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SEQUENCED REACTIONS INVOLVING SQUARATE ESTERS. THE FIRST SUGGESTION THAT HELICAL EQUILIBRATION WITHIN THE ADVANCED OCTATETRAENE INTERMEDIATE IS RESPONSIBLE FOR STEREOCHEMICAL CONTROL

Leo A. Paquette,* Julien Doyon, and Lung Huang Kuo

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

Abstract: When a chiral (racemic or nonracemic) alkenyl anion is added to a squarate ester, an approximate 1:1 mixture of diastereomers results. Further reaction with a second alkenyl anion leads only to a single product, a finding compatible with helical equilibration at the 1,3,5,7-octatetraene stage of the cascade.

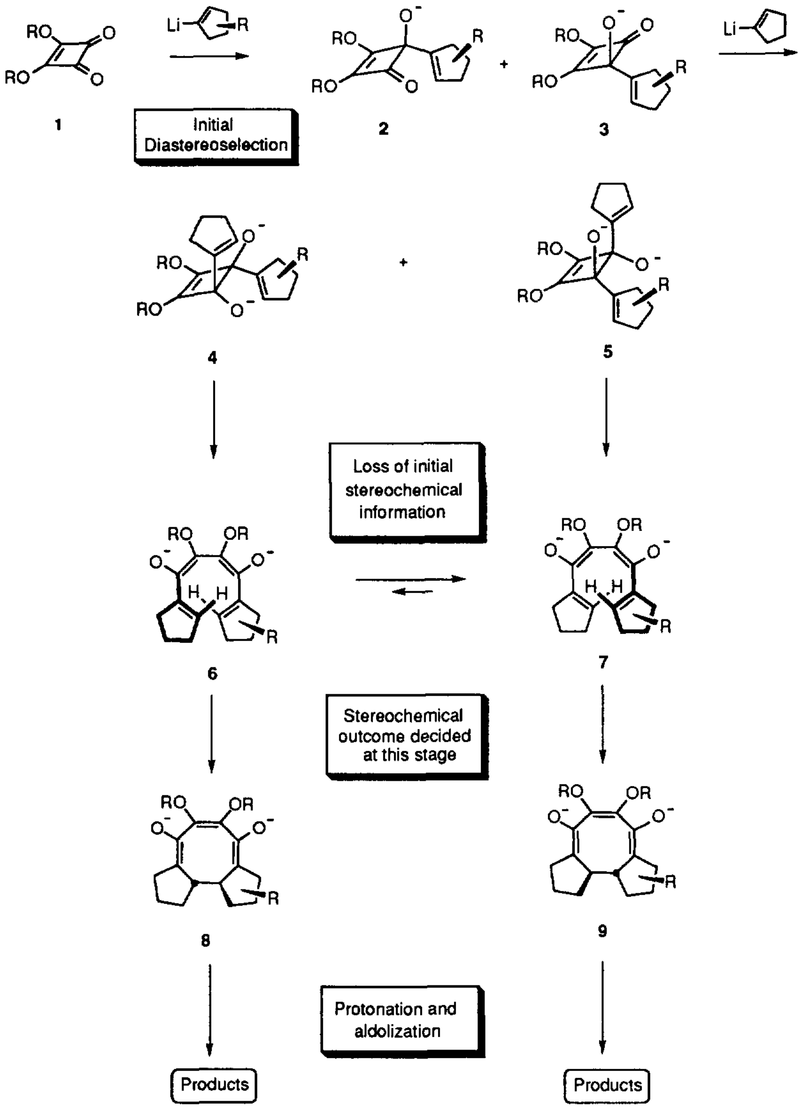
Recently, Negri discovered that twofold addition of an alkenyl anion to a squarate ester triggers a cascade of chemical events that culminates in the direct formation of polycyclic products.[1] Structural complexity develops rapidly. When *achiral* reagents are involved, as many as five continuous stereogenic centers can be generated. Notwithstanding this substantial embellishment of chirality, the extent of substitution deployed earlier has proven insufficient to allow proper delineation of that segment of the cascade which is controlling of product stereochemistry.[2] We have more recently gained important new insight into this complex question and report here the discovery of an unprecedented means for the regulation of relative or absolute configuration.

An overview of the stages of stereoselection preexistent in this remarkable process is presented in Scheme 1. Monoaddition of a *chiral* vinyl anion to **1** can be expected to give rise to the two diastereomeric alkoxides **2** and **3**. In most examples, the **2**:**3** ratio is unlikely to be very disparate because of the near-perfect planarity of the four-membered ring and the very close similarity of the diastereomeric attack trajectories. The stereochemical information inherent in **2** and **3** is carried forward through the dialkoxides **4** and **5** to the conformationally interrelatable tetraenes **6** and **7**. This is so because the electrocyclic cleavage of **4** and **5** is strictly modulated by those electrostatic effects that cause outward rotation of the oxido ions to be strongly favored.[3] Conrotatory cyclization of rotamers **6** and **7** would then lead to **8** and **9** in direct proportion to the original distribution of **2** and **3**.

As will be demonstrated, the stereochemical outcome of the cascade is seemingly not determined at step 1, but dictated instead by rapid equilibration of the helical bisenolates **6** and **7**, which undergo kinetically controlled ring closure from the less sterically congested of the two coiled conformers. The compelling stereochemical tests reported herein bring to light the first examples of helical equilibration as a control element in unimolecular structural reorganization.[4]

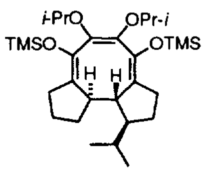
Diisopropyl squarate was initially treated with a molar equivalent of enantiopure (*S*)-3-isopropylcyclopentenyllithium[5] at -78 °C in THF. Quenching of small aliquots of the resulting monoadduct solution afforded a 1:1 mixture of α-hydroxy ketones corresponding to **2** and **3** in high yield.

Scheme 1

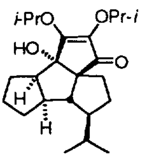


Subsequent addition to the original reaction mixture of excess cyclopentenyllithium (-78 °C → rt) and subsequent quenching at -50 °C with Me_3SiCl and $(C_2H_5)_3N$ gave rise to **10** (64%) as the only observed product. *This observation confirms the lone existence of the late-stage intermediate **9**.* Ensuing treatment of **10** with $(n\text{-Bu})_4N^+F^-$ under aqueous workup conditions resulted in more rapid protonation at the sterically less hindered enolate center in **9** to deliver **11** (93%). The structural assignments to both **10** and **11** rest on the corroborative 2D NMR analysis of the ozonolysis product **12** (COSY, HETCOR, and NOESY at 300 and 500 MHz).

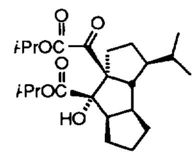
A very similar reaction profile was exhibited by (±)-3-*tert*-butylcyclopentenyllithium,[6] although the increased steric bulk of this substituent resulted in lower efficiency. Following production of the



10



11



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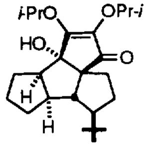
monoadducts corresponding to **2** and **3**, recourse to cyclopentenyllithium as the second anion afforded uniquely **13** (49%), whose structural features were ascertained by X-ray crystallographic analysis. Alternative use of 2-propenyllithium as the co-reagent also resulted in adherence to the mechanistic model and furnished the angular triquinane **14** (23%) and its linear equivalent **15** (6%), the relative stereochemistries of which were established by means of confirmatory NOE and COSY studies.[7] Protonation at the methyl substituted carbon of the bisenolate occurred more rapidly as expected.[2b]



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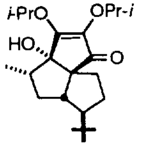

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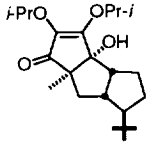

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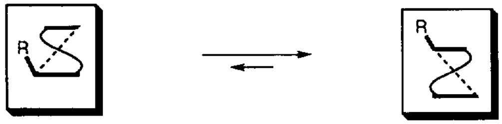
The kinetic bias favoring **7** can be described pictorially as in **A** (corresponding to **6**) and **B** (corresponding to **7**). Quite evidently, the involvement of an isopropyl or a *tert*-butyl group as R on the interior of the coil sufficiently impedes the rate of ring closure that conrotation operates preferably when the substituent is projected outwardly as in **B**. The profound consequence of the ready **A**/**B** interconversion is that the configuration of the R substituted carbon controls the stereogenicity (either absolute as in the *i*-Pr case or relative as in the *tert*-Bu example) developing at the many additional chiral centers (see particularly **11** and **13**).

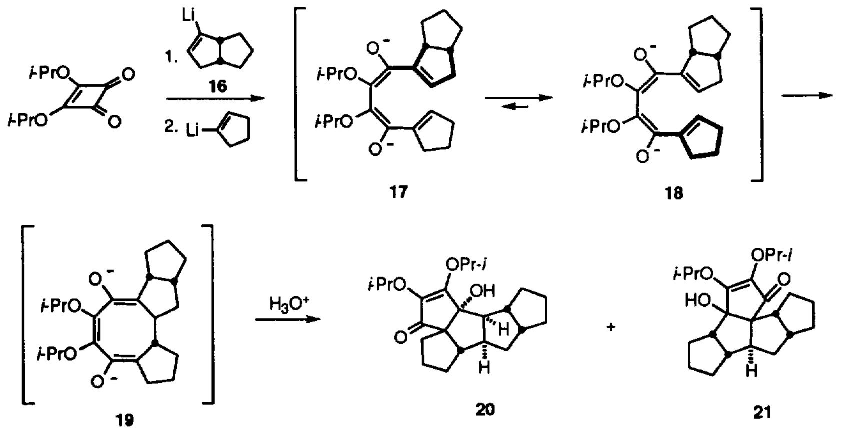


A **B**

On this basis, adherence of the racemic bicyclo[3.3.0]octenyllithium reagent **16** to the same mechanistic paradigm leads to the anticipation that helix **18** (**B** type) will exhibit a faster cyclization rate than **17** (**A** type) (Scheme 2). The diastereoselectivity for the monoaddition of **16** to the squarate was 1.2:1. Recognition that the production of **19** is subsequently favored is derived from the isolation of **20** (27%) and **21** (38%) in addition to 10% of a 1,4-addition product. These pentaquinanes arise from competitive protonation at the two available sites in their common precursor **19**. The high crystallinity of **21** allowed for securing its structural features by crystallographic methods.

In conclusion, the formation of unique bisenolates stereochemically related to **9** suggests that only one of the two diastereomeric 1,3,5,7-octatetraenes formed subsequent to conrotatory

Scheme 2



opening of the co-produced dialkoxides **4** and **5** undergoes electrocyclization. The helical intermediates, which differ in the handedness of their coiling as in **A** and **B**, must therefore mutually equilibrate more rapidly than they undergo ring closure.[4] The latter step is rate-determining, influenced strongly by steric effects, and totally determinative of product stereochemistry. All of the stereochemical information associated with the earlier steps is lost during the pre-equilibration of **6** with **7**, only to be decided in favor of **9** during cyclooctatriene formation. More intricate aspects of this remarkable and unique means for chirality control are under active investigation.[8]

References and Notes

(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) (a) Morwick, T.; Doyon, J.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 2369. (b) Paquette, L. A.; Morwick, T. *J. Am. Chem. Soc.* **1995**, *117*, 1451. (c) Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799. (d) Wilson, P. D.; Friedrich, D.; Paquette, L. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1351.

(3) (a) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (b) Thomas, B. E., IV; Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165.

(4) To prove equilibration requires either high yields of a single product or preferably independent demonstration that the sterically more crowded helix, when purposely formed, also gives rise to the same product rather than uncharacterizable materials. Due to the many individual steps associated with the cascade, overall reaction efficiencies usually peak at the 50-70% level. However, it has recently proven possible to separate a pair of diastereomeric monoadducts and to demonstrate that these compounds lead to the identical polycyclic product when subjected to further reaction (Kuo, L. H., unpublished results).

(5) Prepared by treating the bromide [Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.* **1991**, *56*, 6199] with 2 equiv of *tert*-butyllithium in THF at -78 °C.

(6) This cyclopentenyl anion was accessed by carbomethoxylation of 2-*tert*-butylcyclopentanone [Chan, T. H.; Peterson, I.; Pinsonnault, J. *Tetrahedron Lett.* **1977**, 4183], followed by NaBH$_4$ reduction, dehydration (MsCl, Et$_3$N; DBU), saponification, and brominative decarboxylation according to reference 5.

(7) The 300 MHz ^{1}H NMR spectra of these isomers in CDCl$_3$ display other distinguishing features as well. For example, while the methyl substituent in **14** appears as a doublet ($J = 7$ Hz) at δ 1.17, that in **15** is seen as a singlet at δ 1.12.

(8) We thank the National Science Foundation for support of this research.

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