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USE OF METALATED ENECARBAMATES IN THE SQUARATE CASCADE. DIRECT ACCESS TO HIGHLY FUNCTIONALIZED 2,4-CYCLOOCTADIENONES BY INTRAMOLECULAR INTERCEPTION OF THE MESOCYCLIC DIENOLATES

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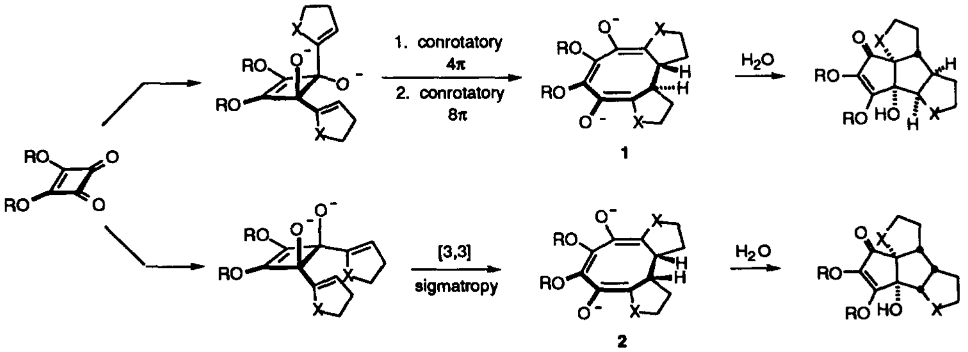
Abstract: A new method for constructing highly functionalized eight-membered ring ketones, fused to one or two additional rings as desired, is reported. © 1997 Elsevier Science Ltd.

Cyclooctane rings annulated to 5- or 6-membered rings and rich in functionality and stereochemical complexity are recognized to be the central structural components of a diverse group of sesqui-, di-, and sesterterpenoids.[1] An impressive variety of methods has been developed in recent years for accessing these intricate carbocycles, the vast majority of which involve assembly of the mesocyclic sector[2] in the latter half of the synthetic scheme. In this note, we outline several applications of a useful new approach that consists of the direct, one-step construction of extensively substituted 2,4-cyclooctadienones by combined reaction of a squarate ester, metalated enecarbamate, and alkenyl- or cycloalkenyllithium reagent. This unusual and highly stereocontrolled process stems from interception of the sigmatropic variant[3] of the squarate ester cascade[4] and involves the tandem formation of four new bonds, three of which are of the carbon-carbon type.

Scheme 1

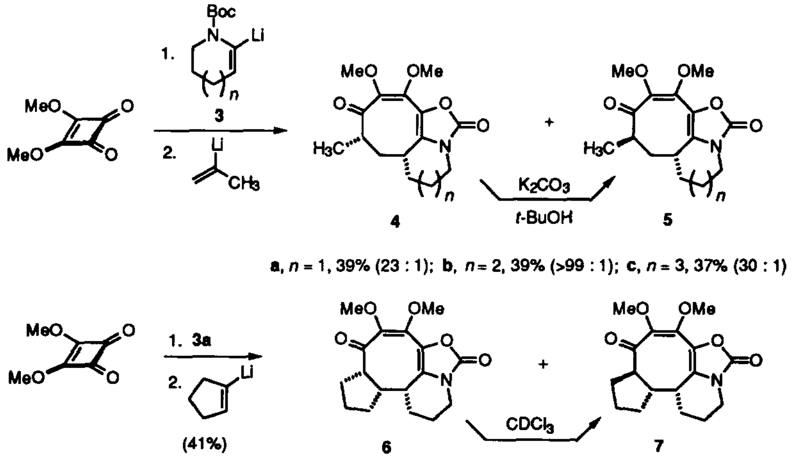


This investigation is an outgrowth of our earlier development of a general synthesis of polyquinanes from squarate esters.[5] When trans 1,2-addition of two alkenyl anions occurs, sequential 4π and 8π electrocylization ensues to deliver trans-fused bis-enolates such as **1** (Scheme1). When the proper adjustment of stereoelectronic factors causes cis addition to be kinetically favored,[3] dianionic oxy-Cope sigmatropy occurs spontaneously to generate cis diastereomers of type **2**. Subsequent protonation results in irreversible ring closure via transannular aldolization. As concerns extension of this mechanistic paradigm into the present context, it was necessary to divert this final, thermodynamically favorable step.

From among the various methods available for preparing enecarbamates,[6] we have utilized the tactic recently reported by Dieter and Sharma. The lithiation to generate **3** (1.5 equiv) was accomplished with *tert*-butyllithium in tetrahydrofuran at -78 °C.[9] Introduction of a molar equiv of dimethyl squarate was followed 1 h later by 2 equiv of 2-lithiopropene and slow warming to room temperature during 12 h (Scheme 2). With the piperidine derivative **3a**, a chromatographically inseparable 23:1 mixture of **4a** and **5a** was isolated. This diastereomeric ratio is a reflection of kinetic control since subsequent treatment of the mixture with K_2CO_3 in *tert*-butyl alcohol resulted in a pronounced increase in the proportion of **5a** (distribution now 1:10). Stereochemical assignments were made possible by virtue of the high crystallinity of **5a**, whose three-dimensional structure was confirmed by x-ray diffraction. The transformations involving **3b** and **3c** were equally diastereoselective. Comparative NOE studies on **4a-4c** established that these products shared in common an α-methyl substituent.

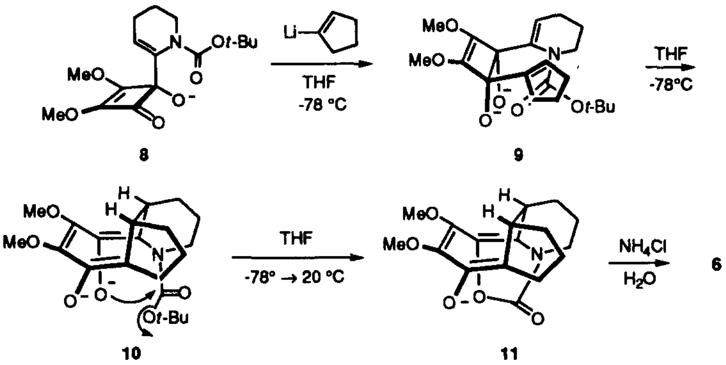
The combined action of **3a** and cyclopentenyllithium on dimethyl squarate delivered a mixture of **6** and **7** in highly variable ratios. Any given product distribution was shown to be intimately linked to the time elapsed after quenching and the speed with which the products were removed from the aqueous environment. In this instance, the epimerizability of **6** is especially facile. For example, dissolution of **6** in $CDCl_3$ results in conversion to a 1:3 mixture of **6** and **7** within 5 min.[8] The trans,cis arrangement of the three contiguous stereogenic centers in **7** was deduced by NOE measurements. The stereochemical features resident in the kinetic product **6** hold

Scheme 2



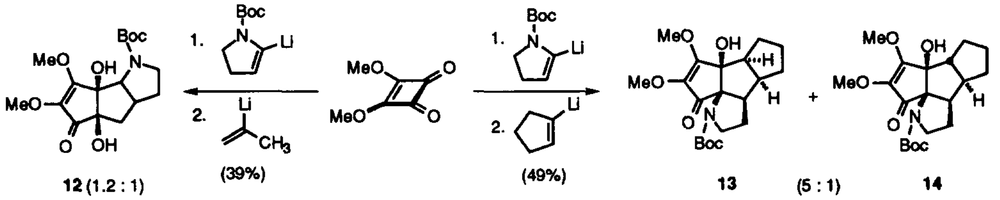
considerable mechanistic significance. Presumably, as a direct consequence of chelation, cyclopentenyllithium adds to **8** from the syn direction to generate **9** (Scheme 3). The combination of charge-charge repulsion and strain energy present in **9** is conducive to rapid oxy-Cope rearrangement at low temperature. With arrival at **10**, two cis hydrogens have been set; warming to room temperature brings on the intramolecular acylation to generate **11**. This conformationally inflexible intermediate undergoes protonation from the exterior of the tub, thereby delivering the all syn stereoisomer **6**. In those cases where 2-propenyllithium is involved, the same mechanism is presumably followed, with the resultant production of **4** under kinetic control.

Scheme 3



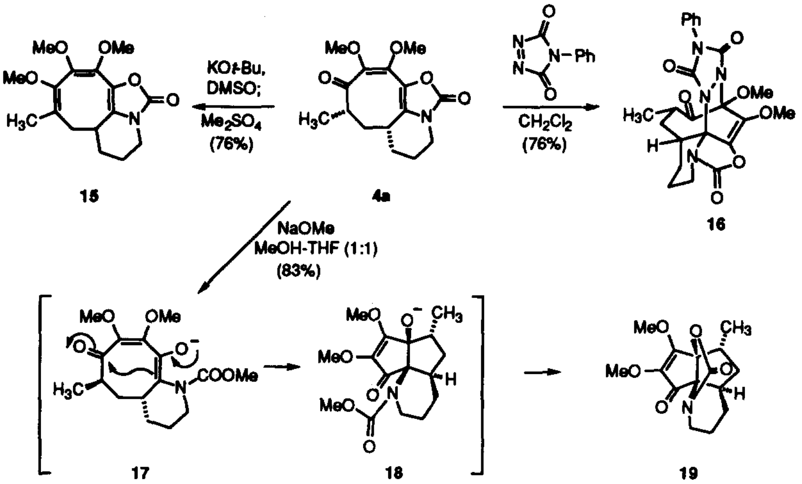
The cyclization associated with the **10** → **11** conversion will operate only if the nitrogen-containing ring is sufficiently large and flexible. Once the pyrrolidine level is reached (see Scheme 4), the bis-enolate is no longer intercepted in this manner and azapolyquinanes such as **12-14** are produced. Although all of the yields reported are moderate, control experiments have shown that the lowered levels of product formation are due predominantly to the efficiency of the enecarbamate metalation step and are not intrinsic to the cascade. No attempt was made to enhance yields by making stoichiometric adjustments different from the above.

Scheme 4



A few transformations of **4a** have been briefly examined. As illustrated in Scheme 5, the O-methylated cyclooctatriene **15** could be obtained in good yield by conventional means.[9] Although quite unreactive to most dienophiles, [4+2] cycloaddition to **4a** did occur in the presence of N-phenyltriazolinedione. The overwhelming π-facial diastereoselectivity of the process gave rise to **16** as corroborated by X-ray crystallography. When dissolved in methanol and THF (1:1) containing sodium methoxide, **4a** underwent efficient rearrangement to **19** (83%), an isomer in which five

Scheme 5



hetero atoms are bonded to the same cyclopentene. This interesting chemical transposition is made possible because the release of enolate anion **17** triggers transannular aldolization and generation of **18**. In turn, the proximity factors that now develop allow for reintroduction of a cyclic carbamate moiety.

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