

Stereoselective Synthesis of Eight-Membered Cyclic Ethers by Tandem Nicholas Reaction/Ring-Closing Metathesis: A Short Synthesis of (+)-*cis*-Lauthisan

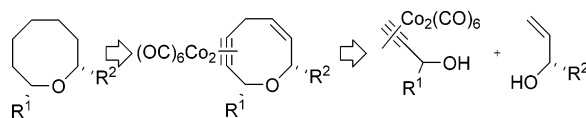
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ABSTRACT

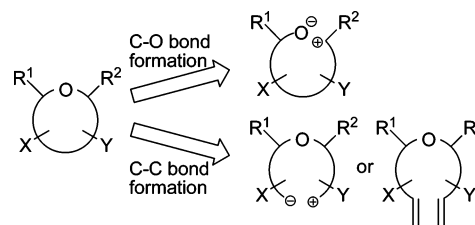


Cis-2,8-disubstituted oxocanes and the parent unsaturated precursors were prepared from the corresponding $\text{Co}_2(\text{CO})_6$ -cycloalkynic ethers. Key steps in such synthesis were the ether linkage formation by intermolecular Nicholas reaction, RCM of the suitable acyclic dienyl ether and montmorillonite K-10 induced isomerization of the complexed cycloalkyne. A short synthesis of (+)-*cis*-lauthisan taking advantage of the developed methodology is described.

Polyfunctionalized medium sized cyclic ethers are the structural milestone of a wide range of biologically active natural products, including ladder marine toxins, lauroxanes, antibiotic, etc.¹ Based on the construction of the ring two major strategies to access such oxacycles have been developed: via a final C–O formation using a nucleophilic oxygen or, alternatively, by C–C formation over a preconstructed linear ether (Scheme 1).²

Within the last approach, the combination of the synthesis of the suitable unsaturated branched ether and RCM provided

Scheme 1. Major Approaches Used in the Synthesis of Polyfunctionalized Cyclic Ethers



a powerful methodology to the synthesis of isolated and fused medium sized cyclic ethers.^{3,4} Two critical issues in such strategy are the stereoselective access to the ether linkage between two stereogenic secondary carbons and the unfavorable entropy factors of eight-membered rings.⁴

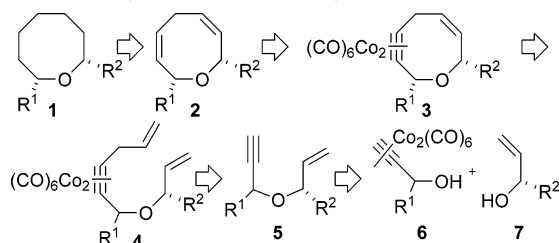
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In this paper, we report on a new approach to the stereocontrolled synthesis of 2,8-dialkyl oxocanes **1** through the parent 5,8-dihydro-2*H*-oxocine **2**, taking advantage of the chemical and structural properties induced by the formation of Co₂(CO)₆ complexes in propargylic systems (Scheme 2).⁵ We envisioned the synthesis of these hetero-

Scheme 2. Retrosynthetic Analysis for the Stereoselective Synthesis of 2,8-Dialkyl Oxocanes



cycles through the Co₂(CO)₆-cycloalkynic ether **3** that could be synthesized from the unsaturated alkyne-cobalt **4** by means of a RCM.⁶ This precursor could be unveiled upon allylation of alkyne **5**. Finally, this propargylic ether, having two stereogenic centers close to the oxygen, was disassembled to the complexed propargylic alcohols **6** and the secondary allylic alcohol **7** through an intermolecular Nicholas reaction.⁷ The power of the developed methodology is exemplified in the synthesis of (+)-*cis*-lauthisan (**1**, R¹ = C₂H₅, R² = C₆H₁₃-*n*).^{8,9}

The synthesis of the cobalt-complexed ether **4** (R¹ = C₂H₅, R² = C₆H₁₃-*n*) was initiated applying our previously reported

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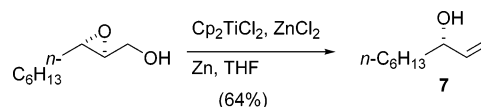
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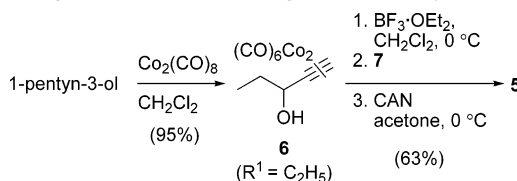
methodology based on the trapping of propargylic cations using alcohols as nucleophiles.⁷ Initial work using (*S*)-non-1-en-3-ol¹⁰ (**7**, R² = C₆H₁₃-*n*) (Scheme 3)¹¹ as the incoming

Scheme 3. Preparation of (*S*)-Non-1-en-3-ol from (2*S*,3*S*)-2,3-Epoxy-1-nonanol



alcohol over the cobalt complex of racemic oct-7-en-4-yn-3-ol¹² was fruitless yielding a complex mixture, presumably by internal participation of the double bond of the enyne substrate. Trying to overcome this difficulty, we turned our attention on the cobalt complex of commercially available racemic 1-pentyn-3-ol (**6**, R¹ = C₂H₅) relying the allylation process for a latter step in the synthesis. However, when applying the reported conditions⁷ yield and conversion to the desired linear ether **5** were again scarce. Trying to improve the conditions, we thoroughly examined many experimental variables such as temperature, rate and order of addition of reagents, amount of Lewis acid and concentration. As a result of this study, we found that the best conditions needed relative high concentration (0.2 M), 2 equiv of Lewis acid and slow addition of the secondary alcohol (Scheme 4).¹² Although at this point of the synthesis

Scheme 4. Direct Preparation of Linear Ethers Having the Linkage between Two Stereogenic Secondary Carbons



it was very difficult to ensure the stereoselection of the newly created stereocenter in compound **5**, more elaborated fragments in the synthesis (vide infra) showed us a ratio of approximately 1:1.7 of both diastereoisomers in favor of the undesired stereoisomer.

With the ether **5** in hand, the preparation of the necessary diene for the RCM step requires only a simple alkylation. To this end, copper-catalyzed homologation of **5** with allyl bromide provided the dienyl derivative **8** in excellent yield. To overcome the unfavorable entropic and enthalpic factors involved in the formation of the eight membered ring (the final ring has an endocyclic triple bond) we decided to take advantage of the bending in the acetylenic system when

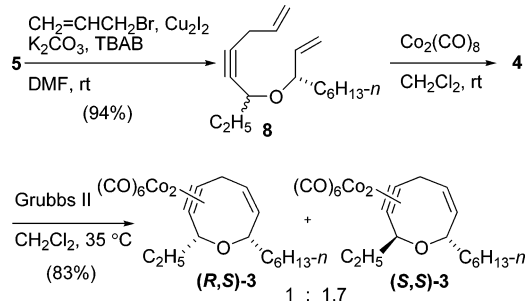
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(12) See the Supporting Information for experimental details.

forming the cobalt complex.^{6,13} In addition, the cobalt complex should avoid the undesirable participation of the triple bond in the metathesis process.¹⁴ Thus, when **8** was submitted to $\text{Co}_2(\text{CO})_8$ the cobalt complex **4** was obtained in quantitative yield (Scheme 5). Any attempt to perform

Scheme 5. Preparation of $\text{Co}_2(\text{CO})_6$ -Cycloalkynic Ethers by RCM

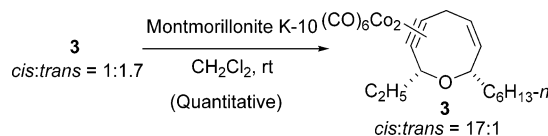


cyclization using first-generation Grubbs' catalyst led to poor conversion and yields of cyclic ethers (ca. 18%). Satisfactorily, when second-generation Grubbs' catalyst was used under diluted conditions (0.001 M) an 83% yield of **3** was obtained.¹⁵ Interestingly, at this point of the synthesis both diastereoisomers were separated very easily by silica gel column chromatography. NOE studies of both isomers permitted the assignment of the relative stereochemistry.

As aforementioned, separation of both diastereoisomers was very simple at this step. However, considering that the major isomer isolated was *trans*-**3**, we pondered the possibility of performing an isomerization to the *cis*-isomer considering that such stereoisomers are usually thermodynamically more stable.^{7b} Disappointingly, treatment of *cis*/*trans* mixture of **3** under various acidic conditions (including $\text{BF}_3 \cdot \text{OEt}_2$, CF_3COOH , and TsOH) produced either decomposition or complete recovery of the starting mixture.¹⁶ Fortunately, our recently reported conditions relative to the use of montmorillonite K-10 as acid in the Nicholas reaction

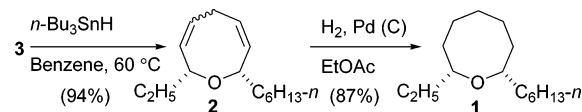
proved to be highly efficient to perform the desired conversion.¹⁷ The original mixture evolved quantitatively to a nice *cis*/*trans* ratio of 17:1 (Scheme 6).

Scheme 6. Isomerization of 2,8-Dialkyl $\text{Co}_2(\text{CO})_6$ -Cycloalkynic Ethers by Montmorillonite K-10



The last steps required to complete the synthesis of the target lauthisan were the cleavage of the cobalt complex and reduction to the final oxacycle (Scheme 7). The reductive

Scheme 7. Reductive Cleavage of $\text{Co}_2(\text{CO})_6$ -Cycloalkynic Ethers and Hydrogenation



decomplexation reported by Isobe et al. produced very efficiently the cyclodiene **2** ($\text{R}^1 = \text{C}_2\text{H}_5$, $\text{R}^2 = \text{C}_6\text{H}_{13-n}$), although as a inseparable mixture of stereoisomers in the newly created double bond.¹⁸ However, the hydrogenation under standard conditions of **2** provided cleanly (+)-*cis*-lauthisan **1**, $[\alpha]^{25}_{\text{D}} = +4.1$ (c 0.9, CHCl_3).^{9j}

In summary, we have described a new and efficient approach to the stereocontrolled synthesis of saturated eight membered 2,8-dialkyl cyclic ethers. Our methodology involved a new way to prepare linear ethers having two secondary carbons next to the oxygen. In addition to the ring formation using RCM, a key step is also a new isomerization of $\text{Co}_2(\text{CO})_6$ -cycloalkyne ether complexes catalyzed by montmorillonite K-10. All these procedures were exemplified in the synthesis of (+)-*cis*-lauthisan.

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Supporting Information Available: Experimental details, spectroscopic characterization, and ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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