Successive Electrocyclic Rearrangements initiated by the Addition of a Lithiated Cyclopropenone Acetal to a Squarate Ester

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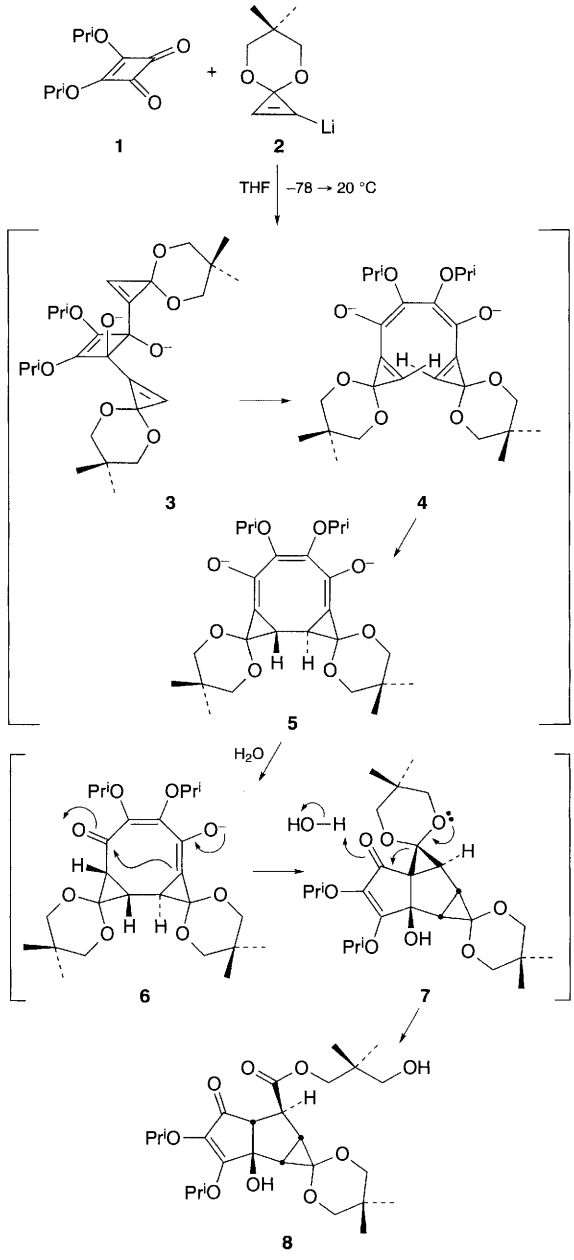
The ability of a cyclopropenone acetal to trigger a reaction cascade following nucleophilic addition to diisopropyl squarate is illustrated with three different examples.

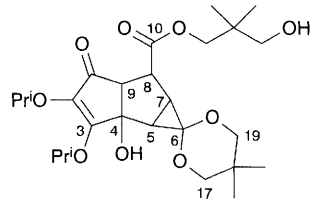
The options for exploring the chemistry of functionalized cyclopropenes have been significantly increased by the recent discovery that cyclopropenone acetals are amenable to metalation and reaction with an electrophilic reagent.[1] A second substituent can be comparably introduced with equivalent ease.[2] The present effort was undertaken to evaluate the readiness with which such highly strained lithiated species would become involved in a tandem series of reactions known to be initiated by the twofold addition of vinyl anions to squarate esters.[3] In the generic process, the first-formed *trans*-cyclobutene dialkoxide undergoes stereocontrolled conrotatory 4π electrocyclization (with the oxido anions moving outwardly) to generate a doubly-charged 1,3,5,7-octatetraene. The latter species undergoes conrotatory 8π ring closure from a Möbius-like helical conformation[4] with formation of an eight-membered cyclic dienolate, protonation of which results in transannular aldolization. The substitution pattern provided by the cyclopropenone acetals was expected[5] to be conducive to the coiled arrangement needed for completion of the reaction sequence, which would necessarily involve the π bonds of the three-membered ring. The basis of these experiments appeared not to have been studied previously and was therefore examined.



Scheme 1

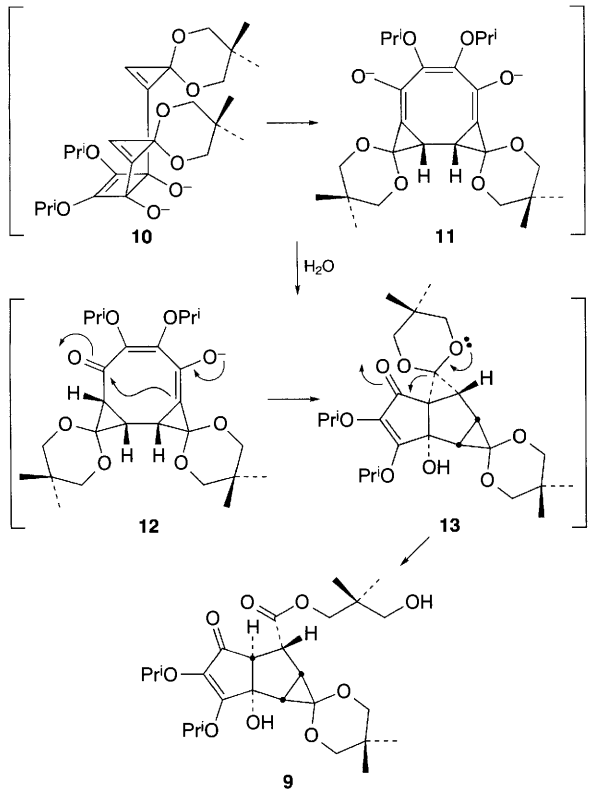
In the first example, diisopropyl squarate **1** was treated with a threefold molar excess of **2** in tetrahydrofuran at −78 °C. The reaction mixture was allowed to warm to 20 °C overnight and quenched with saturated sodium hydrogencarbonate solution. The two principal products were separated chromatographically and identified spectroscopically as **8** (21%) and **9** (23%) (Scheme 1). The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of **8** in C_6D_6 solution clearly defined a total of 40 protons and 26 carbons. ^{13}C multiplicity analysis (DEPT) showed 38 of the protons to be directly bonded to carbon, as the 26 carbons comprised eight methyl, four methylene, six methine, and eight quaternary centres. The remaining two protons must be hydroxylic. This constitution requires that a hydration event must have occurred; likewise, one of the cyclopropane rings must have fragmented. Through the application of COSY, HMQC, HMBC and NOED techniques, the various atomic interconnections present in **8**, as well as its

Table 1 NMR Data for compounds **8** and **9**

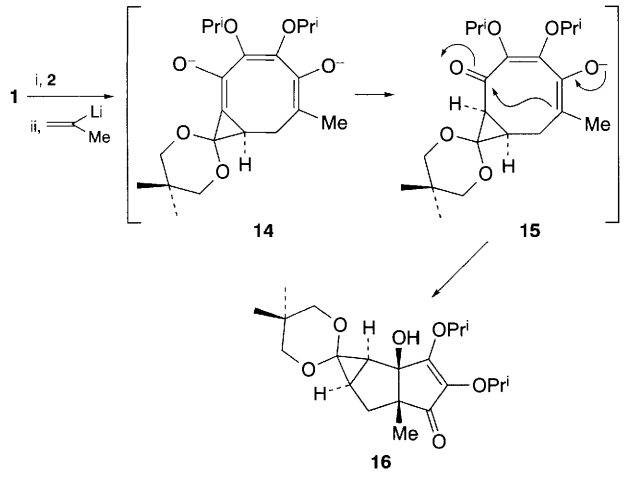


		8	**9**
$^3J_{H,H}$	H-7/H-8	0.8 (*anti*, close to 90°)	6.5 (*syn*)
	H-8/H-9	3 (*anti*, approaching 90°)	6.5 (*anti*)
$^4J_{H,H}$	H-5/H-9	0.8 (*syn*, W-arrangement)	zero (*anti*)
	H-7/H-9	0.4 (*syn*, W-arrangement)	zero (*anti*)
$^3J_{C,H}$ (HMBC)	H-7/C-10	yes (*syn*, close to 0°)	no (*anti*, close to 90°)
	H-9/C-10	yes (*syn*, close to 0°)	yes (*syn*, close to 90°)
	H-8/C-4	yes (close to 180°)	no (*close* to 90°)
	H-5/C-3	no (*anti*, close to 90°)	yes (*syn*, close to 0°)
NOE	irrad. H-7	H-8 (4%), H-19 (none)	H-8 (14%), H-19 (2%)
	irrad. 4-OH	H-9 (8%), H-5 (3%)	H-9 (12.5%), H-5 (none)
	irrad. H-8	H-7 (4%), H-19 (3%)	H-7 (11%), H-19 (none)
	irrad. H-9	H-5 (< 1%), H-7 (< 1%)	H-5 (none), H-7 (none)

relative stereochemistry, could be assigned. An essentially identical analysis showed **9** to be diastereoisomeric with **8** at the cyclopropane ring fusion. Their differentiation is based on the differing magnitudes of relevant vicinal coupling constants ($^3J_{H,H}$ and $^3J_{C,H}$), the presence or absence of diagnostic four-bond couplings ($^4J_{H,H}$), and the results of ^{1}H,^{1}H-NOED experiments, as compiled in Table 1.



Scheme 2



Scheme 3

The formation of **8** can be traced in mechanistic terms to the transient intervention of **3–5**. Since **5** is C_2-symmetric, it is irrelevant which enolate is first protonated. However, it is likely that this proton delivery is stereodirected in order to ensure that a minimally strained *cis*-ring junction develops as in **6**. The ensuing aldolization delivers **7** which can experience a Grob-like fragmentation to rid itself of considerable strain.

Diquinane **9** presumably arises by initial *cis*-addition of **2** to **1** with formation of **10** (Scheme 2). If the obligatory boat-like[6] Cope transition state is adopted, the *meso*-dienolate **11** is reached and the two fused cyclopropane subunits are inextricably locked in a *cis*-relationship. The ultimate conversion of **11** to **9** is envisioned to proceed *via* **12** and **13** as before.

The mixed addition of **2** and a second vinyl anion to **1** has established the broader applicability of this process. Subjection of **1** to sequential treatment with one equivalent each of **2** and prop-2-enyllithium gives rise to **16** (Scheme 3), whose stereochemistry was determined by NMR. As expected, the enolate anion in the immediate proximity of the three-membered ring is preferentially protonated, with the result that formation of the diquinane is highly regioselective.

In order to reverse this trend, it is necessary to incorporate a leaving group into the companion nucleophile.[7] Such an example is provided in Scheme 4. The location of the methoxy group in **17** is particularly conducive to its elimination under kinetically controlled conditions. As a result, transannular cyclization now involves attack by the cyclopropyl enolate on the ketone carbonyl generated in this manner (see compound **18**). This reaction trajectory leads to **19** which, like **7** and **13**, is prone to Grob fragmentation. As a consequence, product **20** carried the characteristic ester sidechain.

In summary, the lithiated cyclopropenone acetal **2** has been shown to participate as a building block in the squarate ester-polyquinane cascade. Its role is amenable to control, with rupture of the three-membered ring occurring when fused angularly adjacent to the first-formed product carbonyl, but not otherwise.

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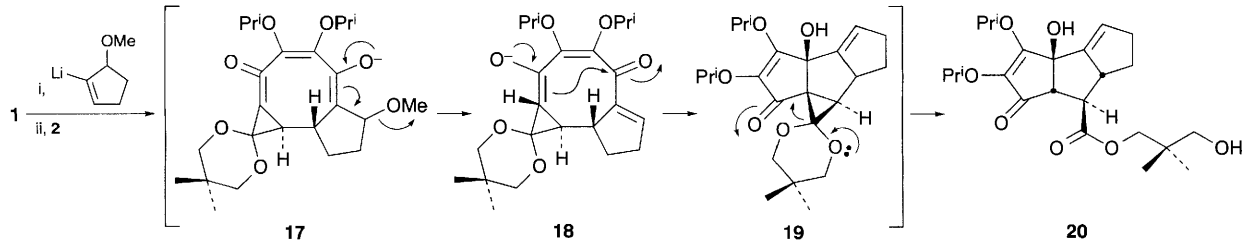

Scheme 4