Full Control of Regioselectivity in Linear and Angular Polyquinane Construction from Squarate Esters by Incorporation of a Leaving Group into a Single Vinyl Anion Reactant

Leo A. Paquette* and Julien Doyon

Evans Chemical Laboratories, The Ohio State University Columbus, Ohio 43210

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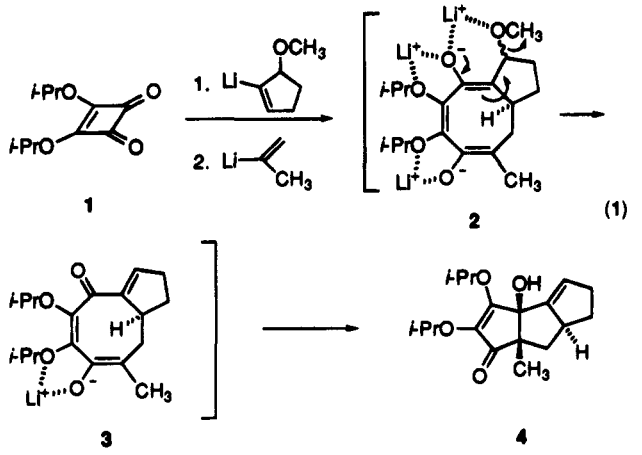
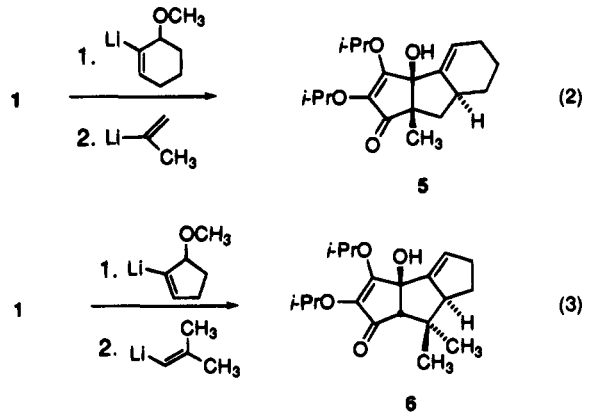
The treatment of squarate esters with 2 equiv of the same vinyl anion or 1 equiv each of two different vinyl anions has been discovered to trigger a cascade of chemical events that ultimately leads to polyquinane products.[1] Trans addition generates a cyclobutene dialkoxide which opens quickly to yield a doubly-charged 1,3,5,7-octatetraene amenable to cyclization from its coiled conformation. Both events proceed conrotatorily, and information about structural effects on reactivity has begun to emerge.[2] In unsymmetrical cases, the resultant 1,3,5-cyclooctatrienes do not necessarily experience monoprotonation at both available enolate centers regioselectively. As a consequence, competing aldolization can give rise to a pair of polyquinanes. Site-selective protonation is achieved when one of the anions is acetylenic in nature.[3] Described herein is a more flexible and utilitarian means for achieving regioselectivity based upon kinetically controlled β-elimination. The formation of a linear or angular triquinane[4] is regulated concurrently.

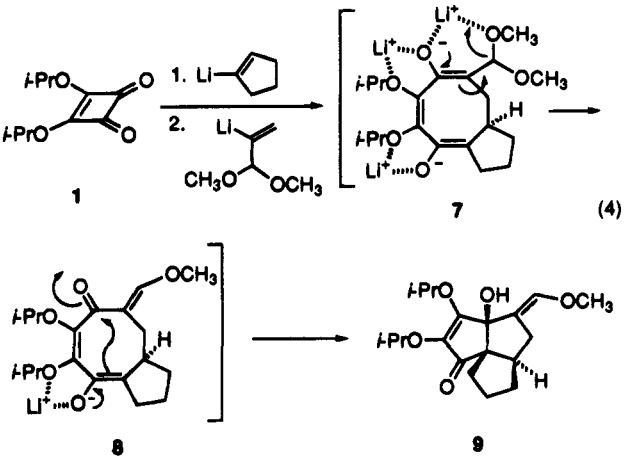
On the basis of the mechanistic profile delineated above, it was anticipated that treatment of **1** as shown in eq 1 would result in the transient formation of **2**. If β-elimination of methoxide were to operate as expected,[5] the lifetime of **2** should be reduced because of conversion to **3**. With arrival at **3**, only one intramolecular aldol pathway remains (giving rise to **4**) via this singular ring closure. Indeed, **4** is isolated as the only product in 64% yield.[6]



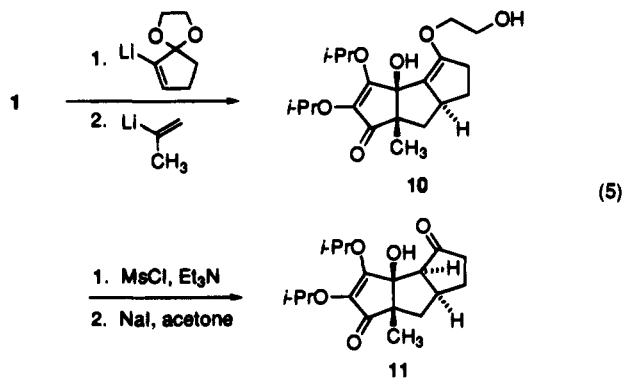
The lithiated cyclohexenyl homolog behaves analogously and, in fact, proceeds to give **5** (78%) with greater efficiency (eq 2). When 2-propenyllithium is replaced by the more sterically encumbered lithiated isobutylene, the consequences are no different and the tetrasubstituted center in **6** is suitably established, although with reduced efficiency (31%) because of steric compression during the 8π electrocyclization (eq 3).[7]



A key feature of these first experiments relates to placement of the leaving group on the cyclic nucleophile. Once elimination occurs to produce an intermediate such as **3**, the reacting system is inextricably directed to linear triquinane formation. The simple expedient of incorporating a potential nucleofuge within the acyclic component constitutes an advantageous means for preparing angular triquinanes instead. The formation of **9** (24%) from **1** via **7** and **8** as illustrated in eq 4 is exemplary. The



modest yield of **9** has been traced to the sensitivity of its



(1) Negri, J. T.; Morwick, T.; Doyon, J.; Wilson, P. D.; Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189.
(2) Paquette, L. A.; Morwick, T. *J. Am. Chem. Soc.* **1995**, *117*, 1451.
(3) Morwick, T.; Doyon, J.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 2369.
(4) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: New York, 1987.
(5) (a) Paquette, L. A.; Shi; Y.-J. *J. Org. Chem.* **1989**, *54*, 5205. (b) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331. (c) Paquette, L. A.; Shi, Y.-J. *J. Am. Chem. Soc.* **1990**, *112*, 8478.
(6) Two equivalents of the oxygen-containing vinyl anion are required to bring the first addition to completion. Since no bis-addition is seen at this stage, chelation involving lithium ions must be important. This behavior is common to all bromo olefins that carry one or more alkoxy groups.
(7) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130.

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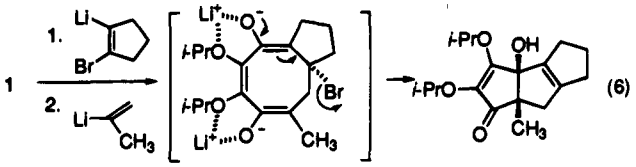
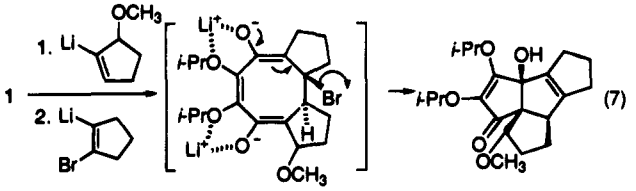
exocyclic enol ether moiety to chromatography. The feasibility of experimental design based on the involvement of acetals in either reactive component is reflected in the ease of generating **10** (54%, eq 5), the hydroxyl-substituted side chain in which can readily be transformed into a ring ketone carbonyl as shown in **11** (91%).

In order to expand the scope of this methodology, 1,2-dibromocyclopentene was monometalated[8] and brought into reaction with **1** in advance of 2-propenyllithium (eq 6). The locus of the bromine atom in **12** leads to installation of an intraannular double bond prior to transannular cyclization and the exclusive formation of **13** (41%). In line with established relative reactivities, cocondensation of two eliminatable anions with **1** resulted in the preferred loss of bromide ion to deliver exclusively **15** via **14** (eq 7). Accordingly, two modes of elimination can be made operative: the *exocyclic* pathway exemplified in **2** and **7** and the *intracyclic* option defined by **12** and **14**.[9,10]

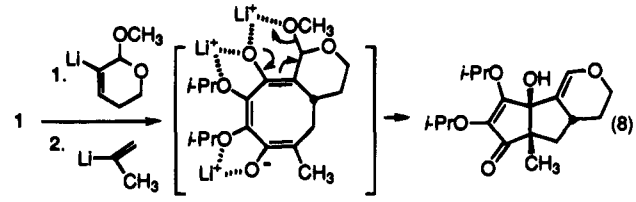


12 **13**

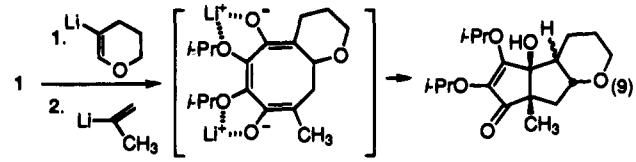


14 **15**

A provocative aspect of the exocyclic alternative surfaces when two oxido leaving groups are made available to the reactive intermediate as in **16**.[11] Of the two ether oxygen atoms suitably positioned for elimination, the methoxyl substituent is uniquely ejected to deliver **17**. No evidence has been uncovered for cleavage of the tetrahydropyran ring either in this example or when the hetero atom is so oriented to serve as an intracyclic nucleofuge (eq 9), where **19** is obtained as a 2.5:1 mixture of epimers (45%). As a consequence, **18** must be protonated with



16 **17**



18 **19** (2.5β : 1α)

very high regioselectivity α to the tetrahydropyran ring. This notable discrimination is believed to stem from the more elevated ring strain at that site. The major constituent was demonstrated to be the β isomer by X-ray crystallographic analysis; cis protonation is therefore kinetically advantaged during workup. Attention is called to the fact that only the methoxyl substituent in **16** is properly positioned to be coordinated to a lithium ion and participate in an *assisted* elimination. An alternative explanation resides in the potential reversibility associated with elimination of the tethered alkoxides, an option not equally available to the methoxide ion. Under these circumstances, it becomes necessary to assume that the transannular ring closure is product-determining since it is unlikely that diquinane formation is reversible under the reaction conditions.

In conclusion, we have demonstrated that the squarate ester 1,3,5,7-octatetraene–polyquinane cascade can be regiocontrolled in a manner which can be directed to linear or angular tricyclic products as desired. More elaborate multicyclic systems are expected to be available with equally striking selectivity. The resident multiple functionality in the products holds promise for the useful application of this methodology in a variety of synthetic undertakings.

Acknowledgment. This research was made possible by financial support provided by the National Science Foundation. We thank Prof. Robin Rogers (Northern Illinois University) for performing the crystallographic analysis.

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(8) Okano, Y.; Sawa, H.; Aonuma, S.; Kato, R. *Chem. Lett.* **1993**, 1851.

(9) The terms exocyclic and intracyclic are intended to be descriptive of the locus of the developing unsaturated center relative to the core eight-membered dienolate ring.

(10) No attempt has been made to define the relative stereochemistry of the methoxyl substituent in **15**.

(11) Some of the vinyl anions involved in this study have been previously described: (a) Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462. (b) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855. (c) Ficini, J.; Kahn, P.; Falou, S.; Touzin, A. M. *Tetrahedron Lett.* **1979**, 67. The others have been prepared by halogen-metal exchange of the corresponding iodo methyl ethers (Johnson, C. R.; Sakaguchi, H. *Synlett* **1992**, 813).