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Hydrazulene Ring Systems via Heteroatom-Assisted [1,2]-Shift of Oxonium and Sulfonium Ylides

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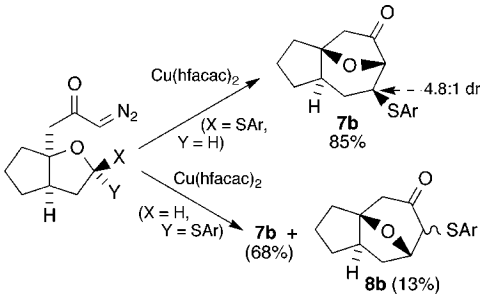
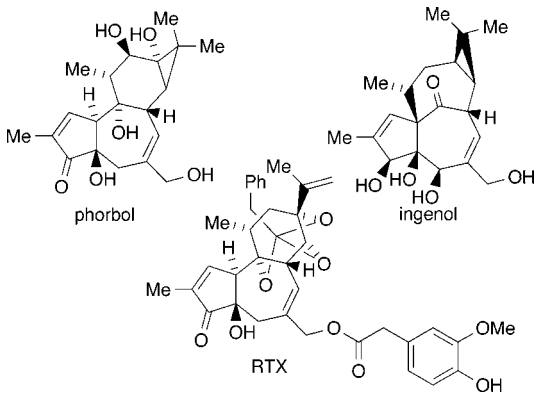
ABSTRACT



Cyclic mixed acetals with pendant diazoketone side chains undergo rearrangement to ether-bridged cycloheptane ring systems on treatment with Cu(hfacac)$_2$. Stevens [1,2]-shift of an oxonium ylide furnishes the major product (7), in some cases accompanied by minor amounts of a product (8) resulting from [1,2]-shift of a sulfonium ylide. In the subsequent sulfur-triggered cleavage of the bridging ether, the desired bicyclo[5.3.0]heptene was obtained, along with the product of novel S$_N$2′ attack on the resulting allylic ketal.

Functionalized hydrazulene ring systems are found in a wide variety of biologically important natural products. Members of the tigliane, daphnane, and ingenane classes, as exemplified by phorbol, resiniferatoxin (RTX), and ingenol, are of particular interest as a result of their potent biological activity.[1] New methods for constructing their ring systems or substructures thereof are desirable as an entry point for the chemical synthesis of the natural compounds[2] or structural analogues.[3]

A key challenge in any such method is the controlled introduction of the oxygen functionality found at one or more angular positions. We recently reported 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, and demonstrated that subsequent sulfur-triggered cleavage of the bridging ether moiety furnished bicyclo[6.3.0]undecenes with bridgehead alcohol functionality.[4] Here we describe an analogous strategy directed toward hydrazulene units corresponding to the AB portions of the tigliane, daphnane, and ingenane ring systems. Along with a concise and high-yielding route to these targets, we also detail unexpected minor pathways via a sulfonium ylide rearrangement and the transannular S$_N$2′ attack on an unsaturated ketal by an angular alkoxide intermediate.



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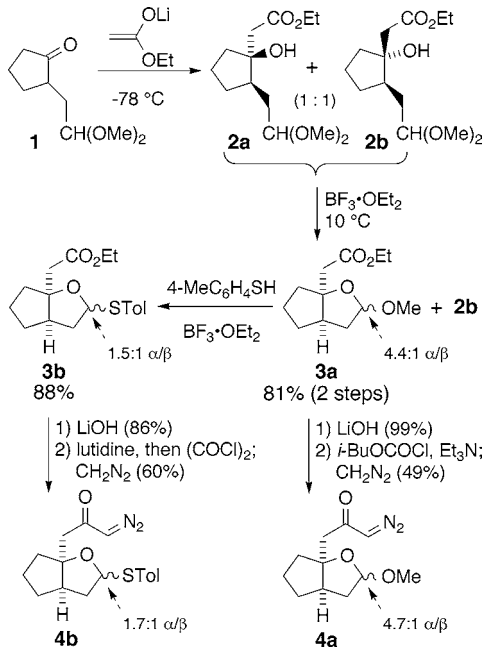
Preparation of the necessary acetal substrates began with the addition of the lithium enolate of ethyl acetate[5] to the known[6] 2-(3,3-dimethoxyethyl)cyclopentanone **1** (Scheme 1).

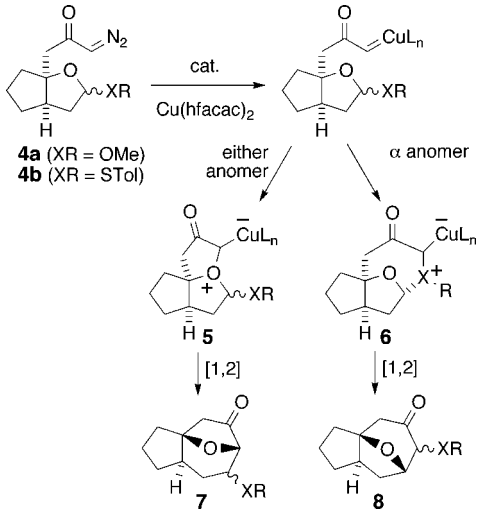
Scheme 1



The crude addition products **2** were then subjected to BF_3•OEt_2, which effected cyclization of *cis* isomer **2a** to give cyclic mixed acetal **3a** in 81% yield and 4.4:1 anomer ratio (based on a 1:1 ratio of **2a** and **2b**). The *trans* diastereomer **2b** was recovered unchanged and was easily separated from **3a**. Exchange of the methoxy group for STol (BF_3•OEt_2, HSTol) proceeded smoothly to give mixed acetal **3b** in 88% yield as a 2.5:1 mixture of α/β anomers. Intermediates **3a** and **3b** were then saponified in high yield to give the corresponding carboxylic acids. The methoxy mixed acetal could be converted to diazoketone **4a** in moderate yield via the mixed carbonic anhydride, but this protocol could not be applied to the corresponding thioacetal due to unacceptably low yields. Conversion to the acid chloride under standard conditions[4] resulted in extensive decomposition of the thioacetal; however, carrying out the reaction in the presence of excess 2,6-lutidine permitted the isolation of **4b** in 60% yield (1.7:1 mixture of α and β anomers).[7]

With diazoketones **4** in hand, we could examine the key transformation. Of the common reaction conditions for the selective generation of oxonium ylides,[8] we proceeded with those found to be optimal in our previous study,[4] $Cu(hfacac)_2$ in CH_2Cl_2 at reflux. The expected (and desired) pathway for the intermediate metallocarbene was ring closure to form five-membered oxonium ylides **5**, followed by [1,2]-shift of the anomeric carbon to give **7** (Scheme 2). In contrast to the earlier studies, another reactivity pathway had to be considered. The presence of both mixed acetal anomers permitted the possible alternative cyclization of the α anomer to bridged bicyclic ylides **6**.[9] If formed, these intermediates would also be expected to undergo [1,2]-shift to furnish isomeric ring-expansion products **8**. The strong preference for oxonium ylide formation via five-membered ring closure[8] suggested that the pathway via ylides **6** should be minor.

Scheme 2



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(5) In contrast to the previous study (see ref 4), no improved stereoselectivity was observed for the corresponding Reformatsky addition.

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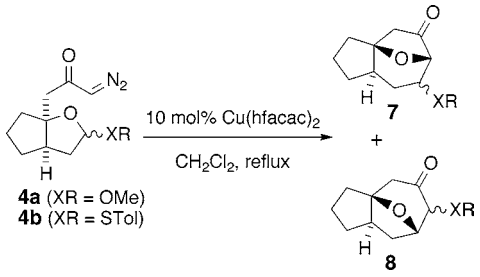
(7) The anomers of **4b** were distinguished through 1D TROESY experiments showing proximity of the anomeric proton to the diazoketone side-chain protons in the β anomer, but not the α anomer.

(8) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657−1660.

(9) Formation of the corresponding bridged bicyclic ylide from the β anomers is considered unlikely due to the excessive strain associated with the required inside−outside geometry.

In the event, the β anomers of **4a** and **4b** underwent efficient conversion to ether-bridged hydrazulenes **7** upon treatment with catalytic $Cu(hfacac)_2$, as expected (Table 1).

Table 1. $Cu(hfacac)_2$-Catalyzed Ring Expansion of Anomeric Mixed Acetals[a]



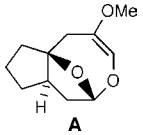
substrate	% yield of **7** (dr)[b]	% yield of **8** (dr)[b]
4a (β anomer)	67 (2.4:1 β/α)	
4a (α anomer)	61 (1.6:1 α/β)	
4b (β anomer)	85 (4.8:1 β/α)	
4b (α anomer)	68 (1.6:1 α/β)	13 (1.9:1 α/β)

[a] Experimental conditions: A solution of **4** in CH_2Cl_2 (0.03 M) was added dropwise to a refluxing solution of $Cu(hfacac)_2$ (10 mol %) in CH_2Cl_2 (0.001 M), and the reaction was stirred at reflux until consumption of **4** (30−45 min). [b] Yields are for isolated material after chromatography. Ratios determined by GC.

In both cases, an epimeric mixture was obtained at the migrating center, indicating some erosion of the stereochemical retention during the [1,2]-shift, and in sharp contrast to the six-membered acetals.[4] The α anomer of **4a** also furnished **7a**, albeit in lower yield and accompanied by traces of a second product.[10] The α anomer of **4b** gave **7b** in 68% yield, along with minor amounts of isomeric hydrazulene **8b**.

The partial stereochemical retention in the formation of **7** in all four examples deserves comment. We have noted incomplete stereospecificity in other cases involving [1,2]-shift of ylides containing an oxoniabicyclo[3.3.0]octane skeleton.[11] Erosion of stereochemical retention strongly suggests a stepwise mechanism for the migration involving radical or ion pairs, as opposed to concerted or metal-assisted[12] rearrangement. Plausible mechanisms can be suggested involving initial cleavage of the oxonium ylide via either homolytic[13,14] or heterolytic[15] manifolds (Scheme 3; shown for the specific case of **4b**-β). In either instance,

(10) This structure of this labile compound, which was isolated in ca. 2% yield, has been tentatively assigned as methyl enol ether **A**, suggesting possible formation of the alternative oxonium ylide derived from the methoxy group, followed by 1,4-migration of the methyl group.



A

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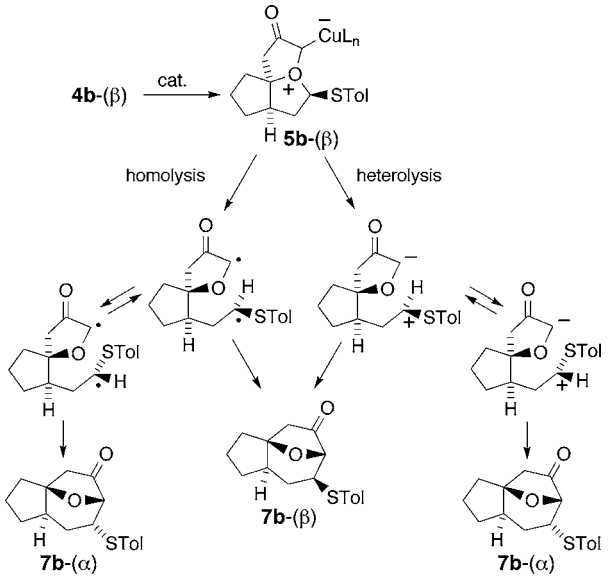
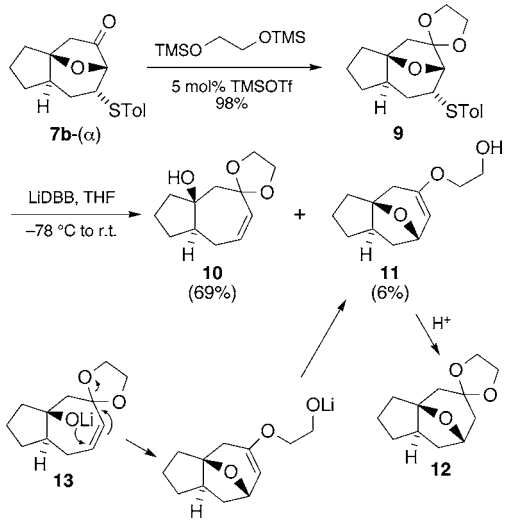
Scheme 3



the rate of bond rotation by the intermediate biradical or zwitterion must be comparable to that of recombination in order to explain the observed diastereomer ratios.

Regardless of the mechanistic uncertainty, it is clear that the thioaryl group facilitates the overall [1,2]-shift process. Having done so, it can then be used to trigger the opening of the ether bridge. Compound **7b** (α-STol diastereomer) was first ketalized to give **9** (Scheme 4). Subjection of this

Scheme 4



intermediate to reductive sulfurization with LiDBB[16] using Rychnovsky's modified conditions[17] at low temperature

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effected smooth lithiation of the sulfur−carbon bond with concomitant cleavage of the bridging ether to produce the desired alcohol **10** in 69% yield. A second more polar product was also formed in minor amounts and was determined to be enol ether **11**. Upon standing in $CDCl_3$, **11** underwent slow reketalization to give **12**, apparently catalyzed by trace amounts of acid. Compound **11** is presumed to form via the alkoxide intermediate **13** by way of a transannular S_N2' attack on the unsaturated ketal moiety.[18] As evidence for its involvement, subjection of purified **10** to reaction conditions or treatment with *n*-BuLi resulted in a mixture of both **10** and **11**. Conformational preferences in the hydrazulene system may permit the occurrence of this minor pathway, which was not observed in the corresponding 5−8 bicyclic substrate.

This work describes the efficient synthesis of functionalized ether-bridged seven-membered rings via generation and rearrangement of oxonium ylides derived from easily prepared mixed acetals. Where geometrically possible, minor amounts of a sulfur ylide rearrangement product were also seen. In the case of the thioacetal rearrangement product, the resulting bridging ether was cleaved under reductive conditions in good yield, accompanied by minor amounts of an alkoxide initiated transannular S_N2' opening of an unsaturated ketal to give an enol ether.

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Supporting Information Available: Experimental procedures and spectral data for all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050396P

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