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Iterative Approach to Polycyclic Ethers Based on Stereoselective Oxonium Ylide [2,3]-Shifts

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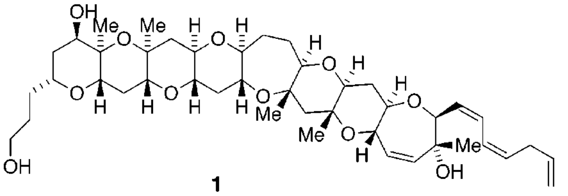
Marine ladder toxins have gained considerable attention in recent years.[1] As exemplified by gambierol (**1**),[2] they contain a unique *trans*-fused polycyclic ether skeleton, and possess interesting biological activity.[3] The repetitive structure of these molecules has inspired several iterative synthetic approaches.[4] Here we report a novel strategy directed toward these ring systems employing iterative generation and rearrangement of cyclic oxonium ylides.



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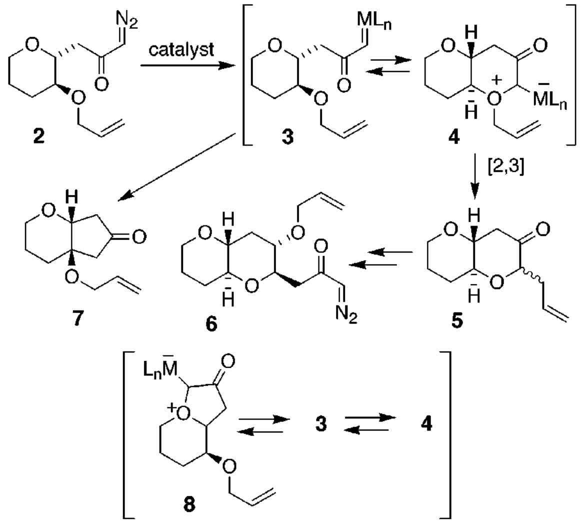
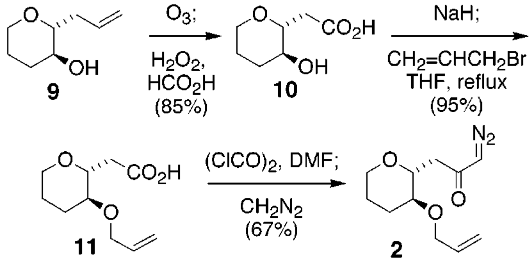
Generation and rearrangement of ylides via catalytic decomposition of diazoketones has emerged as a useful strategy in the construction of functionalized heterocyclic systems.[5] The products resulting from [2,3]-sigmatropic rearrangements of cyclic oxonium ylides appeared to be attractive building blocks for the construction of the polycyclic ether arrays found in the ladder toxins, particularly the poly(tetrahydropyran) domains. Catalytic decomposition of diazoketone substrates such as **2** would lead to ylide intermediate **4**, whose [2,3]-shift would furnish bicyclic ether **5** (Scheme 1). Notably, the ketone and pendant allyl group would be conveniently placed for elaboration to a new diazoketone substrate **6**, allowing for an iterative approach.

Competitive C−H insertion by metal carbenoids via five membered transition states into an activated carbon hydrogen bond (e.g., **3**→**7**) is facile, and this was a concern.[6] However, previous reports by Clark[5b,c] and by us[7] suggested that copper carbenoids favor ylide formation over C−H insertion. Generation of five-membered oxonium ylide **8** by addition of the carbenoid moiety of **3** to the pyran oxygen was also a possibility. While its formation should be straightforward, **8** would not have a low-energy rearrangement pathway available. There is now considerable evidence for equilibration between metal carbenoids[5e] or free carbenes[8] and oxonium ylides; this mechanism would allow the interconversion of unproductive ylide **8** with **4**, which could undergo the desired [2,3]-shift.

Scheme 1



Scheme 2



Diazoketone **2** was synthesized from known hydroxypyran **9** (Scheme 2).[9] Ozonolysis with oxidative workup yielded hydroxy acid **10**, which was followed by allyl ether formation to afford acid **11**. Conversion into the acid chloride and treatment with diazomethane then furnished **2**.

Several copper-based catalysts were examined to effect the desired ylide generation/[2,3]-shift (Table 1). Earlier work had identified copper(II) hexafluoroacetylacetonate (Cu(hfacac)$_2$) as the optimal catalyst for oxonium ylide formation in systems with potentially facile C−H insertion pathways.[5b,7] In the event, treatment of **2** with Cu(hfacac)$_2$ afforded 36% of the desired products **5a** and **b** (1:5) and 5% of the C−H insertion product **7** (Table 1, entry 1). The major component of the inseparable diastereomeric mixture was the α-epimer **5b**. Addition of diazoketone **2** to copper(II) trifluoroacetylacetonate (Cu(tfacac)$_2$) provided the desired products in 66% isolated yield, greatly increased the diastereoselectivity (1:40) and diminished the C−H insertion pathway (entry 2).[10]

Surprisingly, the optimal conditions for the desired transformation were found to be dropwise addition of the diazoketone via

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(8) Sueda, T.; Nagaoka, T.; Goto, S.; Ochiai, M. *J. Am. Chem. Soc.* **1996**, *118*, 10141.

(9) (a) Simart, F.; Brunel, Y.; Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13557. (b) Tetrahydropyran **9** can also be prepared from dihydropyran using a variation of McDonald's methodology (ref 4a).

(10) Other soluble copper catalysts such as Cu(acac)$_2$ and Cu(CH$_3$CN)$_4$PF$_6$ were also examined, but gave diminished yields of **5**.

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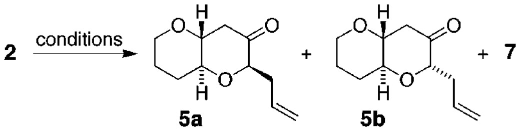
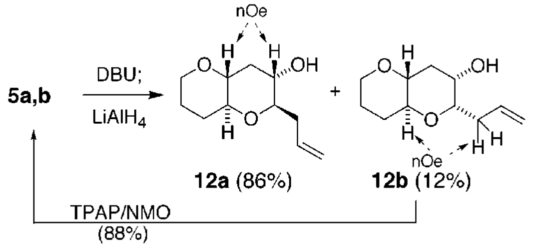
Table 1. Decomposition of Diazoketone **2**



		addn		ratio[c]	yield	(%)[d]
entry	catalyst/mol %	time[a]	solvent[b]	**5a**:**5b**:**7**	**5a**,**b**	**7**
1	$Cu(hfacac)_2$/10	3 h	CH_2Cl_2	1:5:1	36	5
2	$Cu(tfacac)_2$/10	3 h	CH_2Cl_2	1:40:2	66	–
3	$Cu(tfacac)_2$/5	3 h	CH_2Cl_2	1:30:2	72	–
4	$Cu(tfacac)_2$/5	5 min	CH_2Cl_2	1:30:2	80	–
5	$Cu(tfacac)_2$/10	3 h	$PhCH_3$	1:15:6	–	–
6	$Rh_2(OAc)_4$/3	3 h	CH_2Cl_2	4:1:5	32	27

[a] Inverse addition via cannula (entry 4) or syringe pump (all others). [b] All reactions were conducted at reflux. [c] Product ratios determined by GC. [d] Isolated yields after chromatography. Product **7** was not isolated in entries 2–5.

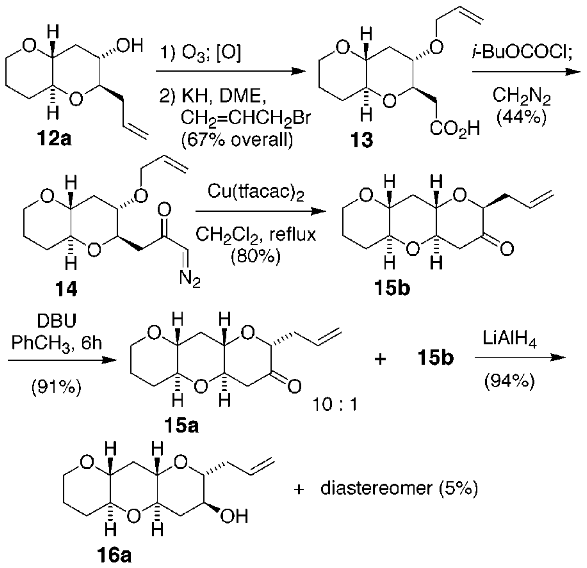
Scheme 3



cannula (5 min addition time) to a decreased amount (5 mol %) of $Cu(tfacac)_2$, which gave **5a**,**b** in 80% yield (entry 4). Higher temperature resulted in reduced stereoselectivity and a significant amount of the C–H insertion product (entry 5). For purposes of comparison, catalysis by $Rh_2(OAc)_4$ was also examined. Not surprisingly, these conditions led to a substantial amount of C–H insertion product **7** along with **5a** and **b** (entry 6). Interestingly, β-isomer **5a** was the major product, in contrast to all of the copper catalyzed examples. It is noteworthy that carbenoid dimerization products were not observed in any of these reactions.[11]

Reduction of the inseparable mixture of epimers **5a** and **b** yielded a separable mixture of alcohols **12a** and **b** (Scheme 3). The relative stereochemistry of **12a** and **b** was determined by 2D NOESY experiments, which showed the expected cross-peaks between the 1,3 diaxial protons in **12a** and between the methylene protons of the allyl group and the bridgehead axial α-proton in **12b**. The β-allyl isomers (**5a**, **12a**) are necessary for further iteration. Fortunately, isomer **5b** could be converted to the desired alcohol **12a** by an epimerization/reduction procedure, and **12b** could be efficiently recycled via TPAP oxidation.

Scheme 4



With **12a** in hand an additional iteration was attempted (Scheme 4). Ozonolysis and oxidative workup followed by allyl ether formation afforded **13**. Activation of the acid and treatment with diazomethane generated diazoketone **14**. When **14** was subjected the optimum conditions from Table 1, **15b** was isolated as the only detectable isomer in 80% yield. To confirm the configuration at the allylated center, **15b** was subjected to the epimerization conditions, furnishing a 10:1 mixture of **15a** and **b**, whose relative stereochemistry was established by 2D NOESY experiments as described above. This mixture could be reduced as before to give **16a** and a trace of an isomer.

In summary, we have developed an efficient iterative route to polypyran ethers based on an oxonium ylide/[2,3]-shift strategy. Copper(II) trifluoroacetylacetonate provides the desired products in good yields and with minimal C–H insertion side products. These results are consistent with previous studies by Clark and by us: rhodium carbenoid intermediates suffer competing C–H insertion along with ylide formation, while copper carbenoids favor ylide formation, keeping C–H insertion minimal. The origins of the apparent catalyst dependent diastereoselectivity are not fully understood, but suggest a metal-associated ylide in the product-forming step.[12] Application of this methodology to the synthesis of medium-sized ethers and polycyclic ether natural products will be reported in due course.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We also thank Dr. Charles L Mayne for assistance with high-field NMR experiments and Professor J. S. Clark for helpful discussions.

Supporting Information Available: Experimental procedures and physical data for all reported products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In a related benzyl [1,2]-shift study, the analogous diazoketone produced 60% carbene dimer products with $Cu(hfacac)_2$. Marmsäter, F. P.; Vanecko, J. A.; West, F. G. Unpublished results; University of Utah.

(12) When **5b** was subjected to the reaction conditions for the formation of **5a** (Rh_2OAc_4, CH_2Cl_2, reflux) no epimerization was observed. For additional support for metal associated ylides, see: (a) Johnson, C. R.; Rosekamp, E. J. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (b) Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120,* 7653. (c) See also ref 5b.