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Synthetic studies of spiroketal enol ethers: an unexpected oxidation by Martin's sulfurane

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Abstract—In an attempt to synthesize a spiroketal enol ether natural product, we found that treatment of alcohol **5** with Martin's sulfurane did not give the anticipated olefin, but instead afforded ketone **15** through an unprecedented oxidation.

Polyacetylene containing spiroketal enol ethers such as **1**–**3** (Fig. 1) comprise a large class of natural products derived from plants in the tribe Anthemideae.[1] All members of this class of compounds contain a [4,4] or [4,5] spiroketal core, with either an enediyne or enethiophene sidechain. The degree of unsaturation and oxygenation of both rings is variable among compounds, and compounds with both *E* and *Z* olefins have been isolated from the same species of plant. Tonghaosu (**1**) exhibits antifeedant,[2] antiphlogistic, and spasmolitic activities,[3] AL-1 (**2**), has been shown to inhibit (TPA)-induced tumor promotion in vitro and in vivo,[4] and compounds **3** are cytotoxic against leukemia cells.[5]

Despite their interesting structures and biological activities, there have been few syntheses of compounds in this class.[6–8] We chose to focus our attention on the unnamed natural product **4** (Scheme 1), which was isolated by Matsuo et al. from *Chrysanthemum boreale* in 1974.[9]

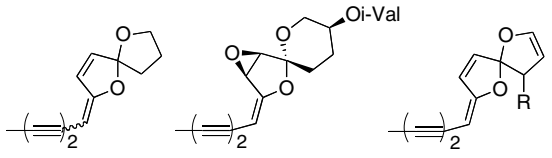

Figure 1. Spiroketal enol ether containing natural products.

Based on coupling constant data, the alkene was reported to have the *Z*-configuration and the relative configuration of the acetates was reported as cis. However, the configuration of the spiro center and the absolute configuration were not determined.

In examining the structure of this natural product, we found that the five membered ring of the spiroketal contains much of the functionality and stereochemistry present in the sugar D-ribose, which we planned to use as the starting material. The retrosynthesis is shown in Scheme 1. Compound **4** will be derived from **5** by dehydration, deprotection and acetylation. Compound **5** can be prepared from **6** by oxidation and acetylide addition of 2,4-pentadiynyl anion. Compound **6** will arise from spiroketalization of **7**, which can be prepared from lactone **8** and the acetylide derived from **9**. Lactone **8**, in turn, can be easily prepared from D-ribose.

Our synthesis of **4** began with the known lactone **8**, which is prepared in three steps from D-ribose,[10] and the acetylide derived from alkyne **9** (Scheme 2).[11] We found that success of the acetylide addition required that the reaction be performed with an excess of lactone and the temperature must not be allowed to warm above −78 °C. Warmer temperatures or an excess of acetylide resulted in considerable amounts of by-products, but by using our optimized conditions, the desired lactol was obtained as a 5:1 mixture of diastereomers, which was inseparable from **8**. Hydrogenation of the crude product mixture afforded **10**, which was now easily separated from **8** by silica gel chromatography. Deprotection of both silyl ethers afforded triol **7**, which readily underwent acid catalyzed spiroketalization to give a single

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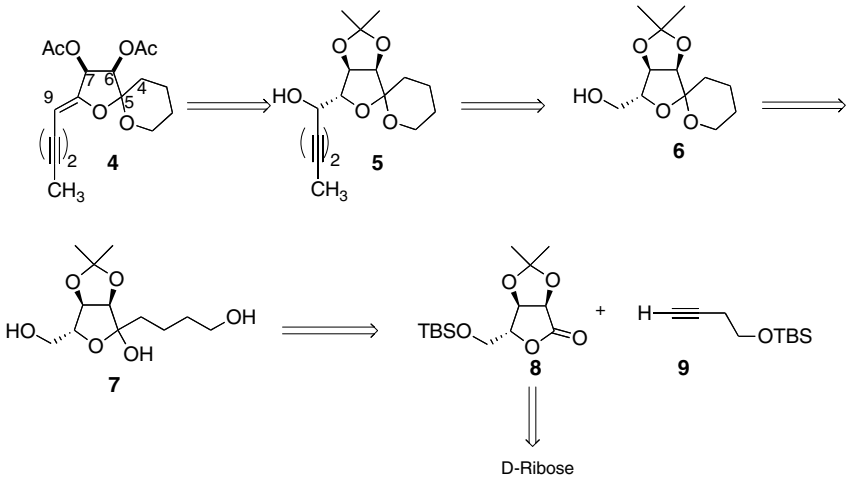
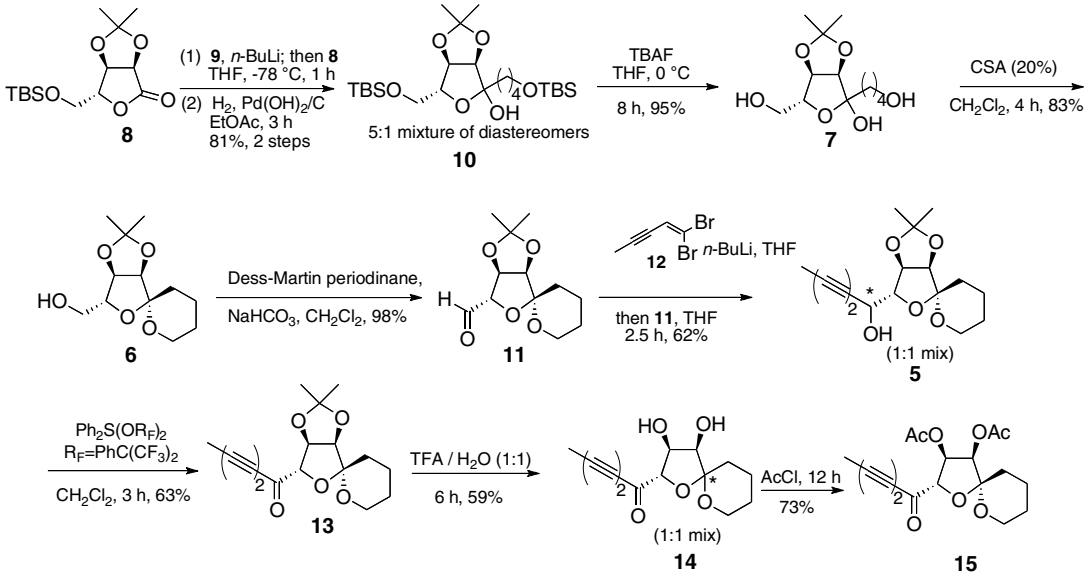


Scheme 1. Proposed retrosynthesis of **4**.



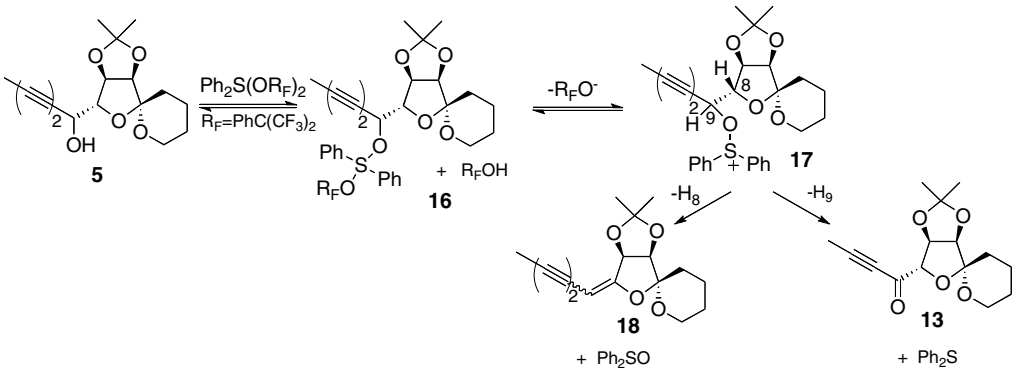
Scheme 2. Attempted synthesis of **4**.

diastereomer of spiroketal **6** whose configuration was verified by NOE studies. Alcohol **6** was then oxidized to aldehyde **11** in preparation for installation of the diyne side chain.

The most obvious method to install the side chain was to add the anion of pentadiyne. However, pentadiyne is not commercially available, and its synthesis is technically quite difficult, due in part to its volatility.[12] Therefore, we thought the pentadiynyl anion could be generated in situ from dibromide **12** (Scheme 2), as a similar approach was used by Chen et al. for their synthesis of tonghaosu analogs.[13] In fact, treatment of **12** with 2 equiv of *n*-BuLi followed by **11** afforded **5** as a 1:1 mixture of diastereomers.

With propargylic alcohol **5** in hand, we proceeded to investigate methods for installation of the exocyclic enol ether. Simple acid mediated dehydration with *p*-TsOH, dicholoroacetic acid, or TFA resulted in no elimination. Formation of the mesylate and in situ elimination with pyridine likewise did not result in product, while treatment of the purified mesylate with refluxing pyridine or DBU resulted in a complex mixture of products. We then attempted to utilize conditions developed by Park and Danishefsky for a similar system, and attempted to convert **5** into the corresponding bromide with Ph_3PBr_2, which would undergo elimination with pyridine.[14] However, the bromide was formed only as a complex mixture with other products. Likewise, treatment of **5** with Burgess reagent also resulted in a complex mixture of products. Finally, we found that Martin's sulfurane gave a product **13** whose spectral properties were consistent with the formation of a *Z*-exocyclic enol ether. Therefore, we continued through the synthesis.

Treatment of **13** with 50% TFA not only removed the acetonide protecting group but also epimerized the spiroketal center. When **14** was subjected to standard basic



Scheme 3. Proposed mechanism of oxidation by Martin's sulfurane.

acetylation conditions (Et_3N or pyr, Ac_2O) complex mixtures of products were formed. However, treatment of **14** with neat AcCl in a tightly capped flask afforded **15** as a single spiroketal diastereomer, whose structure was confirmed by NOE studies. Again, the ^1H and ^{13}C NMR spectra as well as the IR spectrum of **15** were not only inconsistent with a *Z*-exocyclic olefin, but also did not match the natural product **4**. Surprisingly, mass spectral analysis of **13**–**15** revealed that the molecular weight of these compounds was 16 mass units higher than expected, consistent with the presence of a ketone rather than an olefin. It is not unusual for enol ethers such as **4** and ketones such as **15** to be confused for one another. Chen et al. recently revised the structure of a natural product which was originally assigned as a ketone to an enol ether similar to tonghaosu.[13] To verify that **13** was the result of oxidation rather than elimination, it was subjected to reduction with $NaBH_4$, which did indeed reform **5** as a 1:1 mixture of alcohols.

To our knowledge, this is the first example of oxidation of a secondary alcohol by Martin's sulfurane. Arhart and Martin originally proposed the mechanism for dehydration as shown in Scheme 3.[15] Rapid exchange of one of the alkoxy ligands on the sulfurane is followed by ionization to give alkoxysulfonium ion **17**, which typically undergoes either E1 or E2 elimination, depending on the nature of the alcohol. However, intermediate **17** is similar to the alkoxysulfonium ion formed during dimethyl sulfoxide based oxidations such as the Swern oxidation.[16] In the case of **17**, deprotonation of H8 would result in the desired enol ether, as described by Martin, while deprotonation of H9 would result in oxidation (though Swern oxidations are believed to be the result of intramolecular deprotonation, in this case the deprotonation is most likely the result of intermolecular deprotonation by residual R_FO^-). Because propargylic H9 is much more acidic than H8, it is not surprising that the reaction resulted in oxidation rather than elimination. In support of this mechanism, we have observed the formation of Ph_2S by GC/MS during the oxidation of **5**.

In summary, we have developed a short and simple synthesis of alcohol **5**, which, when treated with Martin's sulfurane, underwent an unprecedented oxidation reaction in lieu of the expected dehydration. We are currently investigating other methods to successfully convert alcohol **5** into the natural product **4**. In addition, we are examining the oxidation by Martin's sulfurane in more detail.

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Supplementary data

Experimental procedures for compounds **5**, **6**, **7**, **10**, **11**, **13**, **14**, **15**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2007.01.167.

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