An Iterative Approach to Fused Ether Ring Systems

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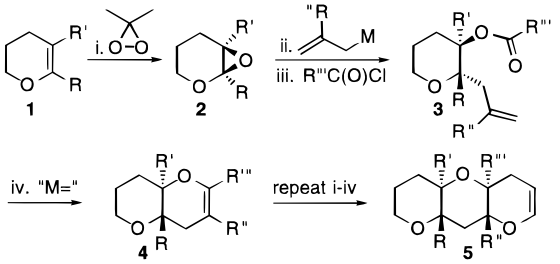
Fused heterocyclic ring systems are the key skeletal arrangement in a vast array of bioactive natural products. The family of compounds which best illustrate this structural feature are the marine "ladder" toxins whose skeletons include cis- and trans-fused six−nine-membered oxygenated heterocycles. Although the members of this family are most commonly associated with neurotoxicity and "red tide" catastrophes,[1] some have shown potent antimicrobial activity and lack neurotoxicity (cf. gambieric acid).[2,3] The very interesting bioactivity of the members of this family when coupled with their molecular complexity would seem to warrant an efficient approach to their synthesis and/or to the synthesis of analogues if they are to be fully evaluated.[4] With this in mind, the regularity in these structures has influenced many, including us, to believe that an iterative strategy to the fused ether skeleton would be ideal. While independent investigations from the laboratories of Mori,[5] Clark,[6,7] McDonald,[8] and Martin[9] approach this ideal, to date there exist no general iterative strategies to synthesize six−nine-membered cyclic ethers.

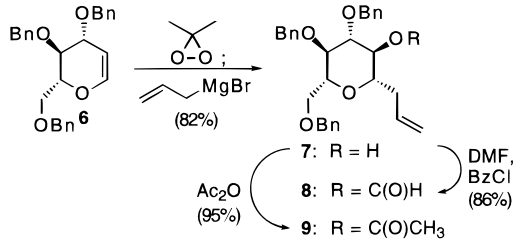
At the outset, we envisioned a novel three-flask protocol toward fused ether ring systems. This strategy centered around stereoselective cyclic enol ether epoxidations and subsequent epoxide opening reactions with carbon nucleophiles (**1** → **3**, Scheme 1).[10−13] While the epoxidation of C-3 substituted glycals appeared to be fairly well understood,[10,14,15] the lack of information regarding the stereoselective epoxidation of C-3 unsubstituted glycals as well as more complex ring systems (bi- and tricyclic enol ethers, medium sized rings) was a concern. Despite this, we decided to pursue this approach because of the considerable flexibility provided by the existence of a large number of epoxidation protocols (vide infra). After C−C bond formation, annulation would result in a new cyclic enol ether and thus complete the iterative pathway (cf. **3** → **4**, Scheme 1). Among the many possible methods that had the potential

Scheme 1



to meet our cyclization needs, carbonyl−olefin and olefin−olefin metathesis chemistry were particularly attractive as they were capable of generating cyclic enol ethers from pendant carbonyls and olefins.[16,17] Additionally, these methods of ring formation have been used in the synthesis of fused ethers.[6,7,18−21] Described herein are our preliminary experiments in this area which utilize the paradigm illustrated in Scheme 1.

The epoxidation of tribenzyl-D-glucal according to Danishefsky's protocol[15] followed by the addition of allylmagnesium chloride gives bis-homoallyl alcohol **7** (eq 1). We have utilized a single-flask conversion of **6** → **7**; concentration of a CH_2Cl_2 solution of the intermediate epoxide, dissolution of the resulting residue in THF, and coupling with allylmagnesium chloride at 0 °C provides **7**. Thus far, the **6** → **7** transformation has proceeded in an overall yield of 82% and can be accomplished in a matter of hours. The addition of anions to the intermediate epoxide appears to be general;[10−13] propargylmagnesium chloride and vinylmagnesium bromide also add in respectable yields. Subsequent conversion of the resulting alcohol to the corresponding acetate or formate esters using acetic anhydride or benzoyl chloride/DMF[22] respectively gives **8** and **9** in high yield.



(1)

We have invested considerable time examining the **8** → **12** and **9** → **13** transformations; our best results to date are illustrated (eq 2). Subjecting acetate **9** or formate **8** to Takai's conditions[23] led to 65% and 28% yields of enol ethers

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(3) Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 7, 5448−5453.
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(17) Despite the substantial work that has been accomplished in this area, there exists considerable room for improvement as the current state of the art involves the use of highly sensitive organometallic reagents, often in stoichiometric quantities. For a discussion of efficiency and organic synthesis, see: Trost, B. M. *Science* **1991**, *254*, 1471−1477.
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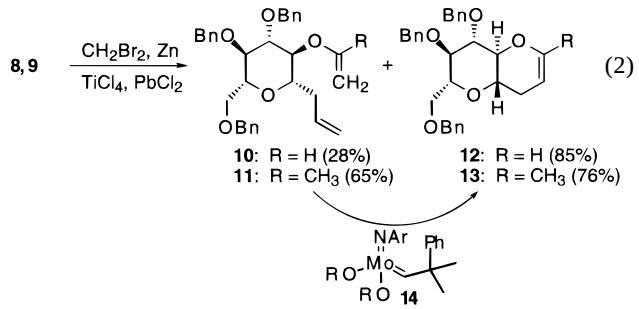
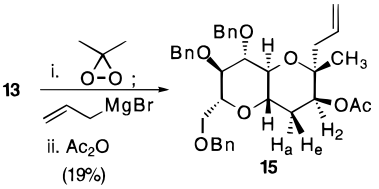
11 and **10**, respectively.[24,25] Alternatively, enol ether **10** can be generated in 58% yield directly from alcohol **7** through the use of ethyl vinyl ether and $Hg(OAc)_2$. The success of the Takai procedure appears to be highly dependent upon the amount of reagent present as four equiv of $TiCl_4$ results in the reisolation of starting material while the addition of a fifth equivalent results in the yields indicated.[26] As was observed by Nicolaou utilizing the Tebbe and Petasis reagents,[20,21] we have also isolated cyclic enol ethers **12** and **13**, albeit in low yield. Although we are currently attempting to optimize this potentially important cyclization reaction,[27] a more efficient approach to **12** and **13** in our hands uses Grubbs' two-step protocol and Schrock's molybdenum alkylidene **14**.[19] Exposure of enol ethers **10** and **11** to **14** (15 mol %) results in the isolation of cyclic ethers **12** and **13** in 85% and 76% yields, respectively. These results demonstrate that an iterative approach to fused ethers which employs cyclic enol ether epoxidations is possible. As these experiments are preliminary, none of the reactions have been optimized; we are confident that some of the moderate yields that we have observed can be improved as would be required for any truly successful iterative strategy.



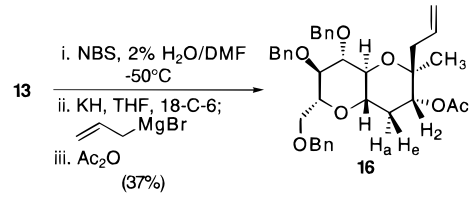
(2)

Bicyclic enol ethers **12** and **13** lacking substitution at the carbon adjacent to the enol ether have been exposed to the pivotal epoxidation/epoxide opening sequence. The same conditions utilized for the **6** → **9** transformation (dimethyldioxirane; allylmagnesium chloride; acetic anhydride) resulted in the formation of acetoxy olefin **15** in 19% overall yield (eq 3). Unfortunately, **15** appeared to be the undesired isomer on the basis of the H_2, $H_{a,e}$ coupling constant of 2.8 Hz.[28]



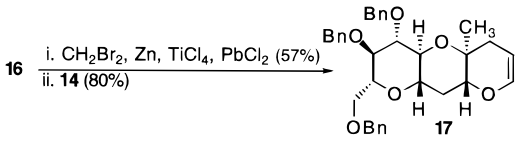
(3)

With the failure of dimethyldioxirane to deliver the desired stereoisomer, we turned to halohydrins as epoxide precursors as, in theory, they would allow us to synthesize the diastereomeric epoxide. Much to our delight, a minor modification of Spilling's epoxidation conditions[29] resulted in the desired vinyl acetate **16** as a 6:1 mixture of diastereomers after allylmagnesium chloride addition to the intermediate epoxide followed by acetylation (eq 4). The relative stereochemistry at the newly formed centers in **16** was determined from the H_2, $C-H_a$ coupling value of 11.8 Hz along with the expected NOESY cross-peaks. These results successfully demonstrate the flexibility of our approach to these systems. We have been able to generate either epoxide isomer by simply altering the oxidation protocol.



(4)

Utilizing the conditions which were successful in the generation of bicycles **12** and **13**, acetoxyolefin **16** was transformed into tricycle **17** in 47% overall yield (eq 5). Interestingly, as in the **8**, **9** → **12**, **13** transformations, the Takai protocol resulted in the formation of the desired enol ether along with a small amount of metathesis product **17**.



(5)

To conclude, we have demonstrated that enol ether epoxidations, when coupled with C−C bond formation and ring-closing metathesis, can provide fused pyran ring systems. Current studies in this area are concentrating on the optimization of this sequence, the incorporation of medium sized rings, and the application of this strategy to the synthesis of bioactive fused cyclic ethers.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7**−**13** and **15**−**17** (33 pages).

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(24) Exposure of acetate **9** to the Tebbe or Petasis reagents has led only to recovery of starting material or decomposition upon more vigorous reaction conditions (110 °C).

(25) As has been discussed,[23] catalytic quantities of $PbCl_2$ have a dramatic influence on these reactions as the absence of $PbCl_2$ resulted in only 15% of **11**.

(26) We believe that this is due to coordination of the four oxygens about the pyran ring with Ti. Addition of more than 5 equiv of reagent resulted in the isolation of significant quantities of alcohol **7** after aqueous workup.

(27) Thus far, we have been able to isolate **13** in 15% yield by extending the time of the reaction, completely decomposing enol ether **11** in the process. The major component from this preliminary experiment appears to be dimeric.

(28) We have tentatively identified the only other recognizable product from this reaction as the exocyclic enol ether from deprotonation and epoxide opening. Thus far, we have been unable to determine the relative stereochemistry at the carbon bearing the hydroxyl group in this compound.

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