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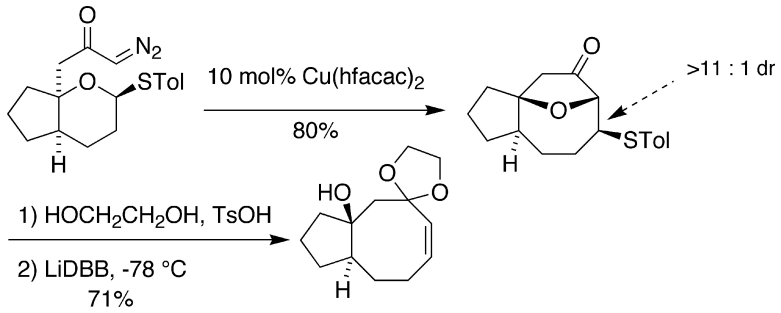

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Cyclooctanoid Ring Systems from Mixed Acetals via Heteroatom-Assisted [1,2]-Shift of Oxonium Ylides

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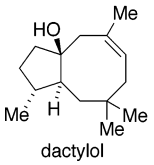
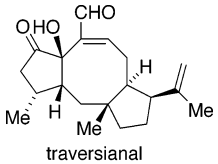
Stereocontrolled synthesis of medium-sized carbocycles is a major challenge in synthetic organic chemistry. Several natural products (e.g., dactylol or traversianal) contain fused bicyclic ring systems involving a medium-sized ring and bearing a bridgehead hydroxyl group. A number of interesting methods have been described for the construction of these structural motifs.[1] One attractive strategy has been the use of a preexisting carbocyclic or heterocyclic ring as a scaffold to form an intermediate bridged bicyclic compound. Fragmentation of the bridge would then reveal a medium-ring skeleton and install a bridgehead hydroxyl group.[2−4] However, attempted cleavage of bridging ethers[3] or their carbon analogues[4] can lead to complications.



dactylol



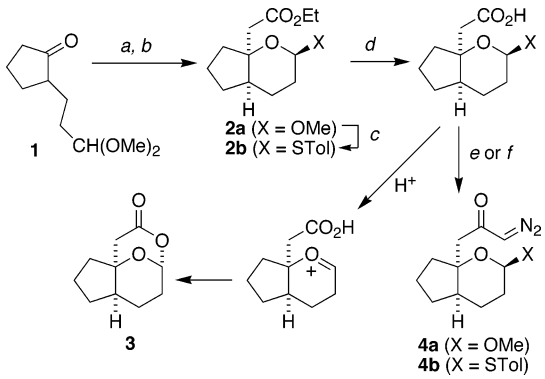
traversianal

We have reported a strategy based on Stevens [1,2]-shift of fused bicyclic oxonium ylides that furnishes medium-ring ethers or carbocycles with bridging ethers.[5] Those examples typically involved the migration of aryl-substituted carbons, leaving relatively few handles in the products for further synthetic manipulation. We now report the highly efficient stereoselective synthesis of functionalized fused 5−8 bicyclic ring systems using a novel *sulfur- or oxygen-directed Stevens rearrangement* of oxonium ylides and, in the former case, the high-yielding, sulfur-mediated cleavage of the resulting bridging ether.

With the eventual goal of applying this strategy to the synthesis of dactylol, we examined a model system lacking the four methyl groups of the natural product. Preparation of the required diazoketone began with the Reformatsky addition of ethyl bromoacetate to the known 2-[3,3-(dimethoxy)propyl]cyclopentanone **1**,[6] followed by conversion to cyclic acetal **2a** with $BF_3{\cdot}OEt_2$. Exchange of the methoxy group for STol to produce **2b** ($BF_3{\cdot}OEt_2$, thiocresol) required careful control of the reaction conditions to avoid formation of cyclic enol−ether and dithioacetal side products. Saponification to the free acid proceeded in high yield, but conversion into the diazoketone was problematic. Acidic byproducts formed during acid chloride formation caused expulsion of the anomeric group and carboxyl trapping of the resulting oxocarbenium ion to provide **3**, even under rigorously dry conditions. In the case of **2b**, this pathway could be minimized at lower temperatures, with immediate transfer by cannula into diazomethane at −45 °C followed by warming to room temperature to provide the desired diazoketone substrate **4b** in 73% yield. Acetal **2a** was converted to diazoketone **4a** via the less reactive mixed anhydride (Scheme 1).

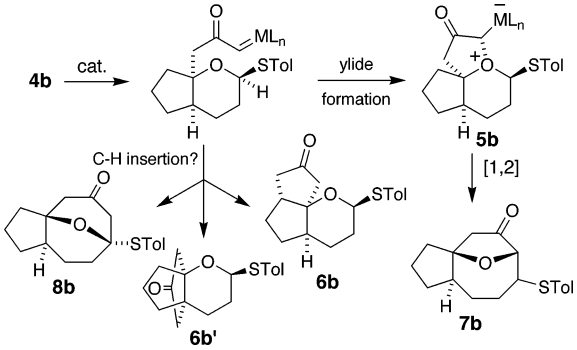
With **4** in hand we could examine the key transformation, with an initial focus on thioacetal **4b**. The desired pathway was ring closure of a transient metallocarbene to form five-membered

Scheme 1 [a]



[a] Conditions: (a) $BrCH_2CO_2Et$, Zn, TMSCl (87%, 3.2:1 dr); (b) $BF_3{\cdot}OEt_2$, −10 °C (65%, + 18% α-anomer); (c) $BF_3{\cdot}OEt_2$, 4-MeC_6H_4SH (82%); (d) LiOH (96%, **2b**; 85%, **2a**); (e) $(COCl)_2$; then CH_2N_2 (58%); (f) *i*-BuOCOCl/Et_3N; then CH_2N_2 (22% + 66% recov. SM).

Scheme 2



oxonium ylide **5b**, followed by [1,2]-shift of the anomeric carbon to give **7b** (Scheme 2). Prior studies by our group[5a] and Zercher et al.[7] had shown that the anomeric carbon of acetal-derived oxonium ylides was a competent migrating center in the Stevens rearrangement. We envisaged the thioaryl group to be comparable if not superior to alkoxy at stabilizing the likely biradical intermediate during [1,2]-shift, but alternative pathways of the metallocarbene were of concern. Formation of the seven-membered sulfonium ylide was deemed unlikely due to ring strain. However, C−H insertion to cyclopentanones **6b** and **6b′** was clearly possible, and the cis relationship of the metallocarbene side chain and the anomeric proton might also permit transannular C−H insertion[5b] to give **8b**. In theory, cyclooctanoid **8b** would be suitable for eventual elaboration to the dactylol system, but its competitive formation would nonetheless complicate the synthesis.

Several reaction conditions previously used for the chemoselective generation of oxonium ylides were surveyed.[8] Both rhodium(II) acetate dimer and the bulkier rhodium(II) triphenylacetate dimer[9] gave an apparent C−H insertion product[10] and

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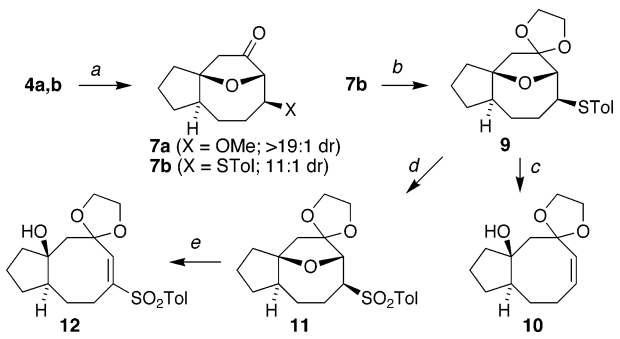
Scheme 3 [a]



[a] Conditions: (a) 10 mol % $Cu(hfacac)_2$, CH_2Cl_2, reflux (80%, **7b**; 82%, **7a**); (b) $HO(CH_2)_2OH$, cat. TsOH, $PhCH_3$, reflux (73% + 25% recov. **7b**); (c) LiDBB, THF, −78 °C to rt (97%); (d) Oxone, MeOH, pH 4 buffer (97%); (e) *n*-BuLi, THF, −78 °C (75%).

relatively small amounts of the desired **7b**. This lack of selectivity between ylide and C−H insertion pathways is consistent with earlier results.[5a,8b] The optimal conditions found for the generation and [2,3]-shift of allyl-substituted oxonium ylides[8a,b] ($Cu(tfacac)_2$, CH_2Cl_2, reflux) furnished only low yields of several unidentified products, confirming our earlier observation that this catalyst is not effective for [1,2]-shift processes. However, treatment with $Cu(hfacac)_2$ provided **7b** in high yield and with excellent diastereoselectivity (Scheme 3). The structure **7b** was confirmed by X-ray crystallography.[11] Notably, products derived from sulfur ylide formation or C−H insertion were not observed. Mixed acetal **4a** was also subjected to the optimized conditions found for **4b**, and furnished the analogous [1,2]-shift product **7a** in good yield as a single diastereomer.

The major diastereomer of **7a**,**b** results from [1,2]-shift with retention of configuration. A high degree of retention is surprising a priori, given the presumed intervention of radical intermediates.[8d] However, similar selectivity in the Stevens rearrangement of both oxonium[6e] and ammonium[12] ylides has been observed. A possible explanation for migration with retention is rapid radical recombination as compared with bond rotation.[13] On the other hand, an alternative explanation in which the transition metal catalyst is directly involved in the rearrangement step cannot be ruled out.[8c,14]

Having already functioned effectively as a directing moiety for the [1,2]-shift, the thioaryl group was next examined as a trigger for cleavage of the bridging ether. Its relationship to the ether oxygen suggested an elimination strategy using either reductive desulfurization or oxidation to sulfone and base-induced elimination. To examine these reactions, the ketone was protected as the ketal to generate **9**. The resulting product was subjected to LiDBB reductive desulfurization[15] using Rychnovsky's modified conditions at low temperature.[16] This effected the smooth lithiation of the sulfur−carbon bond with concomitant cleavage of the bridging ether to produce the desired ring-opened product **10** in 97% yield. The complementary base-induced elimination route, which allows for ring opening while leaving the sulfone in place as a handle for further manipulations, was also explored. Oxidation of **9** to sulfone **11**[11] was accomplished with oxone (97%). Deprotonation with *n*-BuLi at −78 °C produced the desired vinyl sulfone **12** in 75% yield.

This work describes the efficient synthesis of functionalized ether-bridged eight-membered rings via generation and [1,2]-rearrangement of oxonium ylides derived from easily prepared cyclic mixed acetals. The resulting bridging ether can be cleaved under both reductive and basic conditions in good-to-excellent yields. In this approach, the thioaryl group serves to direct the Stevens [1,2]-shift and then functions as a trigger for cleavage of the bridging ether. Further investigations into the generality of this process, application toward other bicyclic systems, and its use in the total synthesis of dactylol are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all intermediates (PDF). X-ray data for **7b** and **11** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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