# Cascade Rearrangements Following Twofold Addition of Alkenyl Anions to Squarate Esters

**Leo A. Paquette**

Evans Chemical Laboratories, The Ohio State University,
100 West 18th Avenue, Columbus, Ohio 43210, USA

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The double 1,2-addition of alkenyl, cycloalkenyl, and alkynyllithium reagents to squarate esters constitutes a very expedient method for rapidly increasing structural complexity with formation of polycyclic end products. The simple one-pot process is amenable to regioselective operation, stereochemical control, self-immolative chirality transfer, 1,5-asymmetric induction, and chemical modulation.

**Contents**



## 1. Introduction

Squaric acid (**1**), the synthesis of which was first reported in 1959[1], is a dibasic 1,2-cyclobutenedione ($pK_2$ = 2.2, $pK_1 \approx 1$). The dianion formed upon ionization is a $(C_nO_n)^{m-}$ species **2** whose aromatic character has been exhaustively studied by West[2]. Its dialkyl esters **3**[3][4][5],

*Leo Paquette received his B.S. degree in chemistry magna cum laude from Holy Cross College in 1956 and his Ph.D. from M.I.T. in 1959. After serving as a medicinal chemist at the Upjohn Company from 1959 to 1963, he joined the faculty at The Ohio State University and was promoted to Professor in 1969. Subsequently, he held the Kimberly Professorship in Chemistry (1981–1987) and now is a Distinguished University Professor there (1987–present).*

*Leo was named an Alfred P. Sloan Foundation Fellow in 1965, a Guggenheim Fellow in 1976–1977, a Senior Humboldt Fellow in 1989, and an Awardee of the Japanese Society for the Promotion of Science in 1992. On several occasions he has been honored by the American Chemical Society: Morley Medalist of the Cleveland Section in 1971 and recipient of the Columbus Section Award in 1979, the national Award for Creative Work in Synthetic Organic Chemistry in 1984, the Arthur C. Cope Scholar Award in 1987, and the Ernest Guenther Award in 1992. He was elected to the National Academy of Sciences and presented an honorary degree from his Alma Mater the same year (1984). The Ohio State University presented him with a Senior Research Award in 1980 and its highest honor, the Sullivant Medal, in 1990. He has also been the recipient of many international awards including, most recently, the Centenary Lectureship of the Royal Society of Chemistry and the first France/Belgium Award for Research Excellence.*

*His current research interests focus broadly on the total synthesis of natural and unnatural products, the development of synthetic methodology and catalytic asymmetric methods, and organometallic chemistry.*

**MICROREVIEWS:** This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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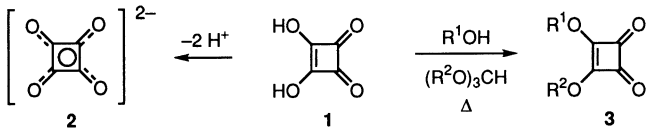
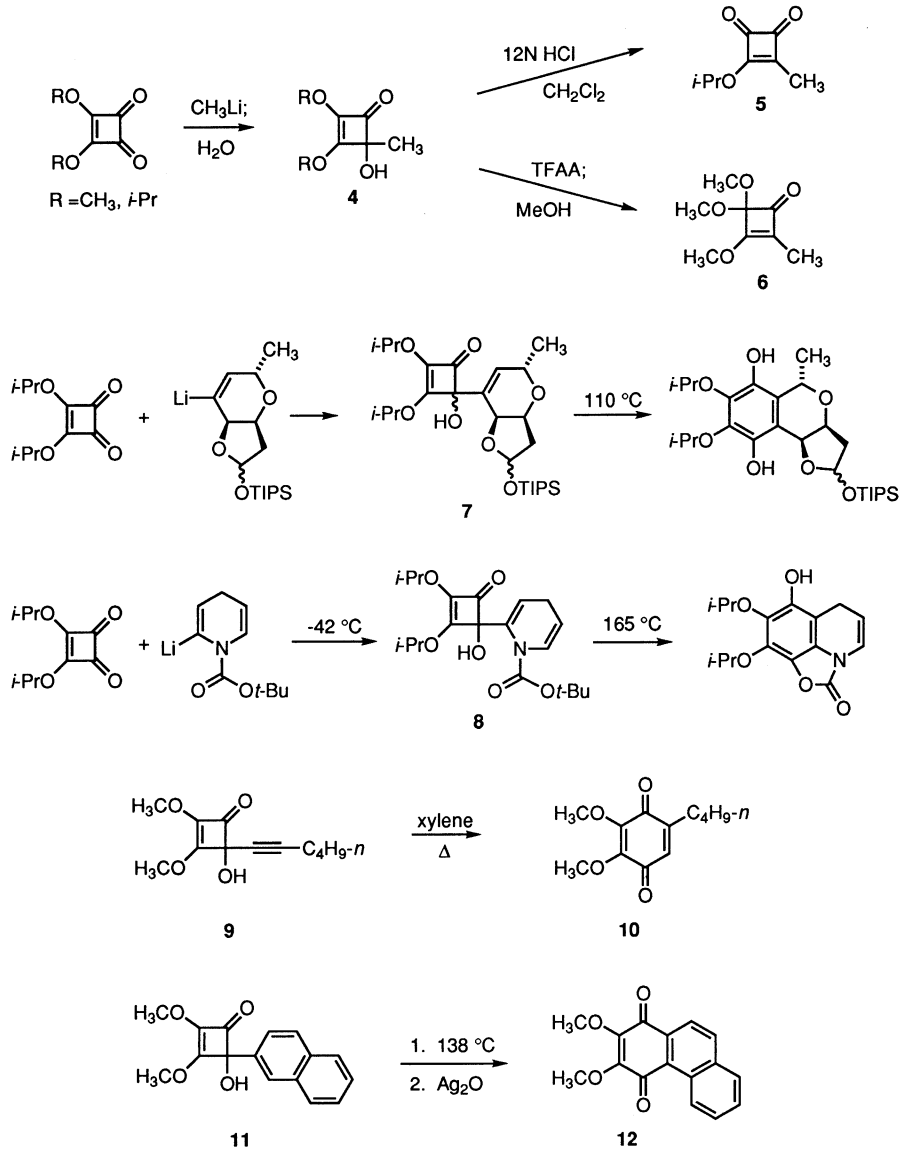
now readily available[6], are widely recognized to be highly strained and extensively oxygenated building blocks having many varied synthetic applications[7][8][9][10].



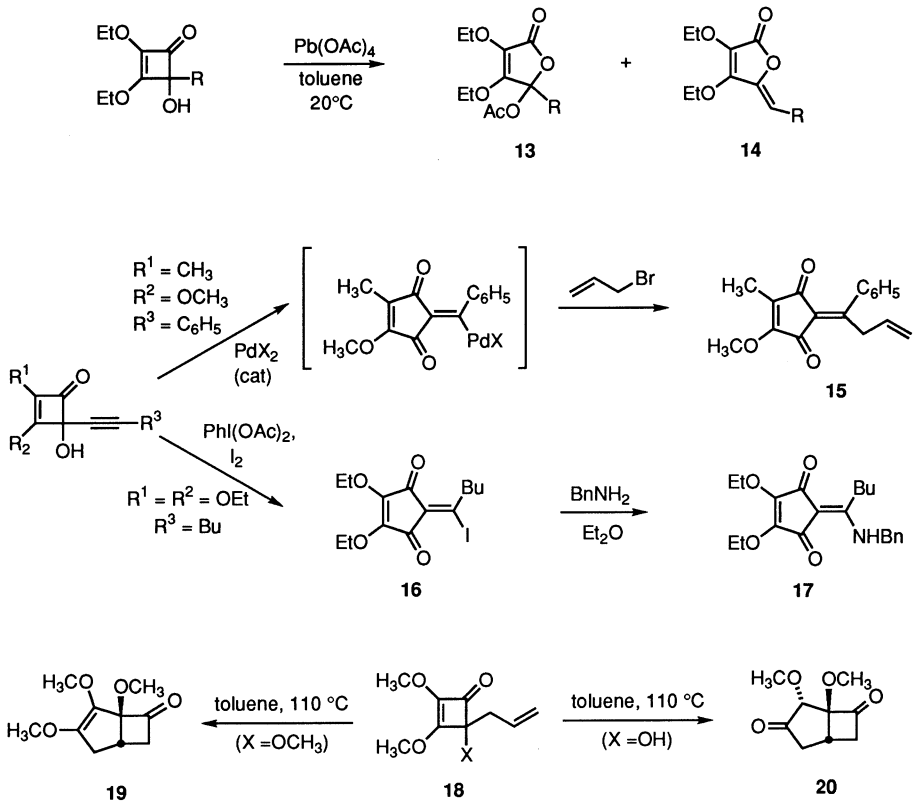

Since squarate esters are electrophilic reagents, many early investigations have been based on the *monoaddition* of an organometallic reagent in advance of further structural change or ring expansion. As shown in Scheme 1, the use of an alkyllithium gives rise to 1,2-adducts such as **4** and provides direct access to semisquarate derivatives **5**[5][11][12] or to cyclobutenedione monoacetals **6**[13]. When the nucleophile is an alkenyl- or cycloalkenyllithium, the resulting carbinols exemplified by **7** and **8** are exceptionally prone to isomerization and are transformed into hydroquinones when heated[14][15]. Recourse to alkenyl- or aryllithiums provides rapid entry to 1,4-quinones typified by **10**[16] and **12**[17]. The success of these unique isomerizations is a function of the ease of ring cleavage with formation of unsaturated ketenes and the readiness with which the cyclization of these intermediates ensues.

The synthetic versatility of these monoadducts is mirrored in a host of other transformations. The reactions illustrated in Scheme 2 are representative. The feasibility of converting carbinols such as **4** into 5-acetoxy-2(5*H*)-furanones **13** and 5-alkylidene-2(5*H*)-furanones **14** with lead tetraacetate has been well documented[18]. The ring enlargement is mediated by the β scission of an oxygen-centered radical and a subsequent 5-*endo* reclosure of the acyl radical so formed. A general route to alkylidenecyclopentenediones

Scheme 1



Scheme 2

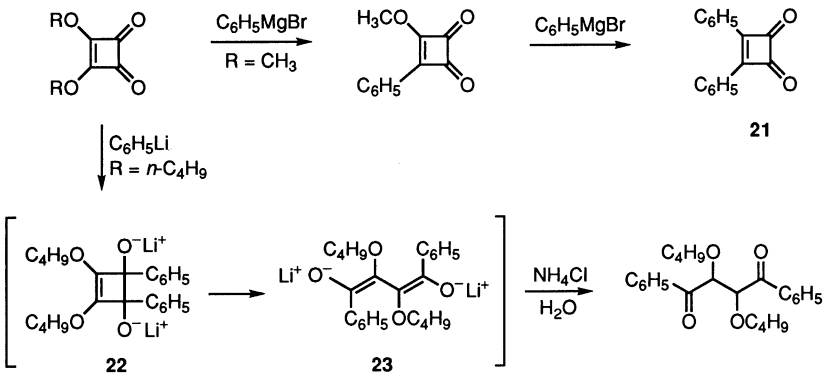



takes advantage of the responsiveness of alkynyl adducts to the action of palladium(II) salts (catalytic quantities)[19] or iodinating agents such as $I_2$/HgO, $I_2$/PhI(OAc)$_2$, or *N*-iodosuccinimide[20]. Thermolysis of allylated adducts **18** leads usefully to either **19** or **20** depending upon the nature of the X substituent[21]. The latter rearrangements are believed to proceed via electrocyclic ring opening to a vinyl ketene capable of intramolecular [2 + 2] cycloaddition to the allyl double bond[22].

The *twofold addition* of organometallics to squarate esters had not been extensively examined at the time that our studies were initiated. Several factors undoubtedly contributed to this end result. Firstly, early reports made evident the contrasting behavior of Grignard reagents and organolithium nucleophiles. In the first instance, 1,4-addition is heavily favored at both stages such that disubstituted cyclobutenediones (e.g. **21**) are formed (Scheme 3)[4][5][23]. Lithium reagents prefer to add 1,2 and generate dioxido intermediates (e.g. **22**), which undergo ring opening cleanly to give unstrained dienolates exemplified by **23**. Ensuing protonation delivers the corresponding 1,4-diketone[24][25].

When 2 equiv. of vinyllithium are added to (benzocyclobutenedione)tricarbonylchromium, the double addition occurs in *cis* fashion because of steric constraints[26]. Di-

Scheme 3



anionic oxy-Cope rearrangement[27] now becomes the kinetically favored ring opening pathway and makes possible access to a variety of benzocyclooctenedione and benzoannulated tetraquinane derivatives[28].

## 2. Mechanistic Alternatives

### 2.1. *trans* Addition and the Electrocyclic Reaction Channel

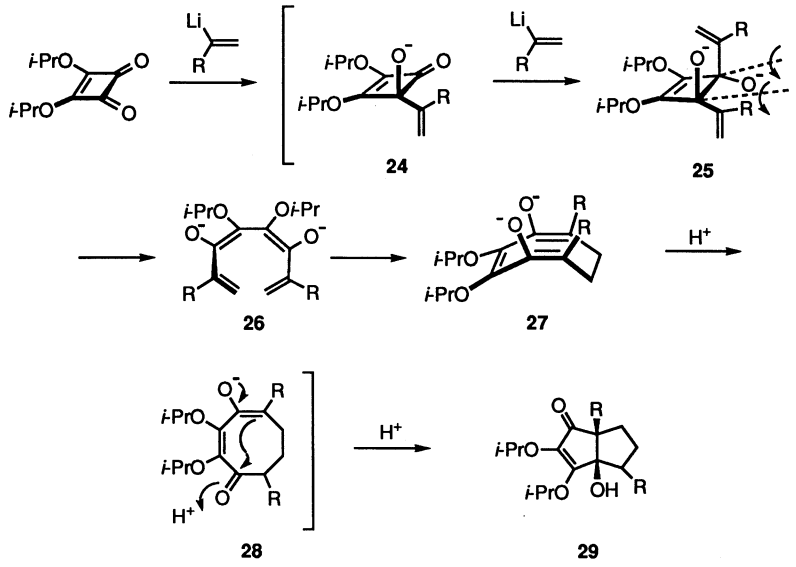
Twofold 1,2-addition of an alkenyl anion to a simple squarate ester can proceed in principle by way of two stereochemically distinctive reaction pathways. If steric factors exert their customary influence, the second nucleophile would be expected to attack from the π surface opposite to that initially utilized (Scheme 4).

This directionality issue holds importance because the conversion of **24** into **25** intiates a distinctive series of chemical events. It is immediately apparent that the alkenyl termini in **25** are too remote from each other to interact. However, the doubly-charged character of this intermediate and its highly strained nature work in unison to facilitate 4π conrotatory opening. Although two conrotatory motions are possible, theory teaches that the donor character of the oxido anions in **25** should give rise to a very large kinetic preference for the outward rotation of these atoms[29]. If this trajectory is adopted, dienolate **26** will be produced in a helical conformation ideally suited for yet another (now 8π) conrotatory electrocyclization[30]. Ultimately, protonation of **27** would provide **28**, transannular aldolization in which would generate **29**.

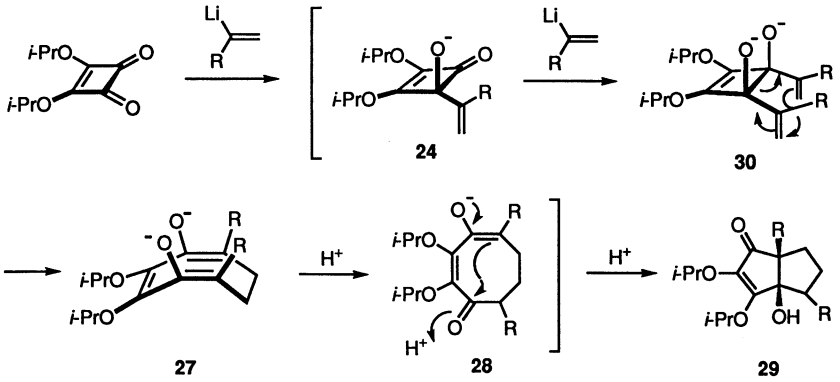
### 2.2. *cis* Addition and the Sigmatropic Pathway

If *cis* addition were to materialize instead, **30** would now necessarily be involved (Scheme 5). Without doubt, this intermediate would undergo [3,3] sigmatropy very rapidly from its boat conformation[31][32] to deliver **27** somewhat more directly. The eventual production of 29 is significant in that it signals that 25 and 30 are inadequately substituted to distinguish between the two mechanistic options on stereochemical grounds. This becomes possible when the

Scheme 4




Scheme 5



terminal carbons of the alkene functionality carry additional groups.

At this point, one must be made aware of yet another major stereochemical feature that further distinguishes Scheme 4 from Scheme 5. When *cis* addition operates, as is generally observed when chelation control is possible (see below), product stereochemistry is immediately established in the very early step that gives rise to **30**. This is because the ensuing dianionic oxy-Cope rearrangement concertedly transmits all structural information resident in **30** directly into the final product.

In contrast, the stereochemistry inherent in *trans*-dialkoxide **25** is subject to being lost if the derived helical (and therefore chiral) polyolefin **26** were to experience rapid equilibration with the coil of opposite pitch. Furthermore, if the rate-determining step is associated with the conrotatory closure of such helices, an entirely different control element would gain importance. More specifically, that coil, experiencing the minimal steric impedance to cyclization would give rise to the major (or exclusive) product.

### 2.3. 1,4-Addition of the Second Nucleophile

Although *trans* addition of two alkenyl anions (either the same or different) is the customarily dominant reaction, the second step has occasionally been found to proceed in a 1,4 manner to a limited extent. When such an event occurs, the resulting **31** isomerizes in a manner parallel to that adopted by **25** and leads via **32** to the doubly charged cyclooctatriene **33** (Scheme 6). The consequence of protonating **33** is to pass via **34** to **35**. A distinctive feature of the operation of 1,4-addition is formation of an α-ketol polyquinane product. The events outlined in Schemes 4 and 5 deliver multicyclic β-hydroxy ketones instead. In all cases, structural complexity is significantly enhanced in a single laboratory operation.

## 3. Generation of Multiple Stereogenic Centers from Achiral Precursors

### 3.1. The Parent Cascade

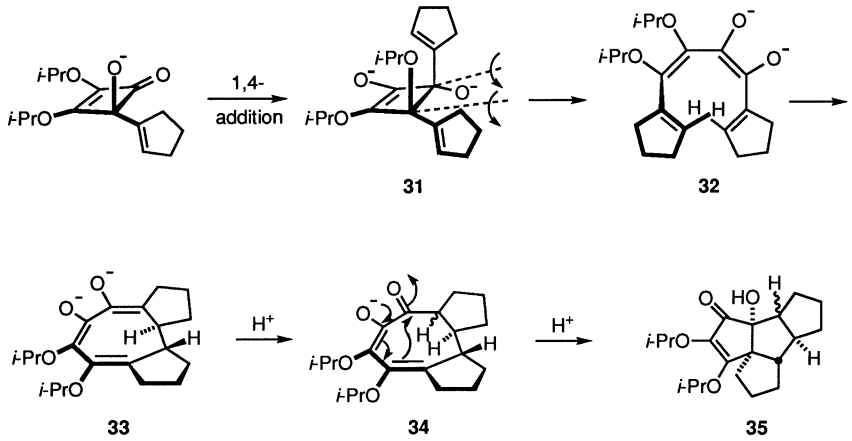
Initial feasibility studies involved the addition of 2 or more equivalents of a common alkenyl anion to **36** in order to maintain symmetry as long as possible in the several intermediates involved[33]. It quickly became apparent that a strong interdependency exists between the efficiency of the reaction cascade and the locus of substitution within the alkenyllithium reagent (Scheme 7). If the conversion to **37** with vinyllithium is regarded as the standard, the presence of an α-methyl group as in 2-propenyllithium is particularly beneficial. Although the level of substitution resident in **37** and **38** remains inadequate to determine mechanistic routing, the high yield associated with formation of **38** requires that all preceding steps proceed almost quantitatively.

Use of excess cyclopentenyllithium allows for the precise definition of mechanistic origin. In this instance, the distinctive stereochemical markers present in the three products (note arrows) reveal **39** and **40** to be the end result of the electrophilic and sigmatropic alternatives, respectively. α-Ketol **41** results from marginally competitive operation of the 1,4-addition process. The cyclopentenyl anion has proven to be distinctive for its elevated propensity for *cis* addition during the second nucleophilic addition step.

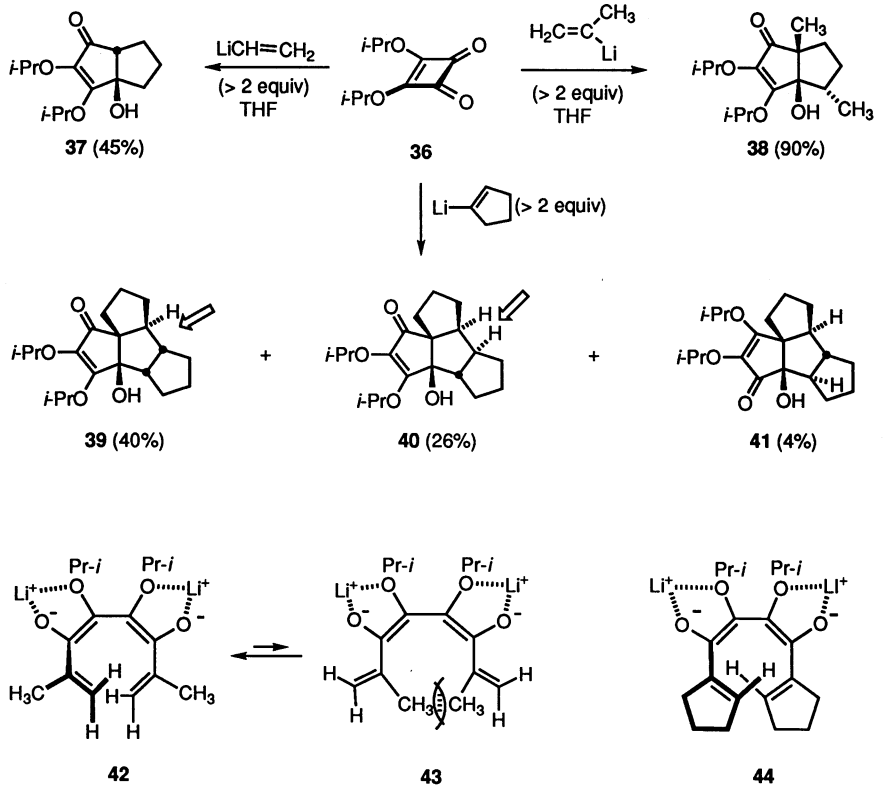
The beneficial effect of substitution on yield has been attributed to preferred adoption of conformer **42** in order to avoid the nonbonded steric repulsion present in **43**. Stereoalignment of the terminal π bonds as in **42** is particularly conducive to ring closure. Along related lines, conrotatory cyclization of **44** necessarily leads to a *trans*-fused product (i.e. **39**), while the sigmatropic variant can only give rise to the *cis* isomer (i.e. **40**).

Entirely comparable advantages surface when two different alkenyllithium species are involved. For the vinyllithium/cyclopentenyllithium and cyclopentenyllithium/*trans*-propenyllithium combinations, an added bonus was un-

Scheme 6

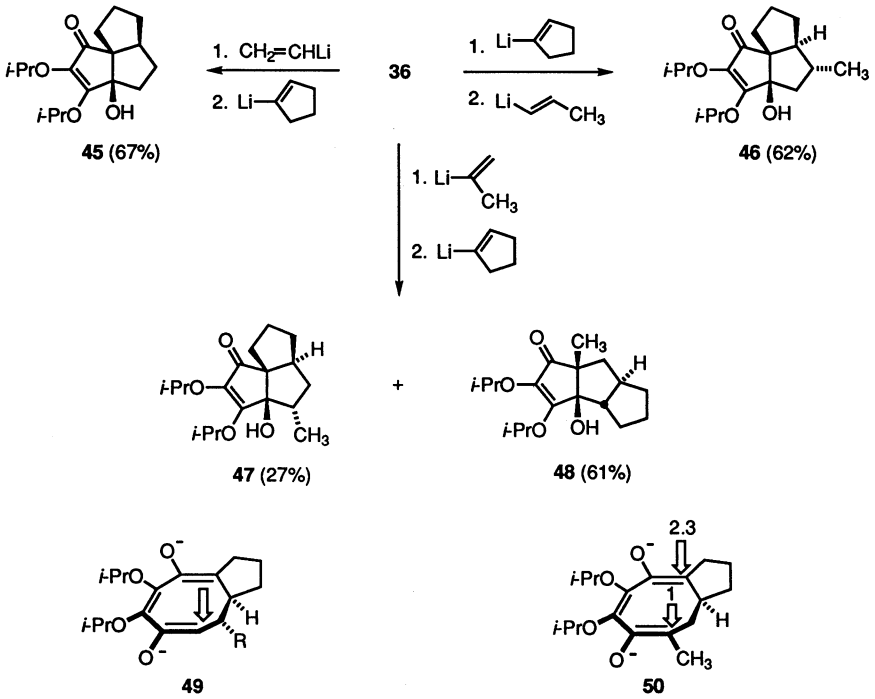


Scheme 7




covered in the form of a highly regioselective aldolization step. Triquinanes **45** and **46** are produced exclusively[33] (Scheme 8). The impressive efficiency of the 2-propenyllithium/cyclopentenyllithium pair must be tempered by the fact that the final ring closure now occurs along dual paths to deliver both **47** and **48**. These findings are consistent with the notion that protonation in **49** (R = H, $CH_3$) operates very predominantly at the less sterically hindered car-

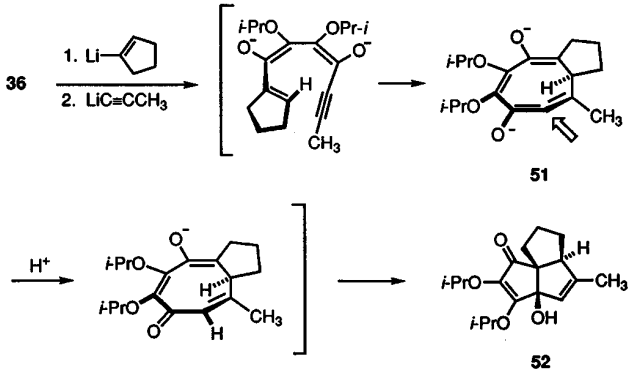
Scheme 8



bon and may come under steric control. Since the two reactive sites in **50** are comparably substituted, both protonation options now operate concurrently.

An alternative ploy devised for fostering regioselective protonation is to increase the reactivity of one enolate center significantly over the other. Productive realization of this plan was achieved by replacing the second alkenyl anion with a lithium acetylide[33c][34] (Scheme 9). Under these circumstances, 8π electrocyclization produces a strained 1,2,4,6-cyclooctatetraene intermediate such as **51**, protonation of which at the cumulenic site leads to substantial relief of ring strain and the ultimate isolation only of **52**. One-step production of unsaturated diquinanes in this fashion exhibits considerable generality. On the other hand, substitution of an allenic anion complicates matters, chiefly because the cumulative π system makes possible the competitive operation of 6π disrotatory cyclizations not possible heretofore[35]. 2,3-Dihydro-5-furanyllithium[36] and lithiated cyclopropenone acetals[37] trigger the normal reaction cascades.

Scheme 9

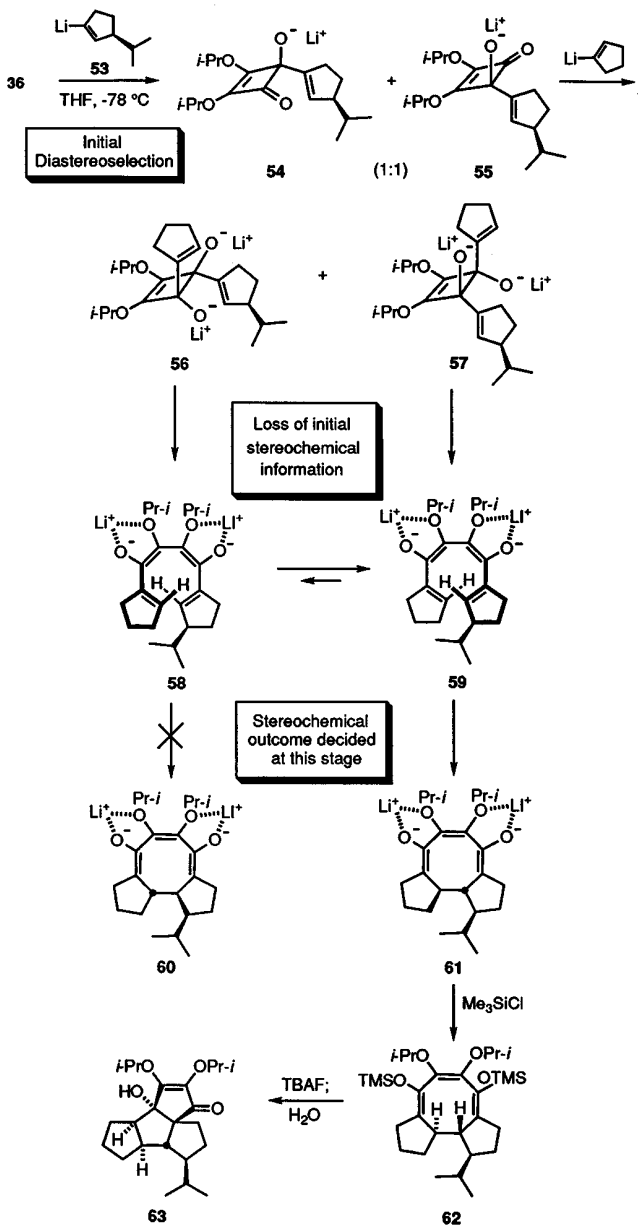



### 3.2. Helical Equilibration and Derivable Stereochemical Control

The first hint that helical equilibration might be operational within advanced octatetraenyl intermediates and ultimately be responsible for product stereochemistry came from an experiment involving enantiopure (*S*)-3-isopropylcyclopentenyllithium (**53**)[38]. As exemplified with **39**–**41**, five contiguous stereogenic centers can be readily established when two achiral reaction partners are involved in the cascade. This number is, of course, increased when one or both nucleophilic reactants contain asymmetric carbons. This situation prevails when **53** is involved.

Treatment of **36** with an equimolar amount of **53** at −78°C generates a 1:1 mixture of diastereomers **54** and **55** in high yield[38] (Scheme 10). The lack of diastereoselectivity in this monoaddition conforms to expectations for nucleophilic attack at carbonyl sites located on a planar platform. Subsequent exposure of the **54/55** mixture to cyclopentenyllithium and then to chlorotrimethylsilane furnished **62** as the sole isolated product in 64% yield! This observation confirms the lone existence of the late-stage intermediate **61**, but provides no insight into the question of whether **60** was formed at all and perhaps preferentially destroyed under the reaction conditions.

Scheme 10

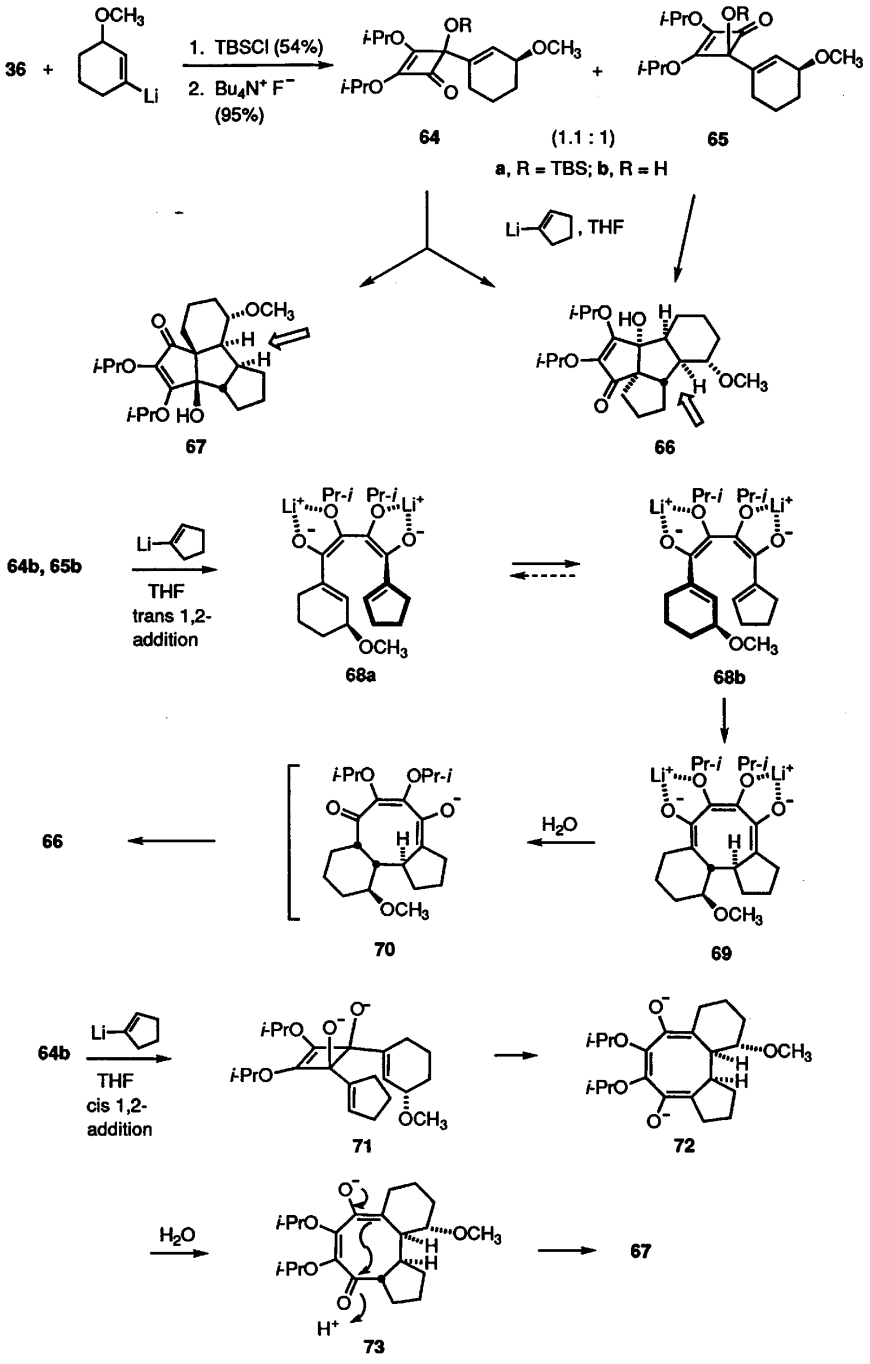



It will be recognized that, if stereochemistry is decided in step 1 and no "leakage" operates during passage through the two conrotatory steps, the electrocyclic model requires that **60** and **61** be formed in approximately equal amounts. Since this eventuality does not materialize, the possibility exists that the presence of an isopropyl group on the interior of helix **58** sufficiently impedes the rate of ring closure that conrotation operates preferably when a substituent is on the outside as in **59**. The profound consequence of a facile interconversion between **58** and **59** is that the configuration of the isopropyl-substituted carbon atom in **53** controls the absolute stereogenicity that develops at the many additional chiral centers in **62** and its hydrolysis product **63**.

The latter transformation proceeds in 93% yield as the result of more rapid protonation at the sterically less hindered carbanion center in the dienolate intermediate.

In order to resolve the outstanding issues, it becomes necessary to separate the diastereomeric monoadducts, to treat each one individually with a common alkenyllithium, and to carry out a careful product analysis. Although the carbinols derived from **54** and **55** were not amenable to chromatographic purification, the silyl ethers **64a** and **65a** proved separable[39] (Scheme 11). Subsequent deprotection of the tertiary hydroxyl group proceeded very efficiently and returned pure **64b** and **65b**. The high crystallinity of **64b** allowed its structural assignment to be corroborated by X-ray diffraction. The squarate cascade was initiated in both monoadducts with cyclopentenyllithium. Indeed, tetracyclic ketone **66** was formed in both experiments. The *trans* relationship indicated by the arrow requires that this common product arise by way of the electrocyclic mechanism. The critical issue here is that the stereochemical features that cause **64b** to be diastereomeric with **65b** are lost during progression through this particular cascade. This eventuality can be so only if **68a** equilibrates fully with **68b** and that the latter helix cyclizes exclusively because of the reduced steric interactions that set in as bonding occurs.

Scheme 11



It is noteworthy that while **65b** leads only to **66**, **64b** gives rise to a 1:1 mixture of **66** and **67**. The *cis* relationship of the hydrogen pair indicated by the arrow identifies this product to be the result of *cis* addition as in **71** with ensuing sigmatropic rearrangement via **72** and **73**. As recognized earlier, this particular reaction channel reliably transcribes the stereochemistry originally present in **64b** into that resident in **67**. Since **65b** exhibits no detectable tendency for entering into *cis* addition in a parallel manner, the relative orientation of the methoxy group has a direct bearing on the π-facial stereoselectivity of nucleophilic capture by the cyclobutenone carbonyl group. The phenomenon of chelation control is accorded specific attention in Section 4.

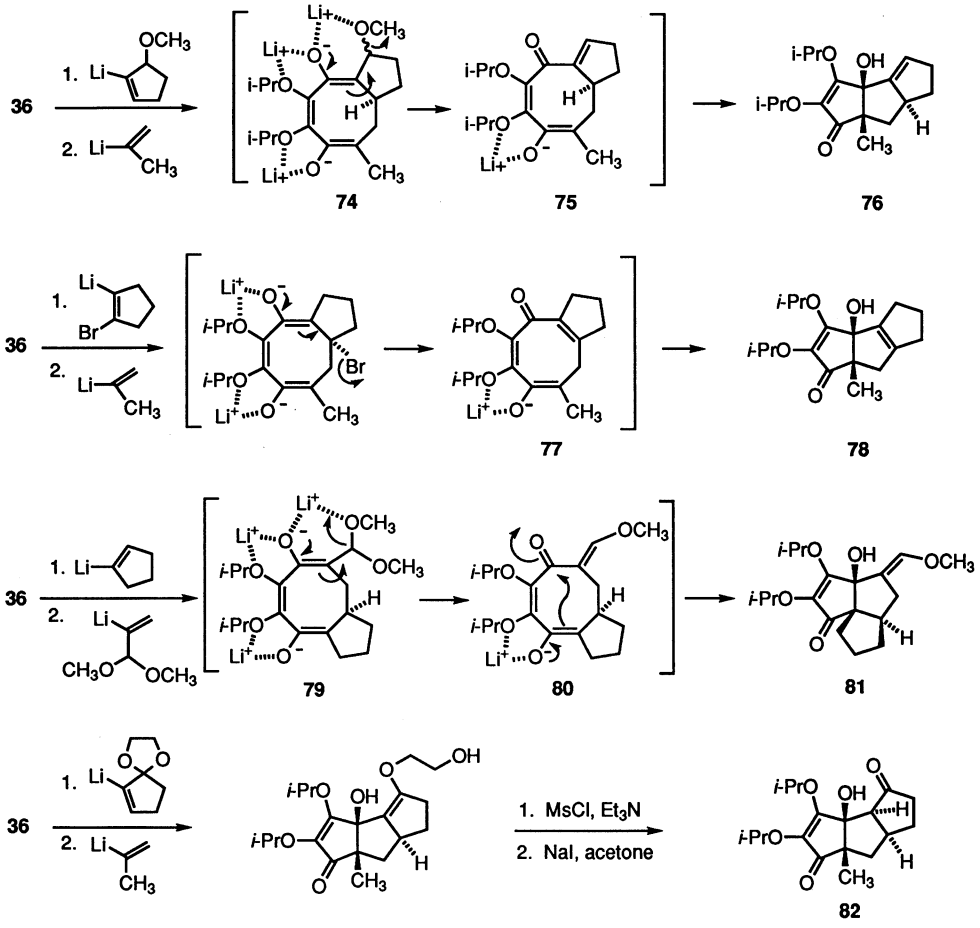
### 3.3. Self-Immolative Chirality Transfer

An entirely predictable means for achieving regioselectivity in the penultimate transannular cyclization has been developed around the principle of kinetically controlled β-elimination. The strategy is based on the proper positioning of a prospective leaving group adjacent to the carbanionic site in one of the alkenyl anions[40]. The methodology is particularly useful for controlling whether a linear or angular triquinane is formed. As seen in Scheme 12, placement of the nucleofuge within a cyclic anion leads ultimately to generation of a linear product. Extracyclic and intracyclic options are possible. Thus, once elimination occurs to generate intermediates such as **75** and **77**, the reacting systems are irreversibly directed to **76** and **78**, respectively. When the leaving group is alternatively positioned on an acyclic reactant as in **79**, the only available option is to proceed via **80** to **81**. The capacity for increasing the oxidation level at the site of elimination is exemplified by the synthesis of **82**.

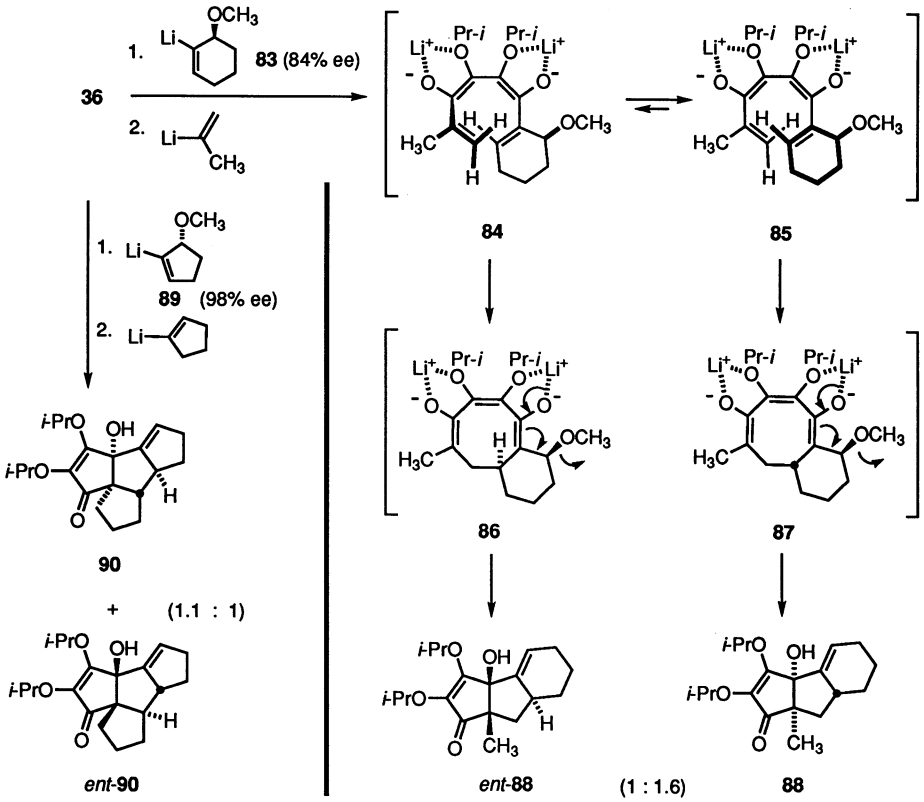
In the specific case of **74**, the methoxy-substituted carbon is stereogenic. Prior developments prompted investigation into the extent to which the chirality at this center might assist in setting the configuration of the methine carbon in this intermediate and, following the generation of **75**, the additional pair of asymmetric carbon atoms in product **76**[41]. The loss of methoxide ion provides a near-ideal forum for assessing chirality transfer during a squarate cascade.

Sequential treatment of **36** with optically active **83** (84% ee) and 2-lithiopropene results in the formation of tricyclic ketone **88** (76% yield) (Scheme 13). Since chiral HPLC analysis indicated that considerable racemization had occurred (now 22% ee), it was concluded that the methoxyl group in the coiled intermediates **84** and **85** resides too far from the bonding sites involved in the 8π conrotatory ring closure to have a major impact. Indeed, the bias was in

Scheme 12



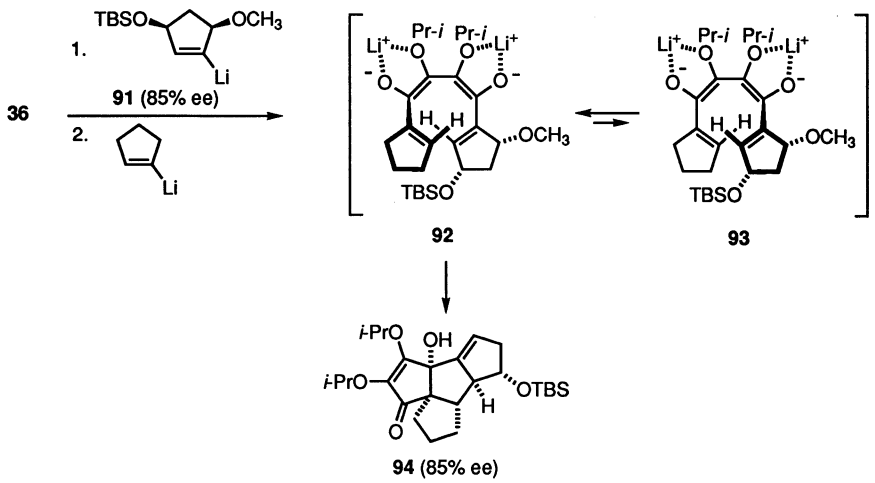
Scheme 13



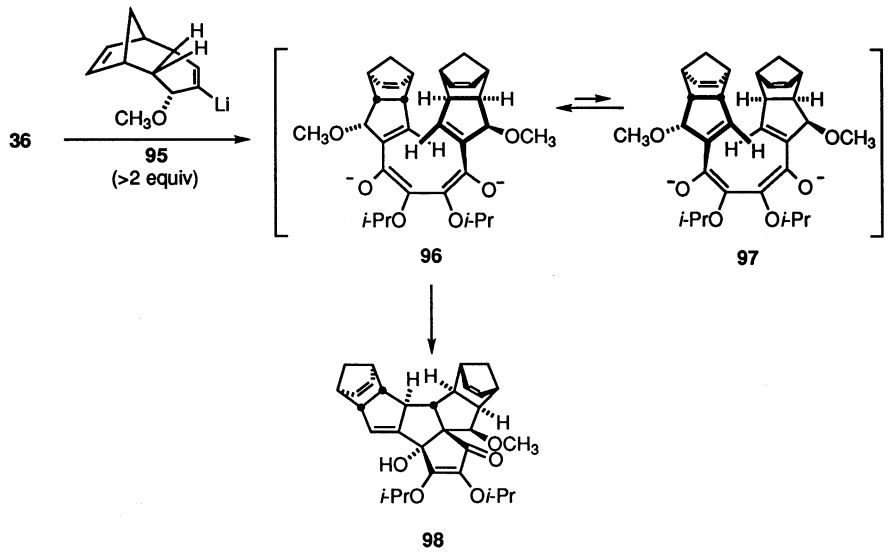

favor of **85** and **87**, but not overwhelmingly so. Companion experiments performed with **89** (98% ee) and cyclopentenyllithium reflected further erosion of helical control. In this instance, almost total racemization materialized.

This situation can be remedied simply by positioning a second substituent nearer to the incipient bonding region. The functionalized cyclopentenyllithium reagent **91** (85% ee) is a good representative example[41]. The two resulting helices of different pitch (Scheme 14) now experience sufficiently imbalanced steric crowding that **92** cyclizes >100 times faster than **93**. Especially revealing is the preservation of stereochemical integrity in **94** (85% ee). Heightened steric control is also attainable with fused norbornenyl systems. Following twofold addition of **95** to diisopropyl squarate, dienolates **96** and **97** are generated in the expectation that **97** will be unable to advance into ring closure because of excessive steric constraints. Rather, equilibration with **96** should occur. The latter helix is arranged such that ring closure operates on the exo surface of both π termini, a structural feature conducive to the ready formation of **98**. Indeed, this one-pot reaction eventuates in the exclusive production of **98**, a compound endowed with 13 stereogenic centers.

Scheme 14



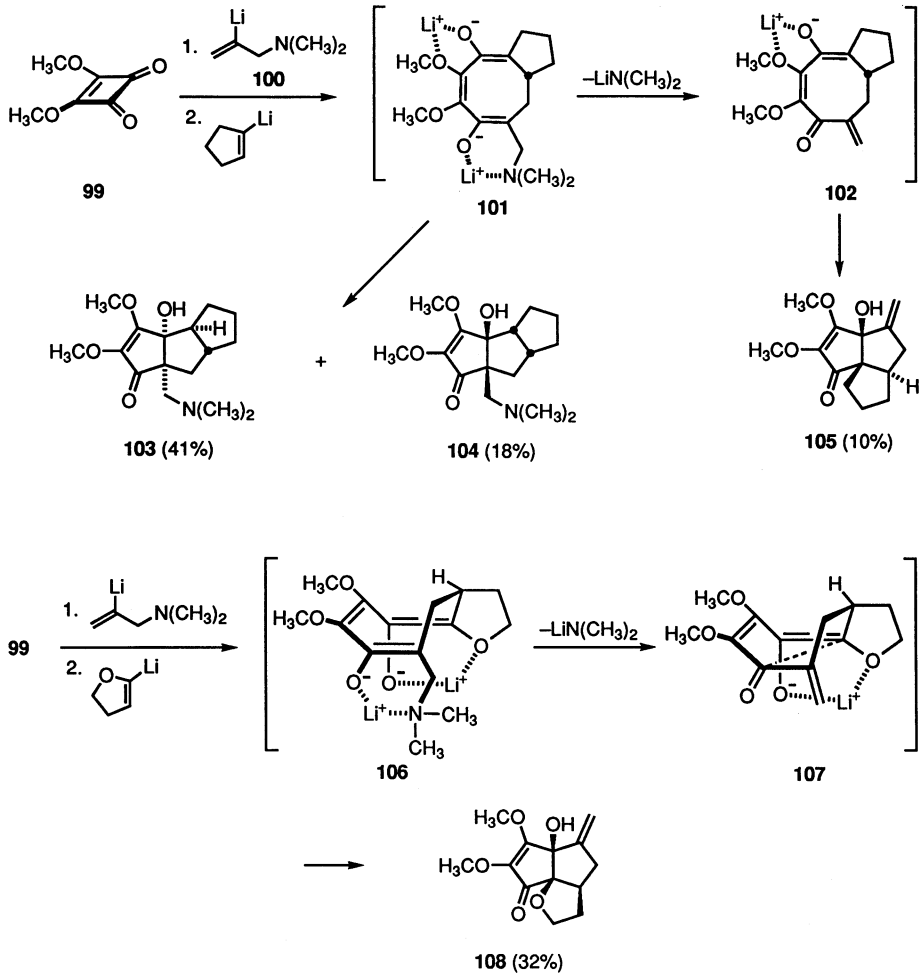
Scheme 14 *(continued)*




### 3.4. 1,5-Asymmetric Induction: Amide Ions as Leaving Groups

The tandem addition of an alkenyllithium and a 2-lithioallylamine to squarate esters has also been systematically examined to determine if amino substituents are capable of serving as nucleofugal controllers of regio- and stereoselectivity. Previously, halogen atoms and oxygenated substituents were shown to be notably effective in this role.

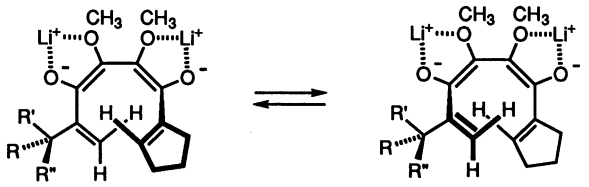
Scheme 15



For amino groups, the extent of elimination has been found to be dependent on the structural features of the companion nucleophile[42]. For example, sequential introduction of 2-lithio-*N,N*-dimethylallylamine (**100**) and cyclopentenyllithium to dimethyl squarate (**99**) generates three triquinanes (Scheme 15). The stereochemical distinction between **103** and **104** stems from the regioselective protonation of **101** from both possible directions. The co-production of **105** is consistent with the capability of **101** to eject lithium dimethylamide. With arrival at **102**, unidirectional ring closure operates to generate the angular triquinane **105** at the 10% level. Substitution of 5-lithio-2,3-dihydrofuran in the second step gives rise to **108** as the only characterizable product. This observation is in accord with the increased basicity of the tetrahydrofuranyl oxygen in **106**, one consequence of which is more effective chelation in the rear sector of the medium-ring dienolate. This added stabilization is construed to provide increased opportunity for the loss of amide ion to materialize with reasonable effectiveness.

Another interesting way of potentially controlling the stereochemically-determining step is to introduce a stereogenic atom at a location close to the cyclization termini as in **109a** and **109b**. The expectation is that the configuration at the chiral center would impact differently on the individual cyclization rates.

While such systems have not yet been examined, attention has been accorded to examples in which the stereogenic center is still further removed and bonded to nitrogen as in



**109a** **109b**

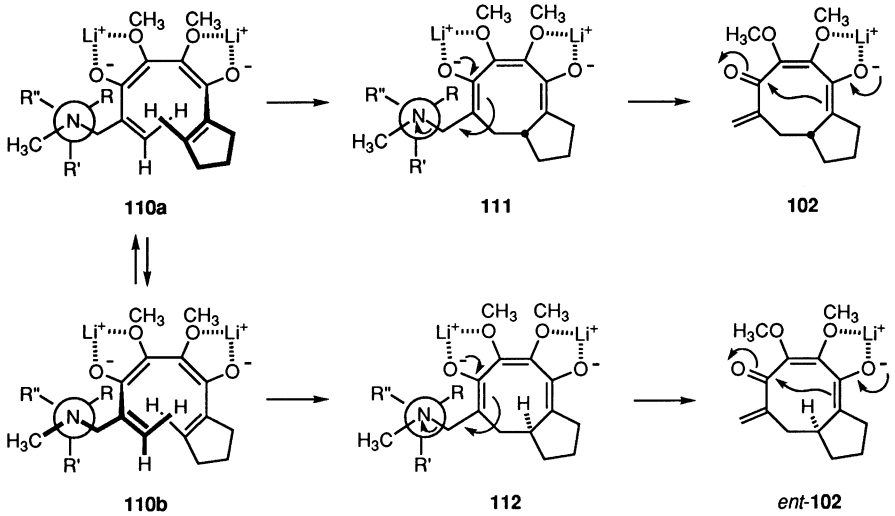
**110a** and **110b**[43]. Competitive conrotation within either of these diastereomeric coiled conformations will be subject to long-range 1,5-asymmetric induction. The absolute configuration of the newly formed methine carbon in **111** and **112** provides a direct measure of this kinetic imbalance, both in magnitude and in direction (Scheme 16). A useful aspect of this particular cascade is the spontaneous loss of the chiral amide ion via β-elimination. Under these circumstances, enantiomers of a single polycyclic ketone would result.

Indeed, a complete dissection of the formation of **108** from **99** has been accomplished[45]. To fully comprehend matters, it is first necessary to appreciate that if the nonracemic lithiated amine is introduced first (condition A), the extent of *cis* addition of the dihydrofuranyl anion is certain to be different than the reverse sequence (condition B). This is because condition A will necessarily generate **113** and **114** in unequal amounts (Scheme 17). This stereoinduction will subsequently be fully transmitted into the products. This is not the situation in condition B, which furnishes only racemic **115** since nucleophilic attack at either carbonyl group from either direction must occur at equal rates. Once **115** has been generated, there remains no opportunity for the enantiopure allylic amine to exert any stereochemical bias at all during *cis* addition.

Distinction between the operation of either the sigmatropic or the electrocyclic cascade requires that the lithiated allylamine be appropriately deuterated as in **116**. The involvement of **116** under both sets of conditions is summarized in Scheme 18. The most striking of these results is the extremely high level of adherence to the electrocyclic pathway under condition A.

Since no *cis* attack of the second anion operates, as revealed by the total absence of **118**, the percent ee necessarily represents the asymmetric partitioning associated with the competitive ring closures of **119** and **120** (Scheme 19). The preferred cyclization of **119** is in line with the conformation

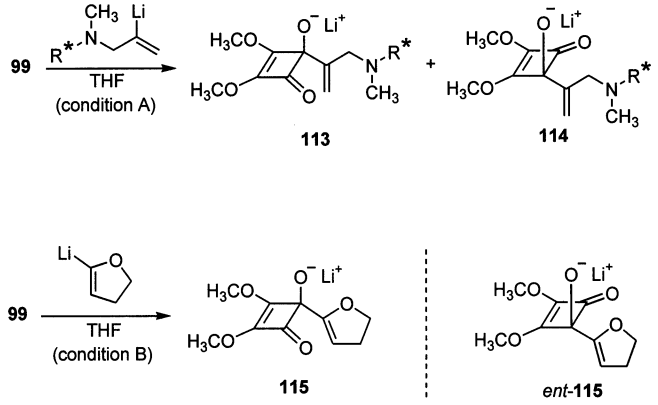
Scheme 16



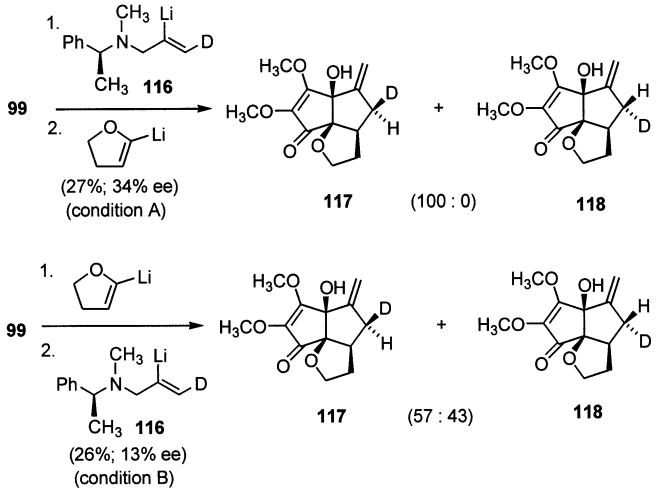
**110a** **111** **102**

**110b** **112** ***ent*-102**

Scheme 17



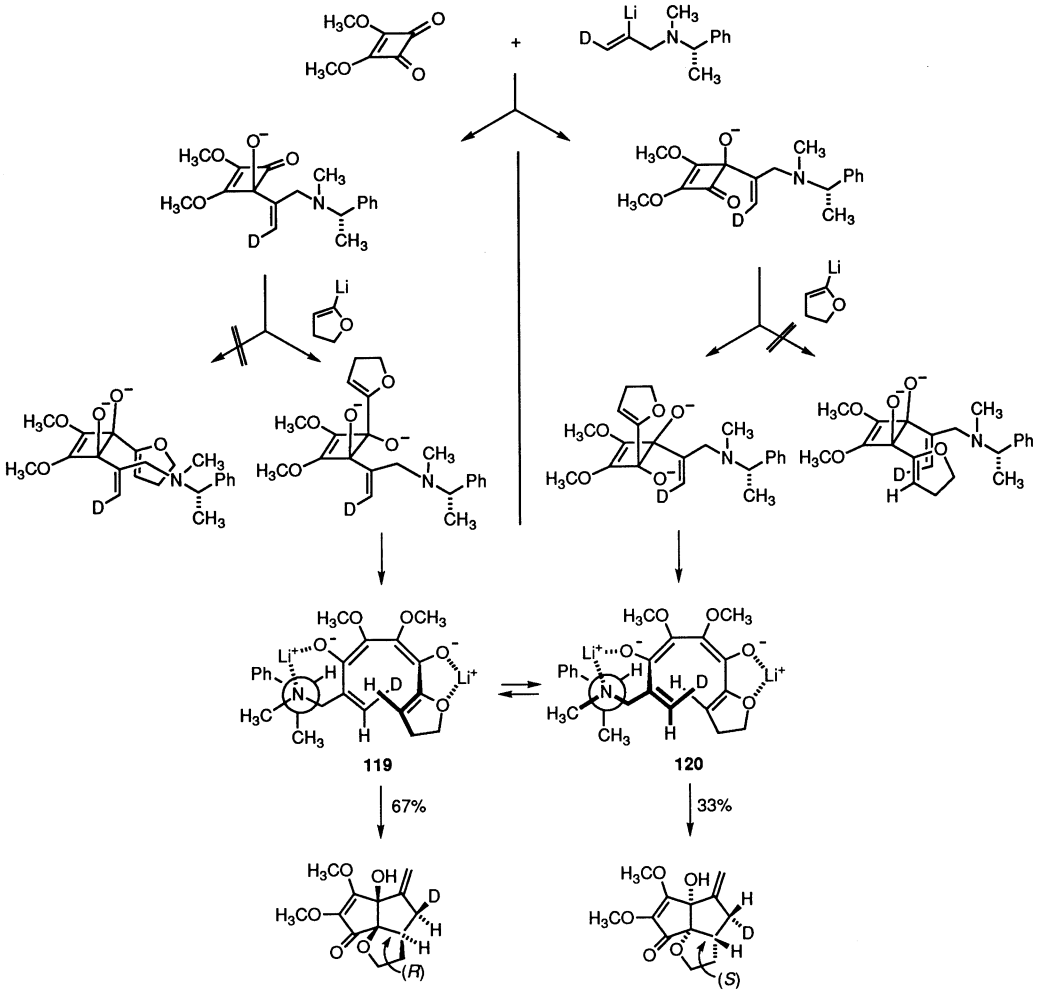

Scheme 18



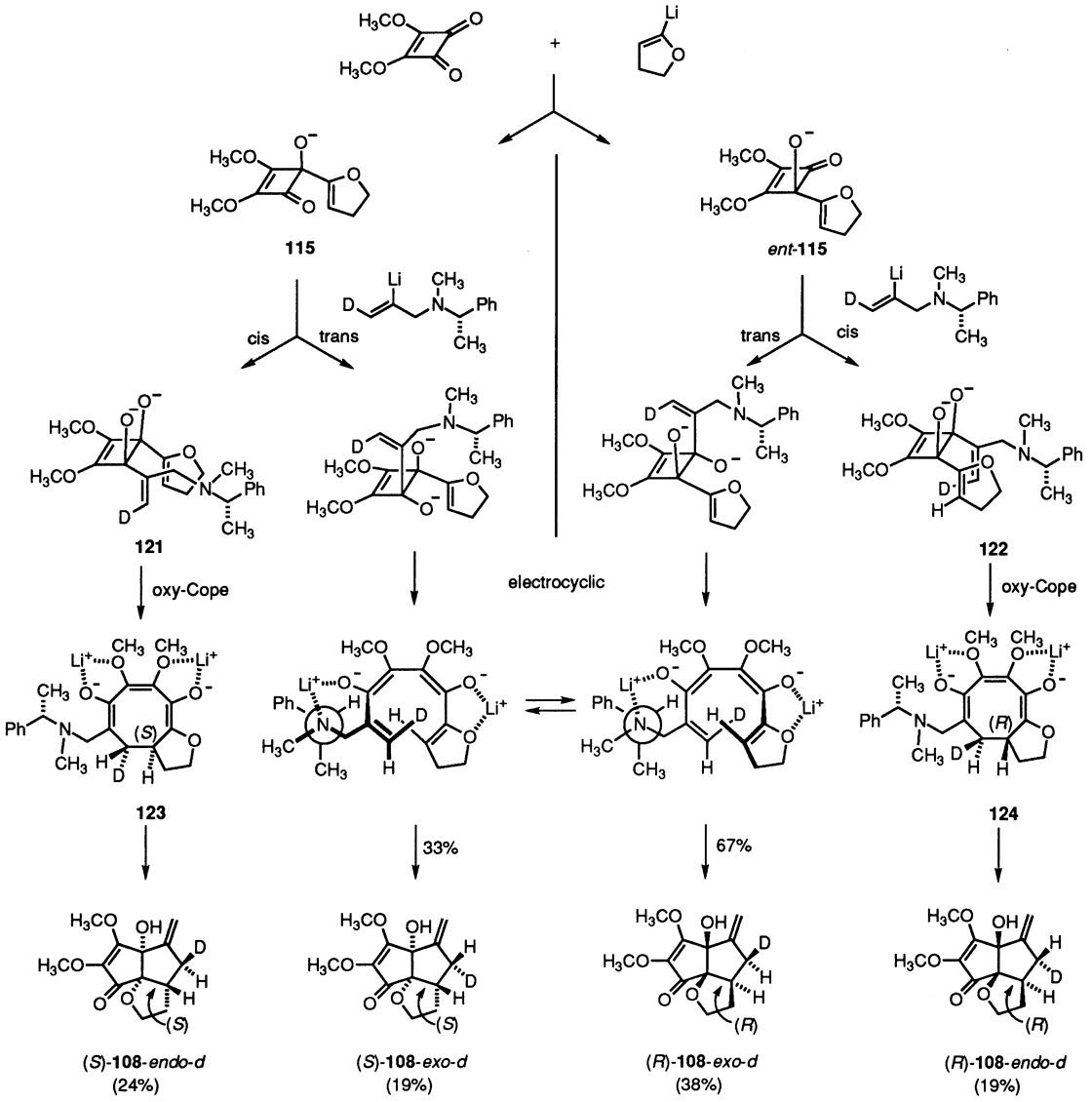

shown, which is known to be preferentially adopted by tertiary amines carrying a stereogenic center at their α-position[44]. With the larger groups positioned anti to each other, the helical orientation in **119** is seen to be quite free of nonbonded steric compression. In contrast, the state of affairs in **120** is such that nonbonded steric interactions between the dihydrofuran moiety and the α-methylbenzyl substituent impedes conrotatory cyclization.

Evidently, the involvement of dihydrofuranyllithium as the lead nucleophile (condition B) introduces in monoalkoxides **115** and *ent*-**115** an ethereal oxygen center which provides a sufficiently good binding site for lithium ions that chelation operates. As a consequence, a certain percent-

Scheme 19



Scheme 20




age of the lithio allylamine is enticed into *cis* addition and eventuates in the transient formation of **121** and **122** (Scheme 20). These steps are followed by [3,3] sigmatropy and complete transmission of stereochemistry to give **123** and **124**, respectively. In the final analysis, it was possible to map the complete dynamic profile for these complex processes.

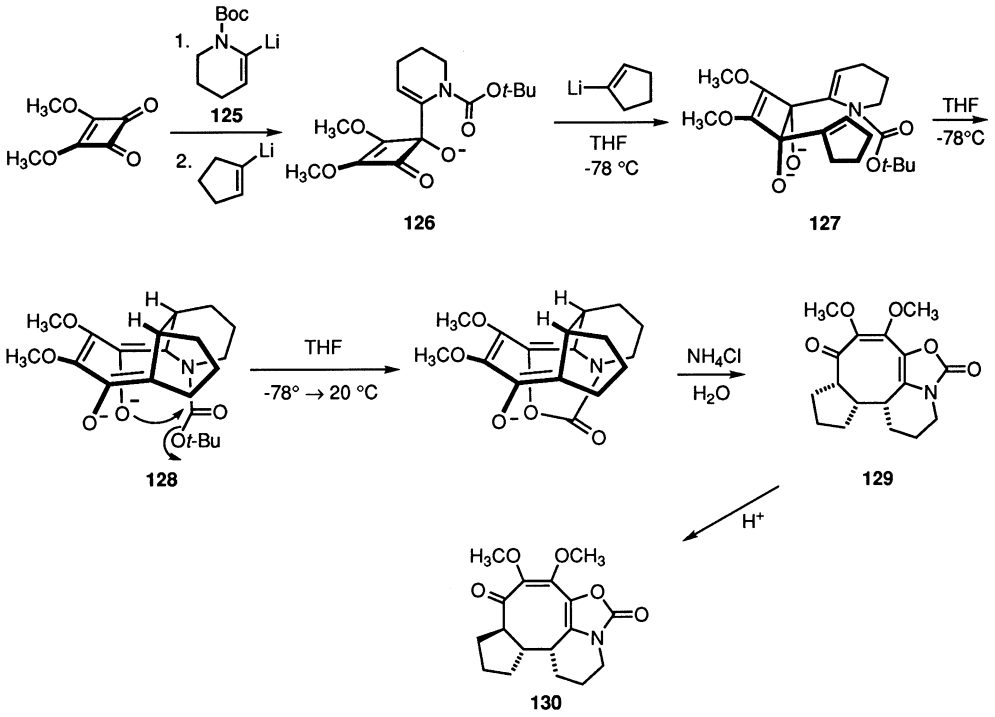
### 3.5. Intramolecular Enolate Interception

Interception of the final, thermodynamically favored transannular aldolization step by an alternative intramolecular nucleophilic process involving the medium-ring dienolate has been shown to be a synthetically useful adjunct to this chemistry[45]. The concept is illustrated for the combined action of lithiated carbamate **125** and cyclopentenyllithium on dimethyl squarate (Scheme 21). As a consequence of strong chelation to **126**, the second nucleophile enters only from the *syn* direction to generate **127**. Following the impending oxy-Cope rearrangement which sets the two methine hydrogens *cis* in **128**, warming to room temperature brings about intramolecular lactonization. The resulting conformationally inflexible intermediate undergoes protonation from the exterior surface of the tub to give the all-*syn* stereoisomer **129** under kinetic control. The epimerization of **129** to **130** is notably facile. Several transformations of **131** that deliver structurally interesting products are depicted in Scheme 22[45].

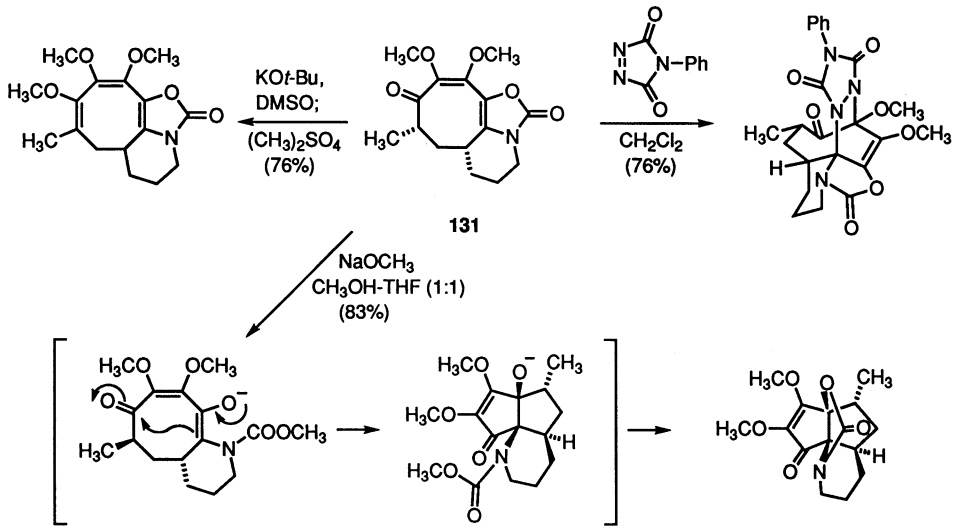
## 4. The Consequences of Intermolecular Chelation

During the course of our investigation of squarate cascades, it was noted that *cis* addition of the second alkenyllithium sometimes became competitive with, or dominated over, the customary *trans* alternative. Without exception, an oxygen atom resided in the first anion and was situated proximate to the four-membered ring. In order to scrutinize

Scheme 21




Scheme 22

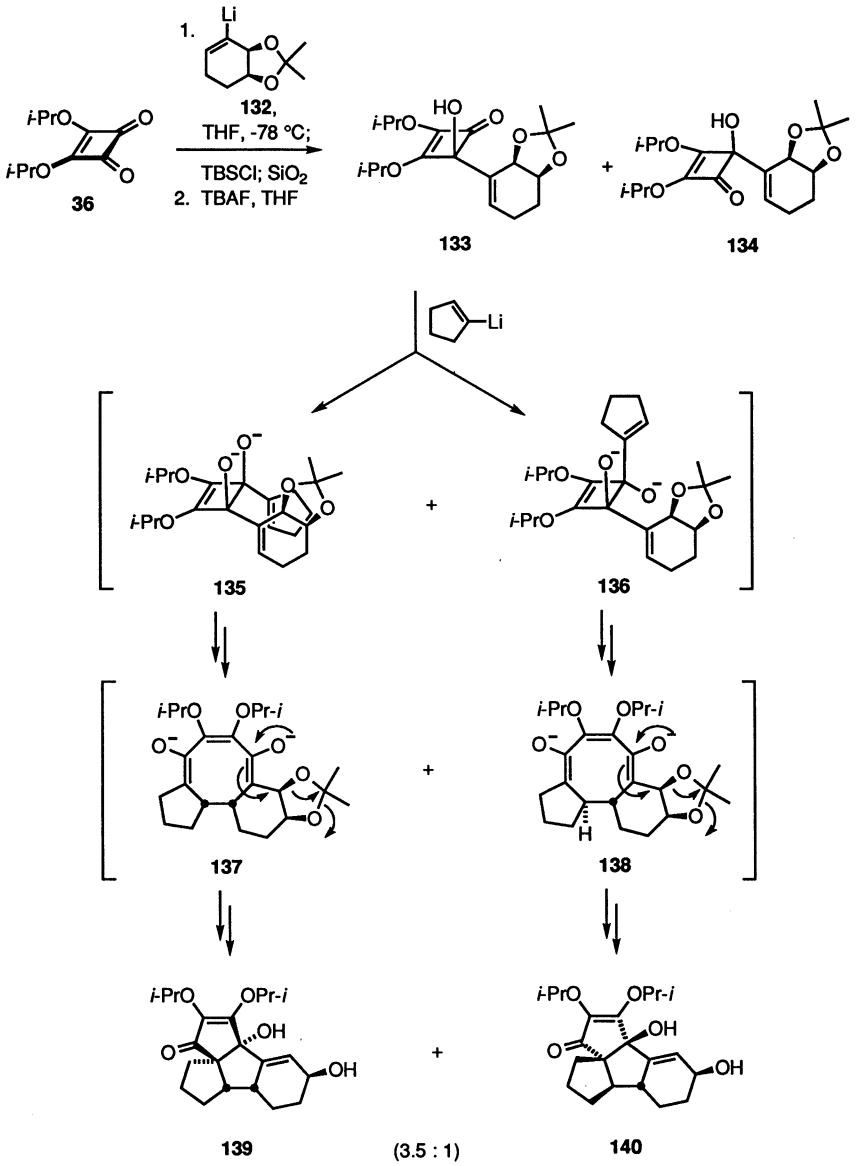


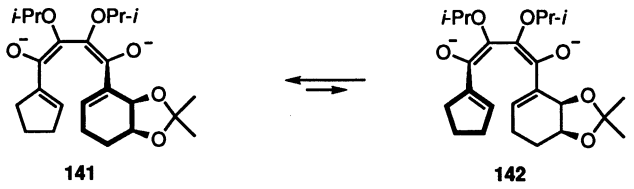

this matter explicitly, a variety of structural modifications were systematically implemented[46][47].

The consequences of adding enantiomerically pure 1-lithiocyclohexene-5,6-diol acetonide (**132**) proved rewarding in that it proved possible to effect the separation of monoadduct **133** from **134** (Scheme 23).

Subsequent treatment of **133** with cyclopentenyllithium initiated both possible cascade rearrangements, but the route via **135** and **137** to **139** was favored 3.5:1 over the electrocyclic alternative. Attention is called specifically to the *syn* orientation of the two new stereocenters in **137** and to the β elimination/fragmentation of the acetonide unit that ensues. This step guarantees that the subsequent aldol cyclization is fully regiocontrolled with ultimate delivery of **139**. To the more limited extent that *trans* addition operates to generate **136**, only **140** results. The obvious implication is that helical dialkoxide **141** experiences cyclization appreciably faster than **142** because the stereochemical disposition of the dioxolane ring offers less steric congestion during ring closure in that case.

Scheme 23

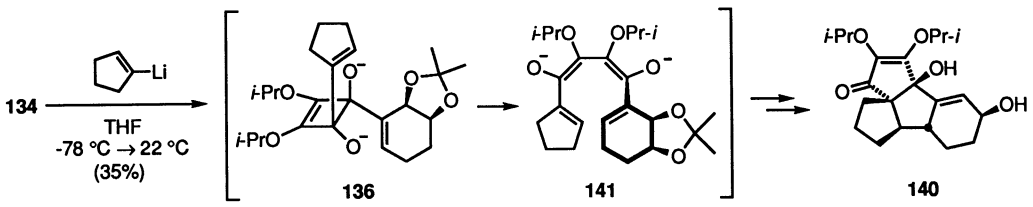


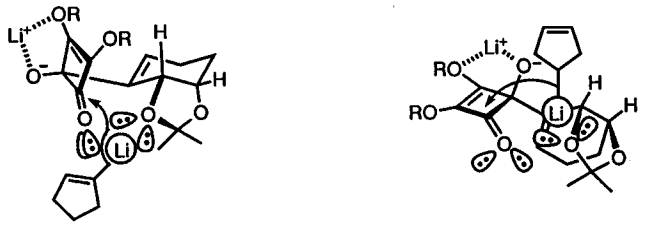

The response of **134** to comparable treatment is to give only **140** (Scheme 24). Consequently, *trans* addition operates to the exclusion of *cis* addition in this diastereomer. A distinction between the potential chelating arrangements available to **133** and **134**, while subtle, are clearly important. An analysis based on the spatial projection of nonbonded electrons in **143** and **144** has been proposed[46].

Other pertinent examples are grouped into Scheme 25. The addition of one equivalent of **145** to **36** followed by

Scheme 24

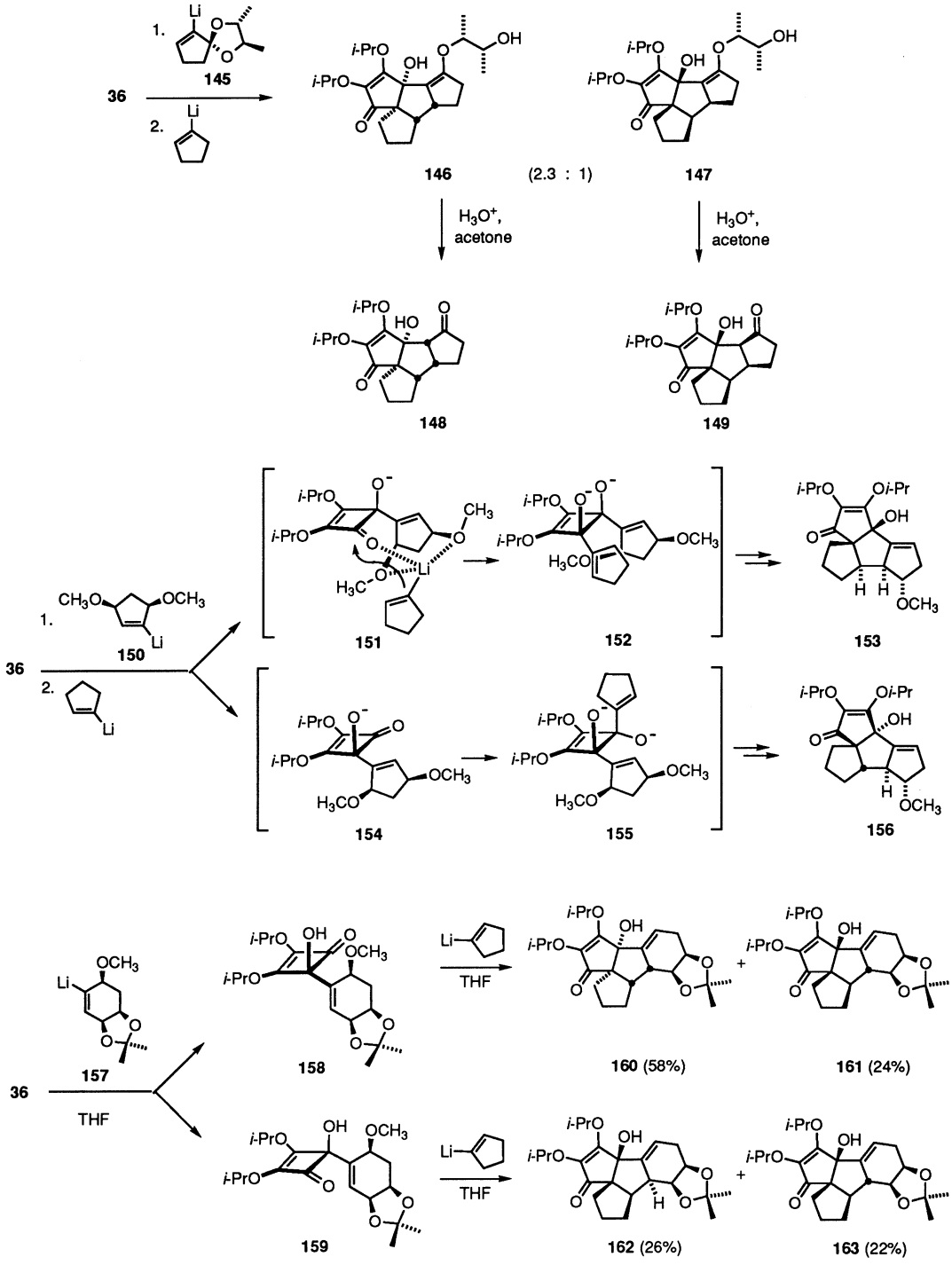


Scheme 24 *(continued)*



**143** **144**

Scheme 25



cyclopentenyllithium gave **146** and **147** in a 2.3:1 ratio. Since the hydrolysis of **146** gave the tetracyclic ketone **148** which proved to be antipodal to **149**, the two products had to materialize from the two possible diastereomeric *cis* adducts. This dominance of one mode of addition to the squarate ester is not shared by **150** which delivers a mixture of **153** and **156** (1.1:1). The significant finding in this instance is the inherent capability of monoadduct **151** to effectively coax the cyclopentenyllithium into *cis* addition with formation of **152** and then **153**. This property is not at all shared by diastereomer **154** which serves as the major and perhaps exclusive precursor to **155** and ultimately **156**.

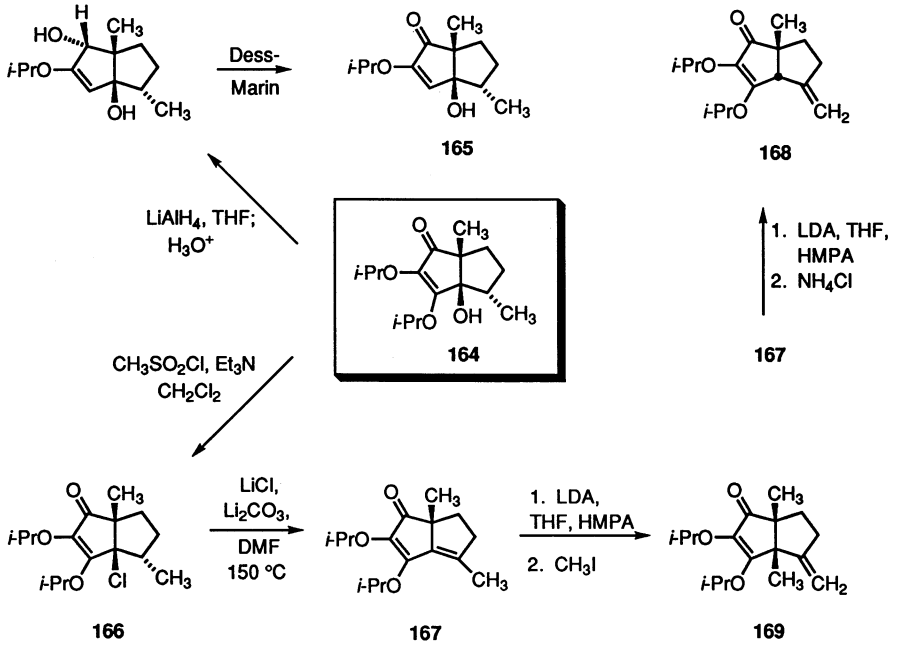
Cyclohexenyl anions based on (−)-quinic acid have provided added insight. Thus, following conversion of **36** into **158** and **159** through deployment of **157** as the lead reagent, each monoketone was treated with cyclopentenyllithium. Both experiments gave rise to two products, with that arising from *cis* addition and ensuing dianionic Cope rearrangement predominating to different extents.

## 5. Conclusions

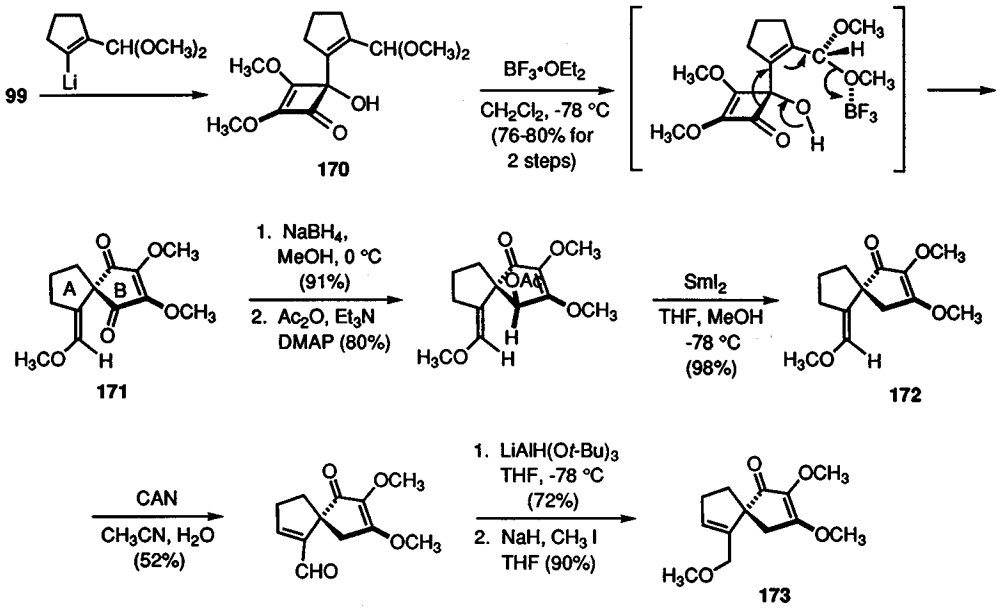
The polyquinanes formed directly upon reaction of squarate esters with two equivalents of alkenyl or alkynyl lithium reagents offer the prospect of serving as useful starting materials for the synthesis of a wide variety of multicyclic compounds. The remarkable scaffolding that accompanies the rapid conversion of these achiral reactants into structural assemblies that possess several stereogenic centers is subject to stereo- and regiocontrol. The structural feature common to the great majority of the products is the α,β-bis(alkoxy)-γ-hydroxycyclopentenone functional array. Selected examples of chemical transformations that have been performed on **164**[48] can be found in Scheme 26[49]. Noteworthy is the ability to remove one isopropoxy group as in **165** by sequential lithium aluminum hydride reduction and oxidation with the Dess-Martin periodinane. The efficient replacement of the angular hydroxyl by chlorine leading to **166** opens possibilities for elimination with the introduction of an added endocyclic (e.g. **167**) and exocyclic double bond (e.g. **168**). Alkylative options are also possible as exemplified by the conversion to **169**.

In our opinion, the synthetic potential associated with the 1,2-addition of alkenyllithium reagents to squarate esters has only begun to emerge. Many other applications are possible. The recently disclosed route to dimethyl gloiosiphone A (**173**) is a good representative example of concise structural assembly based on **99** as the starting material[50] (Scheme 27). The key step involves the boron trifluoride catalyzed ring expansion[51] of monoadduct **170** to give spirocyclic diketone **171**. The carbonyl carbon is seen to migrate exclusively and the exocyclic vinyl ether is generated with high stereoselectivity. Once one of the two equivalent keto groups is reduced to the methylene level as in **172**, only three conventional steps are required to arrive at the algal metabolite. We see future applications of squarate esters to the solution of many diverse synthetic challenges in a way that will provide further enhancement in our appreciation of these strained building blocks.

Scheme 26



Scheme 27





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