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Communications

Participation of Aromatic Groups in Oxy-Cope Reaction Sequences. Synthesis of Highly Substituted Polyquinane Ring Systems

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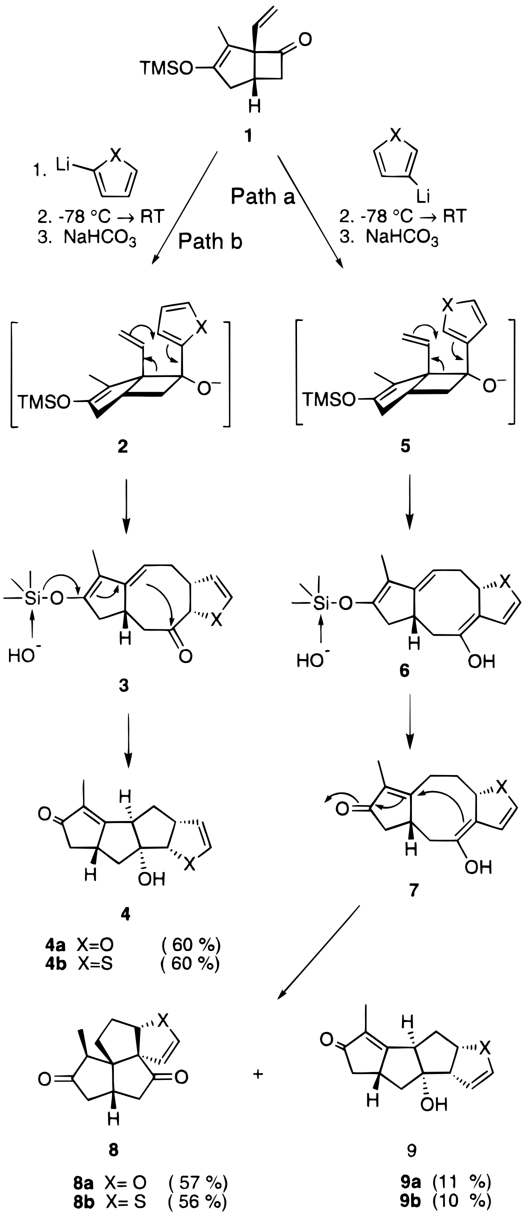
In comparison to the numerous reports describing the participation of alkenyl groups in oxy-Cope reactions,[1] there are few examples of aryl substituents being involved in this important process.[2] We recently described a powerful tandem oxy-Cope−transannular ring closure reaction sequence involving bicyclo[3.2.0]heptenones **1**, in which the ring expansion step is significantly influenced by strain release.[3] As reported herein the exothermicity associated with this step is sufficient to allow an aromatic component to participate in the sigmatropic event. The overall transformations provide efficient regiospecific routes to substituted, highly condensed ring systems that would be most difficult to prepare by other methods.

The results of preliminary experiments are shown in Scheme 1.[4−6] Addition of 2-lithiofuran or 2-lithiothiophene to **1** followed by warming to room temperature and basic workup gave the linearly fused polyquinane **4a** (60%) and **4b** (60%), respectively. Their formation is envisaged to stem from alkoxide **2**, which undergoes an oxy-Cope ring expansion through a cis-boat conformational transition state. Subsequent hydrolytic desilylation of the resulting dienyl ether **3** accompanied by concomitant transannular ring closure affords **4**.[3]

Scheme 1



In comparison, treatment of **1** with the regioisomeric 3-lithiofuran or 3-lithiothiophene provided the respective angularly fused polyquinanes **8a** (57%) and **8b** (56%) along with minor amounts (10−11%) of **9a**,**b**. This reaction is envisaged to arise via the mechanism shown in path a of Scheme 1. Ring expansion of the alkoxide **5** followed by protonation of the resulting enolate results in the conjugated enol **6**, hydrolysis of which provides the enone **7**. Subsequent intramolecular Michael addition followed by stereoselective protonation of the resulting enolate then gives polyquinanes **8a**,**b**. The minor linearly fused polyquinanes **9a**,**b** are envisaged to arise by a mechanism analogous to that involved in the formations of **4a**,**b**.

In related experiments, **1** was treated with 1-lithionaphthalene and 2-lithionaphthalene, respectively. The former gave the polyquinane **10** (48%), and the latter gave nearly equal amounts of **11** (31%) and **12** (30%).[7]

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(1) For recent reviews and leading references, see: (a) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609−626. (b) Paquette, L. A. *Synlett* **1990**, 67−73. (c) Lutz, R. P. *Chem. Rev.* **1984**, 206−243. (d) Wilson, S. R. *Org. React.* **1993**, *43*, 95−246.

(2) (a) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 2463−2464. (b) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4309−4311. (c) Marvell, E. N.; Almond, S. W. *Tetrahedron Lett.* **1979**, *21*, 2779−2780.

(3) For previous work in this area, see: (a) Santora, V. J.; Moore, H. W. *J. Am. Chem. Soc.* **1995**, *117*, 8486−8487. (b) Xu, S. L.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6094−6103. (c) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 6018−6021.

(4) Lithium and cerium reagents were prepared using standard methods. For leading references, see: (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: New York, 1988. (b) Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry 1*; Springer-Verlag: Berlin, 1987.

(5) Satisfactory ^{1}H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data have been obtained for all new compounds except for **9a**,**b**, which was observed to be quite unstable to purification techniques. Thus, its spectral data were obtained on the partially purified samples.

(6) Phenyllithium also reacts with **1** to give only a 10% yield of a polyquinane analogous in structure to **11**. The major product (60%) is a bicyclo[2.2.1]heptene resulting from a 1.3-sigmatropic shift at the alkoxide stage. An analogous 1,3-shift takes place when **1** was treated with 2-lithio-1-methylpyrrole.

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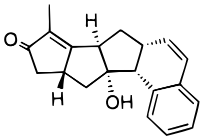
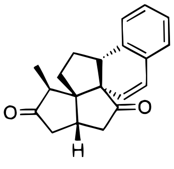
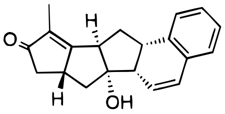


10 (48%)



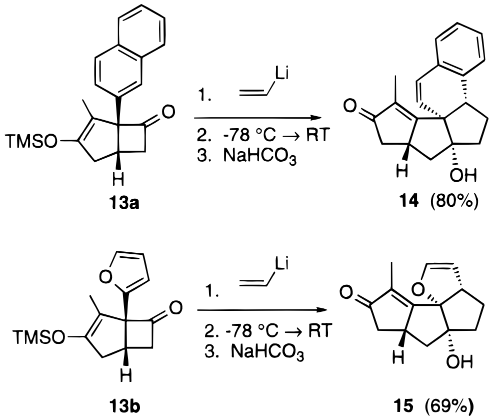
11 (31%)

+



12 (30%)

Scheme 2



The relative success of the reaction of **1** with several arylithium reagents prompted an investigation of the reactivity of bicycloheptenones bearing aromatic groups at the bridgehead position. Compounds **13a**,**b** were prepared from dimethyl squarate according to methods previously developed in our laboratory.[3] Treatment of **13a** and **13b** with vinyllithium gave the linearly fused polyquinanes **14** (80%) and **15** (69%), respectively (Scheme 2).

The structure assignments of the new compounds reported here are in agreement with their observed spectral data. In addition, the structure of **8b** was determined by single-crystal X-ray analysis. These data then provide the foundation for the assignments of the related angularly fused polyquinanes **8a** and **11**. The structures of the other polyquinanes are tentatively assigned on the basis of their spectral data and their relationship to other linearly fused examples that were reported earlier, some of which are based upon X-ray data.[3a]

Participation of aromatic groups in the oxy-Cope–transannular ring closure reaction sequences represents a significant advance in the utility of this method for the construction of highly condensed ring systems. Future efforts in this laboratory will focus on the preparation of appropriately substituted bicycloheptenones to further probe the synthetic scope of these reactions. Optimization and utilization of such tandem sequences in the synthesis of complex polycyclic natural products represent additional goals.

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Supporting Information Available: Experimental procedures for **4a,b**, **8a,b**, **9a,b**, **10–12**, **13a,b**, **14**, and **15** (8 pages).

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