted to the development of new methodologies where examples of these elegant approaches can be summarized into three categories: C−C bond formation, C−O bond formation, and rearrangement of an existing cyclic precursor.[5]

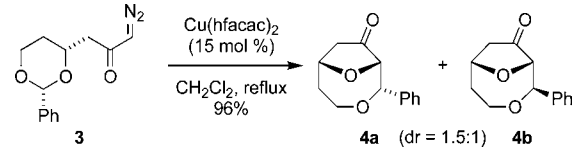
(+)-Laurencin (**1**) (Scheme 1), the first medium-sized ring ether isolated from *Laurencia* species, has attracted considerable attention in the synthetic community since its isolation in 1965.[6] Construction of the oxocene core in a stereoselective fashion is one of the main challenges and a subject of interest in the synthetic community. Laurencin has thus served as a testing ground for various methodologies toward medium-sized cyclic ethers. To date, 13 formal and total syntheses of this compound have been reported, using various strategic approaches.[7] Among them, the total synthesis by Holmes and co-workers[7d] stands as a seminal example, and two formal syntheses have been achieved[7k,l] via interception of advanced intermediates previously described by the Holmes team. Here we describe a convenient and stereoselective route to medium-sized cyclic ethers from simple monothioacetal precursors via Stevens [1,2]-shift, and its application to the formal synthesis of (+)-laurencin by intercepting a Holmes intermediate **2** (Scheme 1).[7d]

We have previously reported that ylides[8] derived from the readily accessible acetal **3** with pendent diazoketone moieties (Scheme 2) underwent an efficient Stevens [1,2]-shift to furnish the oxygen bridged cyclic ethers **4a** and **4b** in the presence of

Scheme 1. (+)-Laurencin and the Holmes Intermediate



Scheme 2. Previous Work on the Stevens [1,2]-Shift of Ylide Derived from Acetal



$Cu(hfacac)_2$,[9,10] but further elaboration to monocyclic medium-ring ethers was impeded by the difficulty in removing the bridging ether moiety. However, if an analogous transformation could be carried out via a sulfonium ylide derived from a six-membered mixed monothioacetal (1,3-oxathiane),[11] the resulting sulfur bridged oxacycle would be amenable to reductive desulfurization to leave a functionalized oxocane. 1,3-Oxathianes **5a**/**5b** were prepared as model substrates to evaluate this approach. When subjected to catalytic $Cu(hfacac)_2$ in toluene at 100 °C, the corresponding sulfur bridged cyclic ethers **6a**/**6b** were obtained in quantitative yields (Scheme 3). In notable contrast to the earlier acetal case, rearrangement products **6** were isolated as single diastereomers. (In contrast to diazoketoesters **5a**/**5b**, the corresponding simple diazoketones either failed to undergo [1,2]-shift or did so with low stereoselectivity.) Prior work

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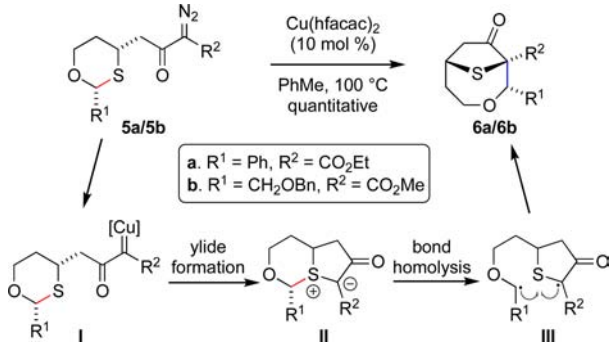
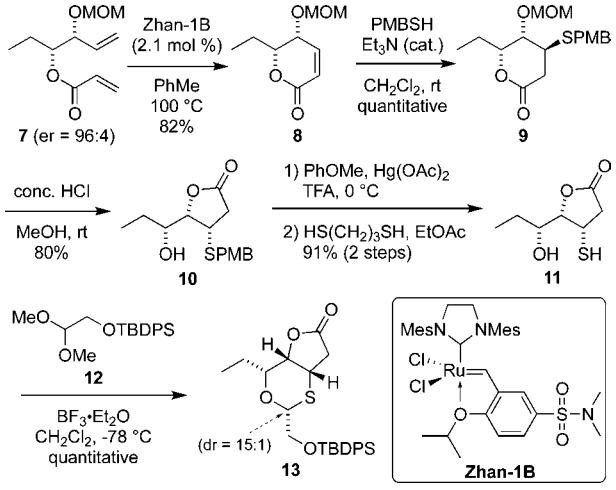
Scheme 3. Stevens [1,2]-Shift of Ylide Derived from Mixed Monothioacetal



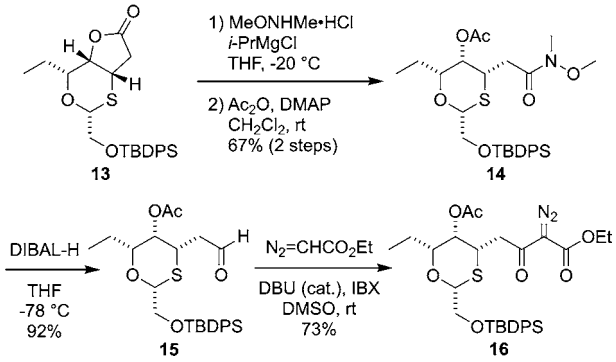
suggests that the major pathway in [1,2]-shifts should occur with stereochemical retention (i.e., to give **6a**/**6b** rather than the epimeric products).[12] However, we could not obtain these products as crystalline solids, preventing unambiguous structural assignment by X-ray diffraction analysis, and TROESY experiments furnished inconsistent correlations. Nonetheless, we have tentatively assigned these products as shown, in analogy to the more substituted example described below. This sequence is presumed to occur via formation of metallocarbene intermediate **I** followed by ring closure via attack of the nucleophilic sulfur atom on the electrophilic carbenoid center to afford sulfonium ylide **II**. The Stevens [1,2]-shift is believed to be a stepwise process,[13] and a homolytic mechanism proceeding through biradical intermediates such as **III** has been implicated in [1,2]-shifts involving ammonium[14a] and oxonium[14b] ylides. However, rearrangement via heterolysis cannot be ruled out in the case of acetal-derived ylides and has been invoked in some previous examples.[11a,d,f] Regardless of mechanism, the high degree of chirality transfer during migration of the anomeric carbon with either a strongly stabilizing phenyl substituent (**5a**) or a weakly stabilizing benzyloxymethyl substituent (**5b**) inspired confidence that this strategy could be adapted to the synthesis of more complex targets such as laurencin. Furthermore, such an application would permit correlation of advanced intermediates with known compounds and thus provide definitive information regarding the stereochemical outcome of the [1,2]-shift.

The more highly functionalized 1,3-oxathiane substrate required for application to laurencin required a multistep synthetic route to install the necessary substituents and stereocenters (Scheme 4). Starting with acrylate ester **7** (prepared from the known homoallylic alcohol, available in 96:4 er via asymmetric allylboration/oxidation),[15] ring-closing metathesis using the Zhan-1B catalyst[16] afforded dihydropyranone **8** in good yield over relatively short reaction times and low catalyst loadings as compared with other conditions (see Supporting Information for details). Subsequent Michael addition of 4-methoxybenzyl mercaptan occurred with high facial selectivity and furnished adduct **9** in quantitative yield as a single diastereomer with the correct relative configuration. Selective hydrolysis of the MOM ether resulted in isomerization to γ-lactone **10**, and removal of the PMB group with $Hg(OAc)_2$[17] in the presence of anisole afforded mercaptoalcohol **11**. At this point, transacetalization of dimethyl acetal **12** with **11** in the presence of $BF_3{\cdot}Et_2O$ provided 1,3-oxathiane **13** as a mixture of separable anomers.[18] Assignment of the relative configurations of the anomers of **13** was accomplished via analysis of their TROESY correlations (see Supporting Information).

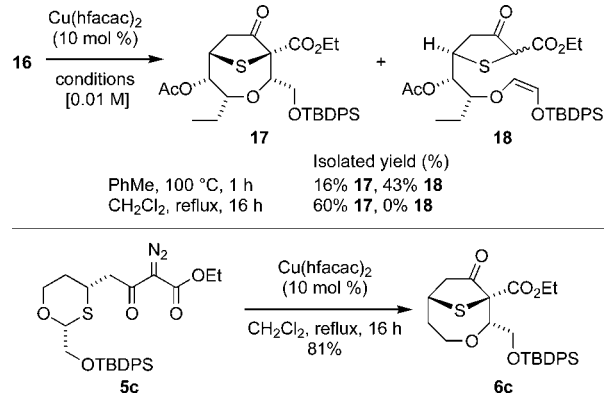
Scheme 4. Synthesis of Bicyclic 1,3-Oxathiane



Scheme 5. Synthesis of the Precursor for the Stevens [1,2]-Shift



Scheme 6. Key Step and Related Model Study



With the desired 1,3-oxathiane ring in hand, it was now necessary to install the diazoketoester side chain (Scheme 5). The lactone ring could be opened with *N,O*-dimethylhydroxylamine to afford the corresponding Weinreb amide,[19] and the resulting secondary alcohol was then protected as an acetate to give **14**. Subsequent reduction of the Weinreb amide was accomplished using DIBAL-H,[20] and the resulting aldehyde **15** was subjected to ethyl diazoacetate in the presence of DBU and IBX to furnish the key diazoketoester substrate **16**.[21]

The key sulfonium ylide rearrangement was examined next, under the standard conditions employed with **5a** and **5b** (Scheme 6). Upon heating in toluene at 100 °C in the presence of

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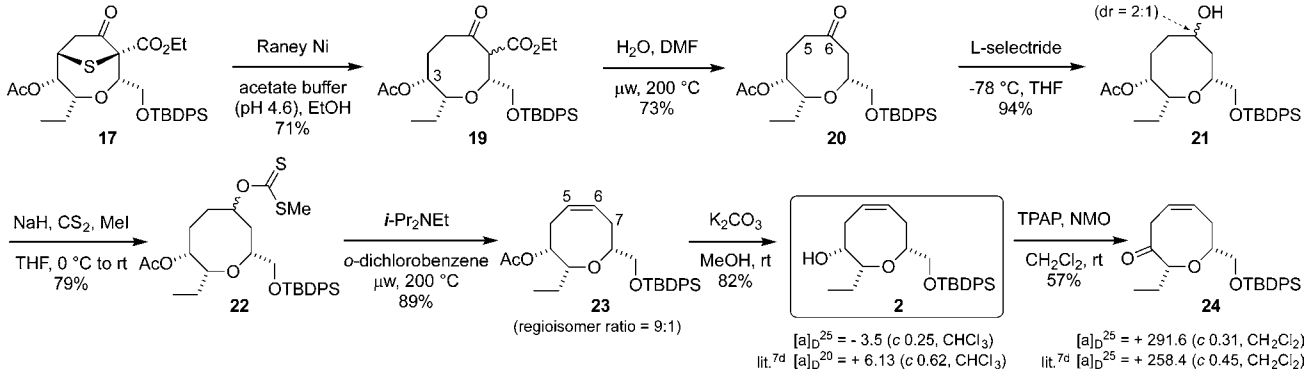
Scheme 7. Completion of the Formal Synthesis of (+)-Laurencin[a]



[a]TPAP = Tetrapropylammonium perruthenate, NMO = *N*-Methylmorpholine *N*-oxide.

$Cu(hfacac)_2$, **16** provided the desired bicyclic oxocane **17** in only minor amounts (16%), with monocyclic olefin **18** formed as the predominant product (43%). This material is presumed to result from α',β-elimination of the intermediate sulfonium ylide.[22] Unfortunately, isolation of **18** as a pure product was complicated by its instability to silica gel chromatography, and this undoubtedly contributed to the diminished material balance. In an effort to find conditions that favored formation of **17**, we surveyed alternative conditions using the simplified model compound **5c** and found that formation of the desired [1,2]-shift product **6c** could be achieved at relatively low temperatures (CH_2Cl_2 at reflux), albeit at the cost of longer reaction times. When **16** was subjected to these conditions, the desired oxocane **17** was obtained in an acceptable yield (60%), uncontaminated with side-product **18**.[23] Most importantly, as in the model series, **17** was isolated as a single diastereomer. However, in this case TROESY analysis provided unambiguous evidence for migration of the anomeric center with retention, an assignment that was confirmed through correlation to **2** and **24** (vide infra). This result strongly suggests that the stereoselective rearrangement of model substrates **5a–c** also occurred with retention, as there is no plausible reason why the presence of fewer substituents on the oxathiane ring would result in a complete stereochemical reversal to migration with inversion.

The sulfur bridge could be removed cleanly via Raney nickel reduction, in the presence of acetate buffer (pH = 4.6) to suppress undesired elimination of the C-3 acetate group (Scheme 7). The resulting oxocane **19** was subjected to decarboxylation via microwave heating in aqueous DMF to afford ketone **20**,[24] which was then reduced with L-selectride to form a 2:1 epimeric mixture of alcohols **21**. Conversion to xanthate **22** set the stage for Chugaev elimination,[25] which was carried out by microwave heating (200 °C) in *o*-dichlorobenzene, furnishing two elimination products as a 9:1 mixture of desired C5–C6 olefin **23** and the C6–C7 regioisomer, which were readily separable by chromatography.

To complete a formal synthesis of laurencin, **23** was subjected to acetate cleavage to provide **2**, previously reported by Holmes and co-workers.[7d] While spectral data were in complete agreement, the specific rotation had the opposite sign to that reported in the original work. In both cases the absolute value of the rotation was small, allowing for significant error. Notably, another fully characterized advanced intermediate of laurencin, ketone **24** had a much larger specific rotation. Alcohol **2** could be oxidized to **24** using TPAP/NMO, and the spectral data were once again in full agreement. Moreover, the specific rotation was also in good agreement with the published value.

We have described a novel, stereoselective route to functionalized medium-sized cyclic ethers via Stevens [1,2]-shift of sulfonium ylides derived from mixed monothioacetals (1,3-oxathianes). The substituted 1,3-oxathianes can be prepared via a short sequence, and the stereochemical information at the anomeric center is retained during migration in the key rearrangement step. As an application of this methodology, a concise formal synthesis of laurencin has been completed. Further applications of this strategy and stereochemical outcome for the model study are under current investigation and will be described in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03719.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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