Direct Elaboration of Complex Polyquinanes through 2-Fold Addition of Vinyl Anions to Squarate Esters

Joanna T. Negri, Tina Morwick,[1] Julien Doyon,
Peter D. Wilson, Eugene R. Hickey, and Leo A. Paquette*

Evans Chemical Laboratories
The Ohio State University
Columbus, Ohio 43210

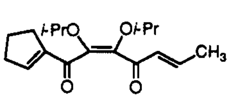
Received August 27, 1993
Revised Manuscript Received October 29, 1993

During the past 15 years, cyclobutene-1,2-diones have emerged from the realm of theoretically interesting molecules to serve as useful synthetic intermediates.[2,3] These achievements have uniformly taken advantage of the appreciable resident funtionality and heightened ring strain present in these four-membered α-dicarbonyl compounds. The feasibility of applying the principle of anionic charge acceleration[4] to such systems has now been investigated. The key question was whether *2-fold* addition of vinyl anions to diisopropyl squarate (**1**) and its congeners would induce ring cleavage at low temperature and lead thereby to charged reactive intermediates amenable to productive transannular bonding. We report here that impressive bond reorganizations can indeed ensue,[5] culminating in the direct formation of complex polyquinanes.[6]

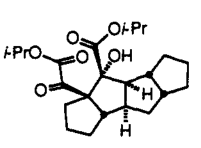
The results of several experiments are compiled in Table I. The conditions involved the addition of an excess of a single lithium reagent or of 1 equiv each of two different nucleophiles to **1** in THF at −78 °C. Slow warming to room temperature overnight was followed by quenching with saturated $NaHCO_3$ solution. Five contiguous stereogenic centers are established when two achiral reaction partners are involved (experiments 2, 3, and 5). This number can be increased if either reactant contains asymmetric carbons as exemplified by experiment 4. More elevated degrees of unsaturation can be equally well accommodated as reflected in equally facile conversion to the unsaturated tricyclic ketol **8** (40%).

In experiment 5, the product composition was found to be dominated by **14** which, like **2–4**, **6**, **7**, **10**, and **12**, arises from the dialkoxide generated by 1,2-addition to the monoadduct. Heterocycles **15–17** arise by 1,4-addition, indicating the dihydrofuranyl anion to possess an inherent bias for conjugate addition.

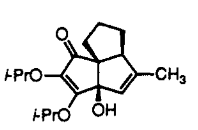
The product structures were elucidated by a combination of 2D, NOE, and semiselective DEPT studies, in addition to X-ray crystallography in selected cases. In experiment 3, the oxidation product **8** (18%) also resulted. High-field NMR analysis of ozonolysis product **13** supported the structural assignment to **12**.



8



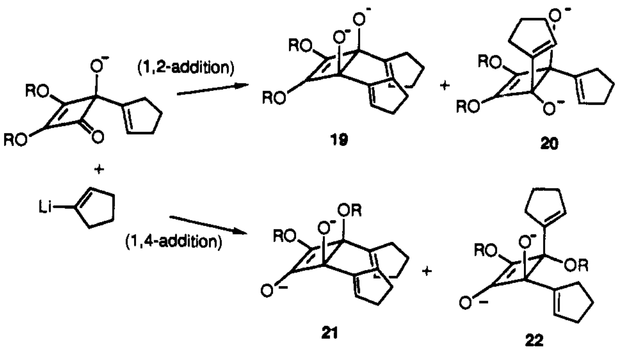
13



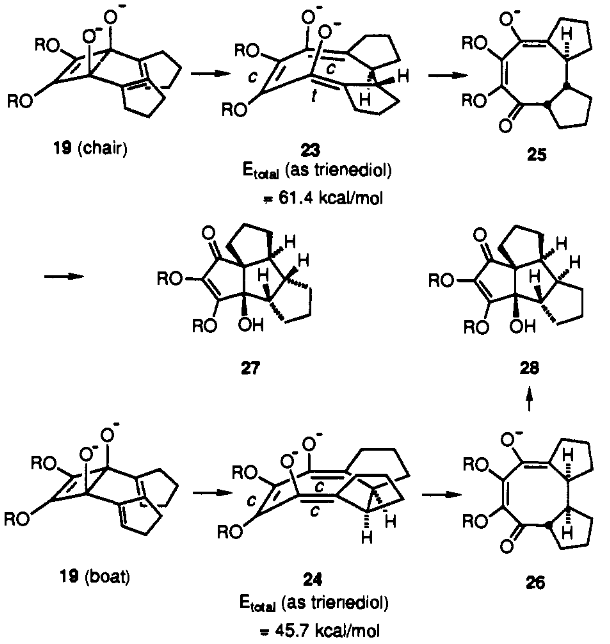
18

Use of the same nucleophile in both steps guarantees that the resultant 1,2-dianionic intermediate be symmetrical, irrespective of whether capture occurs from the cis (C_s as in **19**) or trans direction (C_2 as in **20**, Scheme I). 1,4-Addition leading to **21** and **22** is, of course, also possible. The reactive intermediates of type

Scheme I



Scheme II



19 and **21** can in principle draw on two allied reaction channels while advancing to product formation. If the dianionic oxy-Cope variant[5,7] is selected by **19**, [3,3] sigmatropy can occur by way of a chair or boat alignment of the cyclopentene double bonds to give either **23** or **24** (Scheme II). The relative stereochemistry of two adjacent stereocenters is thereby established. Subsequent monoprotonation of these dienolates delivers **25** and **26**, respectively. The conformational rigidity imposed by the third vicinal asymmetric carbon so limits the conformational freedom of these cyclooctadienones that the final transannular aldolization necessarily proceeds in a single, well-defined stereochemical direction.

The stereodistal arrangement of the cyclopentene double bonds in **20** and **22** mandates that a less direct reaction pathway be adopted. Isomerization of either dianion to its stereoproximal cis isomer[8] is considered quite unlikely under the present circumstances. Alternatively, the *trans*-dialkoxides are capable of conrotatory opening of the four-membered ring. Were this course of action to be followed by **20**, the open-chain tetraene **29** would result. Because this intermediate can rapidly partition itself between two conformations having topologically distinctive features (Scheme III), their subsequent eight-electron conrotatory electrocyclization[9] could give rise to the dienolates **30** and **31**.

---

[1] National Needs Fellow, 1991–1993.

[2] (a) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (b) Moore, H. W.; Yerxa, B. R. *Chemtracts: Org. Chem.* **1992**, *5*, 273.

[3] Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053.

[4] Wilson, S. R. *Org. React.* (*N.Y.*) **1993**, *43*, 93.

[5] For a recent related development, see: Brands, M.; Goddard, R.; Wey, H. G.; Butenschon, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 267.

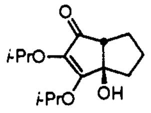
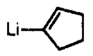
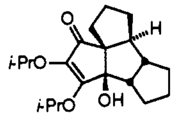
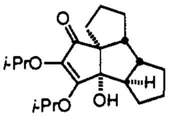
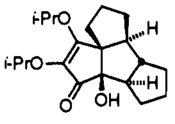
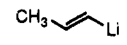
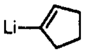
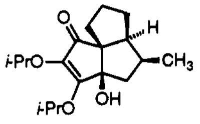
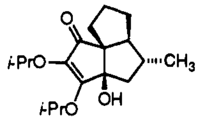
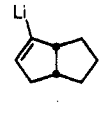
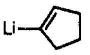
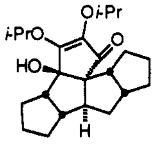
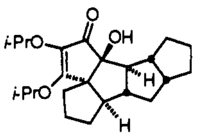
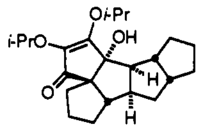
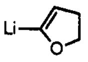
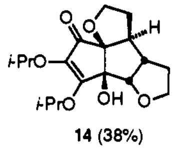
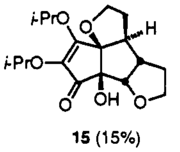
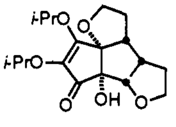
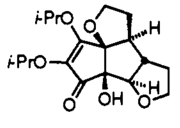
[6] Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: New York, 1987.

[7] (a) Geetha, P.; Huq, C. A. M. A. Rajagopalan, K.; Swaminathan, S. *Tetrahedron Lett.* **1982**, *23*, 569. (b) Alder, R. W.; Colclough, D.; Grams, F.; Orpen, A. G. *Tetrahedron* **1990**, *46*, 7933. (c) Saito, S.; Yamamoto, T.; Matsuoka, M.; Moriwake, T. *Synlett* **1992**, 239.

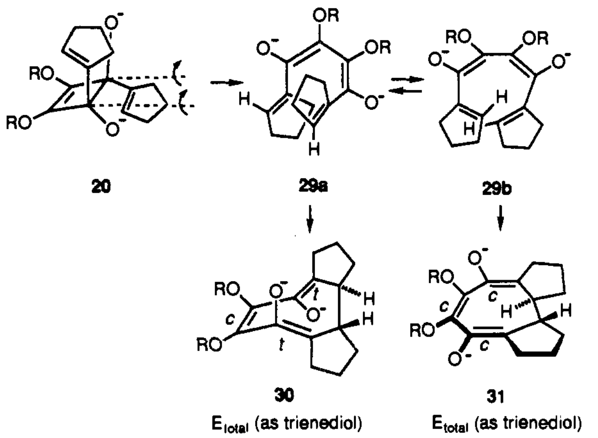
[8] Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268.

0002-7863/93/1515-12189$04.00/0

Table I. Polyquinanes Resulting from 2-Fold Vinyl Anion Addition to Diisopropyl Squarate (1)

Expt. no.	First anion	Second anion	Product(s) (isolated yield)			
1	$LiCH{=}CH_2$ (3 equiv)		 **2** (45%)			
2	 (> 2 equiv)		 **3** (40%)	 **4** (26%)	 **5** (4%)	
3			 **6** (32%)	 **7** (8%)		
4			 **10** (38%)	 **11** (11%)	 **12** (27%)	
5	 (> 3 equiv)		 **14** (38%)	 **15** (15%)	 **16** (5%)	 **17** (4%)

Scheme III

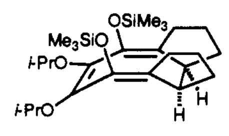


E_{total} (as trienediol) = 70.6 kcal/mol

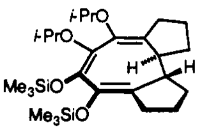
E_{total} (as trienediol) = 48.7 kcal/mol

Obviously, bis-adduct **22** can avail itself of similar opportunities. Molecular mechanics calculations provide insight into the relative stabilities of the four possible dialkoxides (as their neutral forms).

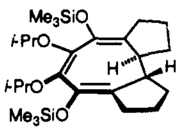
Since the distinctive stereochemical markers present in the four hypothetical dienolate intermediates address the question of their mechanistic origin, trapping experiments were undertaken. The reaction of **1** with 3 equiv of cyclopentenyllithium followed by excess chlorotrimethylsilane afforded a chromatographically separable mixture of **32** (24%), **33** (5%), and **34** (43%). Their individual exposure to CH_3Li and H_2O resulted in high-yield conversion to **4**, **5**, and **3**, respectively.



32



33



34

These data show that vinyl anions add to squarate esters predominantly in trans fashion to generate dialkoxides **20**. These highly strained, doubly charged systems experience conrotatory ring opening. Subsequent electrocyclization occurs exclusively from that conformation of the open-chain tetraene that gives rise to dienolates of type **31**. When 1,4-addition operates, **22** is produced and isomerizes identically. Cis addition functions competitively, generating **19**, which in turn rearranges via a boat, dianionic oxy-Cope transition state.

The ease of obtaining polyquinanes having a prespecified number of interlocking rings, the very mild temperature conditions required for their production, and the capability of the rearrangement process to support the targeted introduction of double bonds and heteroatoms are important features of this new reaction. We hope to report on many other facets of its scaffolding power, including applications to natural products synthesis, in due course.

Acknowledgment. This research has been carried out under the financial auspices of the National Science Foundation and the Eli Lilly Company. We thank Professor Robin Rogers and Dr. Judith Gallucci for crystallography, Dr. Dirk Friedrich for NMR assistance, Scott Edmondson for several MM2 calculations, and Dr. Conrad Kowalski (SmithKline Beecham Pharmaceuticals) for a gift of squaric acid.

---

(9) Thomas, B. E., IV; Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165 and related references cited therein.