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Addition of 2,3-Dihydro-5-furanyllithium to Diisopropyl Squarate as a Means for the Rapid Generation of Structurally Complex Oxygen-Containing Tetraquinane Networks†

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Abstract: The ability of 2,3-dihydro-5-furanyllithium (**11**) to trigger a reaction cascade when added to diisopropyl squarate (**6**) has been examined. Of particular concern were those experiments in which greater than 2 equiv of **11** were added to **6**, as well when 1 equiv of **11** was added prior to or after an equiv of cyclopentenyllithium. The results shed light directly on such issues as whether the second vinyl anion adds cis or trans in reference to the first, and whether the bonding takes place in 1,2 or 1,4 fashion. Also revealed in the unsymmetrical case studies was whether protonation of the 1,3,5-cyclooctatriene intermediates occurs syn or anti to the adjacent proton and the extent to which this materialized at the "conventional" or the oxygen-substituted enolate site. In light of the fact that heterocyclic tetraquinanes containing five stereogenic centers are directly elaborated in one step from achiral building blocks, the transformations described in this work can be justifiably classified as "power reactions".

As extensive as studies involving the use of cyclobutene-1,2-diones as highly electrophilic building blocks have been,[2,3] only recently have the consequences of adding two vinyl anions to such reactive compounds begun to be appreciated. Butenschön, et al.[4] reported that the chromium tricarbonyl complex **1** experiences dianionic oxy-Cope rearrangement under very mild conditions following double addition of a vinyllithium species, both steps of which necessarily occur anti to the $Cr(CO)_3$ moiety for obvious steric reasons to deliver **2** initially (Scheme 1). The conversion to **3** is greatly facilitated by the juxtapositioning of two oxido anions (charge acceleration) and their common attachment to a four-membered ring (strain release). Following protonation, **4** and **5** are obtained depending on the extent to which transannular aldolization occurs.

Independent studies under investigation concurrently in this group have revealed that similar treatment of diisopropyl squarate (**6**) results in predominant trans attachment of the vinyl anions as in **7** (Scheme 2).[5] This event is followed by rapid conrotatory ring opening of this doubly charged intermediate, leading to the stereocontrolled intervention of the helical 1,3,5,7-octatetraene **8**. Subsequent electrocyclization of **8** under orbital-symmetry control (conrotatory mode) results in the formation of **9**. In the specific example shown,[6] protonation occurs exclusively at the less sterically congested enolate center, setting the stage for unidirectional aldol ring closure and production of **10**. Synthetically useful extensions of this cascade reaction sequence have since appeared.[7,8]

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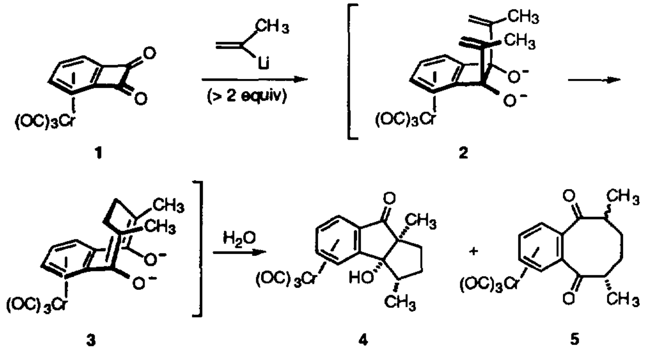
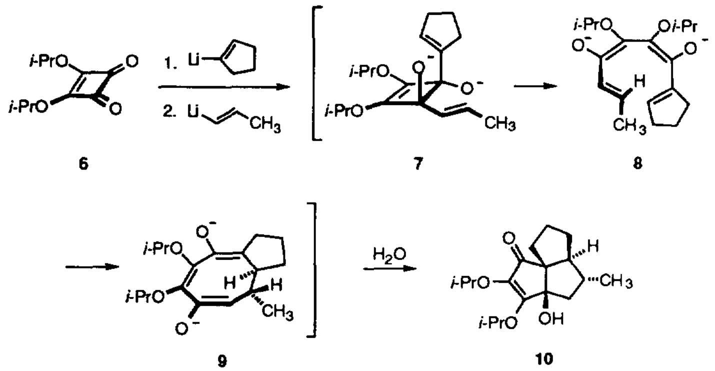
†This paper is dedicated to Professor Manfred Regitz on the occasion of his 60th birthday celebration.

Scheme 1



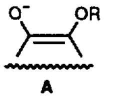
The several valuable features associated with the latter rearrangement include: (a) an impressively rapid buildup of structural complexity;[5-8] (b) the generation of chiral products endowed with many stereogenic centers from achiral starting materials;[5-8] (c) opportunities for regioselectivity control;[8] and (d) the possibility for transfer of stereogenicity by several mechanisms.[9] The present investigation demonstrates the ability to assimilate heterocyclic character into the polycyclic products simply by involving α-lithiated vinyl ethers as reagents. Although recourse has been made exclusively to 5-lithio-2,3-dihydrofuran herein, one needs to be aware that this class of reactive intermediates is readily available by the direct metalation of the parent heterocycles[10] or via transmetalation of stannylated precursors.[11]

Scheme 2

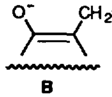


RESULTS AND DISCUSSION

The involvement of oxygenated vinyl anions in the "squarate ester cascade" brings with it several important mechanistic concerns. One of the more pivotal issues concerns the availability of additional coordination sites for lithium ions and the interdependency of this capability with competing cis or trans addition to **6**. Later into the reaction sequence, the step involving cyclization to the penultimate intermediate will generate alkoxy-substituted enolates of type **A**. Since little information relating to this structural entity is available, we have sought to compare their rate of protonation in direct competition with the more conventional species **B**. In addition, the capture of **A** by O-silylation has enabled the direct characterization of advanced intermediates by X-ray crystallographic analysis.



A



B

The consequences of adding >2 equivalents of **11** to **6** are detailed first. Two distinctly different sets of reaction conditions were employed. In the first, the addition was performed in THF at -78 °C and the reaction mixture was stirred at room temperature for 15 h and at reflux for 4 h prior to quenching and *immediate isolation*. Chromatography on silica gel then led to acquisition of the four related diastereomers **12-15** in the yields indicated in Scheme 3 under Conditions A.

The isolation of both major products as colorless rhombic crystals from ether-petroleum ether led us to ascertain their three-dimensional structural features by X-ray methods. The final ORTEP diagrams are depicted in Figures 1 and 2. In the first instance, the space group was determined to be centric $P2_1/n$ from the systematic absences (Table I). The basic structural features of **12** are seen to consist of two tetrahydrofuran rings cis-fused to a diquinane core characterized by a β-hydroxy ketone functional group array. On the other hand, the crystals of **13** were assigned to the C2/c space group. The ensuing refinement revealed an essentially identical framework to be present, with the exception that the A-ring is fused in a regioreversed manner. As a result, the carbonyl and carbinol carbons have a vicinal relationship.

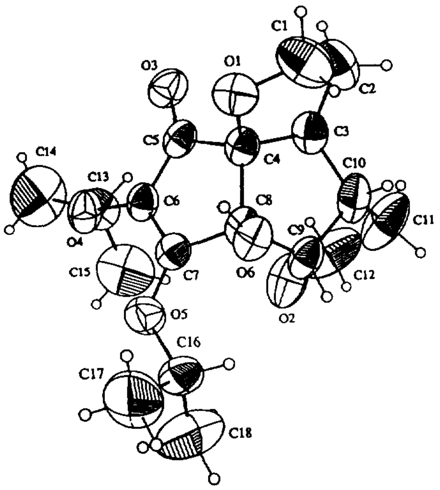


Figure 1. Crystallographically determined molecular structure of **12** as drawn with 50% probability ellipsoids.

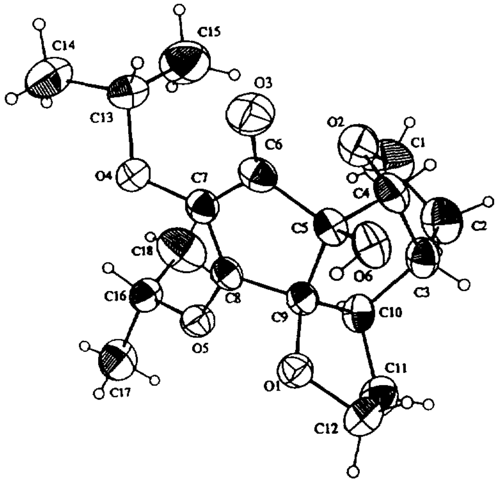


Figure 2. Crystallographically determined molecular structure of **13** as drawn with 50% probability ellipsoids.

The structural assignments to **14** and **15** were derived from a combination of NOE and long-range optimized semiselective INEPT spectroscopy. The latter technique generates ^{13}C NMR subspectra of those carbons that are coupled long-range, i.e. via two or more bonds, to a specific, selectively excited proton resonance. Only two- and three-bond correlations are generally observed due to the qualitative distance dependence of the size of $^{1}H/^{13}C$ long-range couplings: $^{3}J_{C,H} > {}^{2}J_{C,H} >> {}^{n}J_{C,H}$ (n > 3). This extremely powerful and specific tool for structure elucidation reliably reveals connectivity among adjacent quaternary

Table I. Crystal Data and Summary of Intensity Data Collection and Structure Refinement.

	12	**13**	**17**
Formula	$C_{18}H_{26}O_6$	$C_{18}H_{26}O_6$	$C_{24}H_{42}O_6Si_2$
Color/shape	colorless/ parallelepiped	colorless/ parallelepiped	colorless/ parallelepiped
For. wt.	338.40	338.40	482.77
Space group	$P2_1/n$	C2/c	$P\bar{1}$
Temp., °C	18	18	20
Cell Constants[a]			
a, Å	12.136(6)	28.527(9)	10.962(9)
b, Å	9.830(3)	8.499(5)	11.488(4)
c, Å	15.543(6)	14.646(4)	12.284(4)
α, deg			96.21(3)
β, deg	102.25(3)	100.25(3)	106.47(5)
γ, deg			100.47(5)
Cell vol, $Å^3$	1812	3494	1437.7
Formula units/unit cell	4	8	2
D_{calc}, g cm^{-3}	1.24	1.29	1.12
μ_{calc}, cm^{-1}	0.99	1.03	1.58
Diffractometer/scan	Enraf-Nonius CAD-4/ω-2θ	Enraf-Nonius CAD-4/ω-2θ	Enraf-Nonius CAD-4/ω-2θ
Radiation, graphite monochromator	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
Max crystal dimmensions, mm	0.30 x 0.35 x 0.38	0.13 x 0.25 x 0.53	0.35 x 0.40 x 0.60
Scan width	0.80 + 0.35tanθ	0.80 + 0.35tanθ	0.80 +0.35tanθ
Standard reflections	200; 020; 008	800; 020; 004	500; 050; 006
Decay of standards	±1%	±2%	±2%
Reflections measured	3550	3413	5052
2θ range, deg	$2 \le 2\theta \le 50$	$2 \le 2\theta \le 50$	$2 \le 2\theta \le 50$
Range of h, k, l	+14, +11, ±18	±34, +10, +17 (except h+k = 2n+1)	+13, ±13, ±14
Reflections observed [$F_o \ge 5\sigma(F_o)$][b]	1908	2023	2866
Computer programs[c]	SHELX[18]	SHELX[18]	SHELX[18]
Structure solution	SHELXS[20]	SHELXS[20]	SHELXS[20]
No. of parameters varied	229	229	319
Weights	$[\sigma(F_o)^2 + 0.0001\ F_o^2]^{-1}$	$[\sigma(F_o)^2 + 0.00004\ F_o^2]^{-1}$	$[\sigma(F_o)^2 + 0.0010\ F_o^2]^{-1}$
GOF	0.37	1.14	0.90
$R = \Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$	0.056	0.047	0.047
R_w	0.056	0.049	0.060
Largest feature final diff. map	$0.2e^-\ Å^{-3}$	$0.2e^-\ Å^{-3}$	$0.2e^-\ Å^{-3}$

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[a] Least-squares refinement of $((\sin\theta/\lambda))^2$ values for 25 reflections θ > 20° [**12** and **17** or 17° (**13**)].

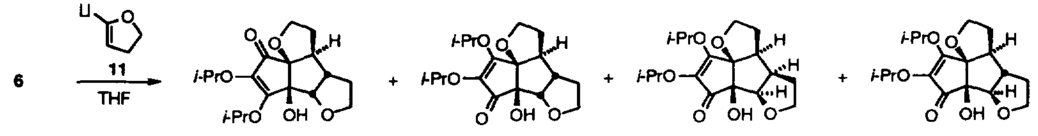
[b] Corrections: Lorentz-polarization.

[c] Neutral scattering factors and anomalous dispersion corrections from ref. 19.

carbons. The means by which the $^{13}C/^{13}C$ connectivities present in **14** and **15** were traced are illustrated in part in the Experimental Section.

In companion experiments involving the condensation of **6** with **11**, *workup was not undertaken immediately after quenching*. Rather, the aqueous THF solution was stirred under argon at room temperature for an additional 16 h. This modification, coded as Conditions B in Scheme 3, resulted in a dramatic improvement in the total amount of **12** obtained (52%).

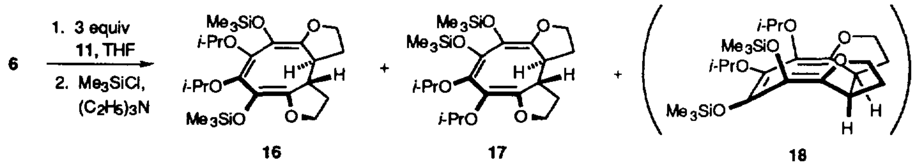
Scheme 3



	12	13	14	15
Conditions A:	(38%)	(15%)	(3%)	(2%)
Conditions B:	(52%)	(18%)	(6%)	(4%)

Since the product structures can be classified into three categories, *viz.* **12**, **13**/**15**, and **14**, three distinctively different reaction pathways are necessarily operative. Significantly, the stereochemical and positional markers present in the three hypothetical 1,3,5-cyclooctatriene dienolates can be directly linked to mechanistic origin. Trapping experiments were therefore undertaken. Reaction of **6** with 3 equiv of **11** followed by excess chlorotrimethylsilane afforded a chromatographically separable mixture of three disilylated compounds. The first two were identified as **16** and **17** (Scheme 4). A third minor isomer, assumed to be **18**,[12] proved to be highly sensitive and decomposed too rapidly to permit its full characterization.

Scheme 4



The trans-fused arrangement present in **16** and **17** causes these medium-ring compounds to be susceptible to slow conformational exchange on the NMR time scale at room temperature. Although their ^1H and ^{13}C spectra are appreciably broadened as a consequence, this characteristic behavior is viewed by us to be diagnostic of the indicated stereochemistry. This conclusion was corroborated in two ways. The high crystallinity of **17** made possible direct scrutiny of its solid-state three-dimensional structural features by X-ray crystallography (Figure 3, Table I). The refinement of structure, successfully accomplished in the centric $P\bar{1}$ space group, defines the vicinal relationship of the pairs of isopropoxy and trimethylsilyloxy substituents. This pattern distinguishes **17** from **16**.

The cis nature of the intra-ring double bonds in **16** and **17** holds additional mechanistic significance. If the dianionic oxy-Cope variant were to occur via a chair alignment, the relative stereochemistry of the two adjacent stereocenters would necessarily be trans. However, one of the immediately adjacent double bonds would need also to be configured trans as shown below. In the electrocyclic scheme, the possibility exists that

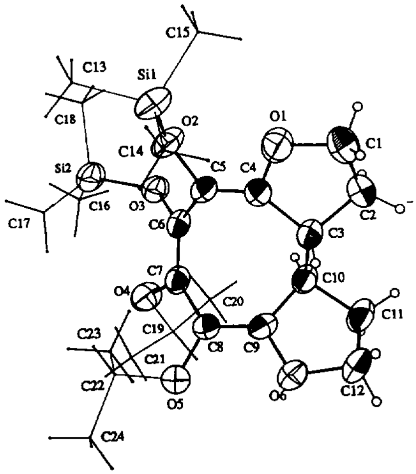
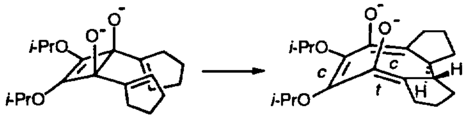
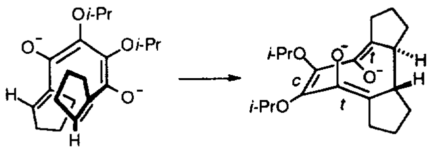


Figure 3. Crystallographically determined molecular structure of **17** as drawn with 50% probability ellipsoids. The methyl groups bonded to silicon and the isopropyl groups attached to oxygen are depicted only in line notation for clarity.

the 1,3,5,7-octatetraene adopts a distinctively different topology, such that conrotatory cyclization would give rise to a *trans,cis,trans*-1,3,5-cyclooctatriene. These added options are evidently higher energy processes, which can now be dismissed from further consideration.





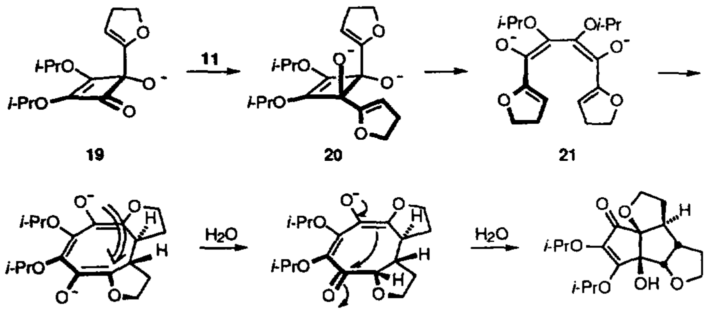
Individual exposure of **16** and **17** to methyllithium in order to regenerate the corresponding diene diolates and subsequent quenching with water resulted in high-yield conversion to **12** and **13**, respectively (Scheme 5). The interrelationship between intermediate and end-product was consequently unambiguous.

Scheme 5

16 **12** **17** **13**

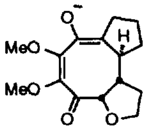
The data presented below show that 2,3-dihydro-5-furanyllithium (**11**) adds twice to **6** in three different ways. Following formation of monoadduct **19**, the major reaction channel involves 1,2-addition from the opposite face to generate the dialkoxide **20** (Scheme 6). Judging from isolated product ratios, the formation of *trans*-**20** operates to the virtual exclusion of the cis isomer. Once generated, intermediate **20** is

Scheme 6

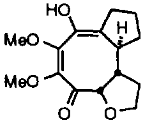


necessarily channeled into a cascade of chemical events involving conrotatory 4π electrocyclization with projection of the oxido anions to the exterior of tetraene 21[13] and conrotatory 8π ring closure, thus giving rise to **22**. The initial protonation of this doubly charged intermediate is seen to occur as in **23**, thereby setting the stage for ultimate transannular aldolization.

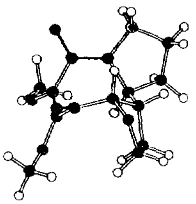
Molecular mechanics calculations involving closely related analogs of **23** have provided some insight into the question of whether cis proton delivery to **22** conforms to the thermodynamic bias of the system or not. For this purpose, the neutral and anionic forms of each relevant diastereomer were minimized in either the MODEL KS 2.96 or KS 2.99 program[14] in order to guarantee a reliable parameterization for the enolate.



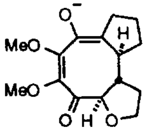
C



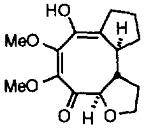
D



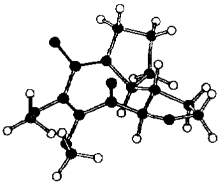
	C	D
ΔE_{Strain}	45.985	26.972
ΔH_f	-135.799	-160.409
ΔE_{Total}	59.17	40.16



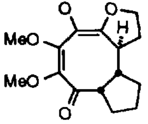
E



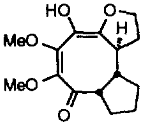
F



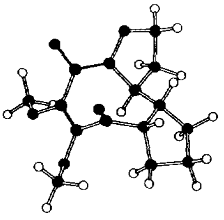
	E	F
ΔE_{Strain}	46.956	26.991
ΔH_f	-135.477	-158.370
ΔE_{Total}	60.15	40.18



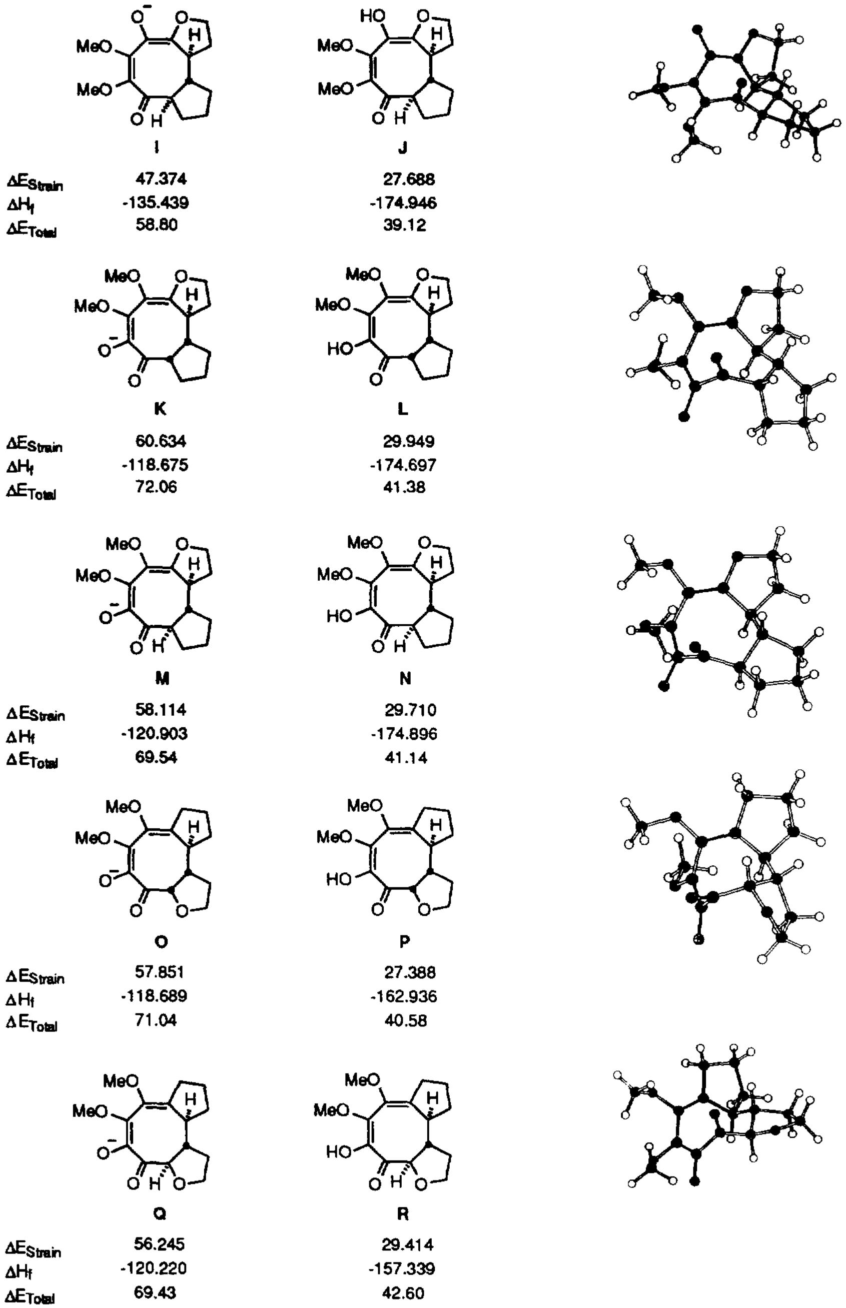
G



H



	G	H
ΔE_{Strain}	50.438	30.356
ΔH_f	-131.899	-174.468
ΔE_{Total}	61.87	41.79



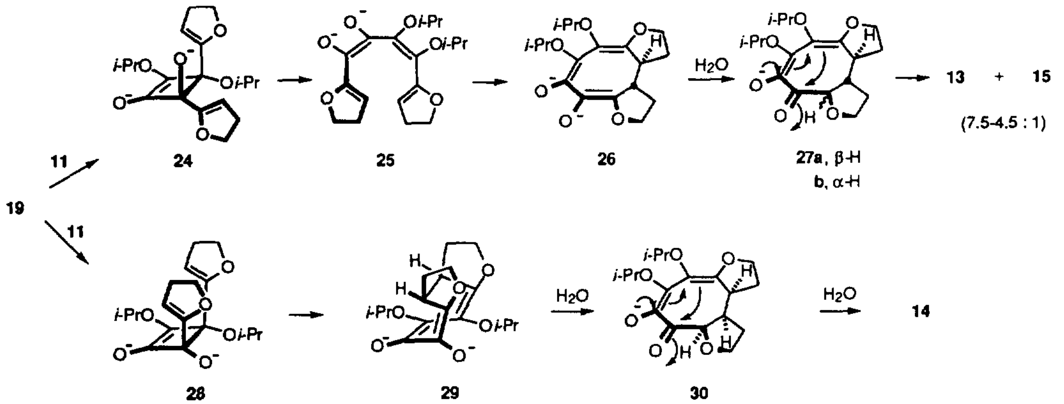
	I	J	K	L	M	N	O	P	Q	R
ΔE_{Strain}	47.374	27.688	60.634	29.949	58.114	29.710	57.851	27.388	56.245	29.414
ΔH_f	-135.439	-174.946	-118.675	-174.697	-120.903	-174.896	-118.689	-162.936	-120.220	-157.339
ΔE_{Total}	58.80	39.12	72.06	41.38	69.54	41.14	71.04	40.58	69.43	42.60

Figure 4. Global minimum energy conformations of monoprotonated trans-fused 1,3,5-cyclooctatriene dienolates as determined by molecular mechanics calculations (Chem 3-D output). All energies are in units of kcal/mol.

Also, the isopropyl groups were replaced by methyl in order to reduce the number of possible sidechain rotamers. The data, compiled in Figures 4 and 5, reveal a close correlation between the neutral and oxido species. More relevantly, irrespective of whether the ring fusion in the monoprotonated intermediates is trans (Figure 4) or cis (Figure 5) and whether they have resulted from initial 1,2- or 1,4-addition, trans proton delivery leads to a more stable product (by 1.5-4.4 kcal/mol) with but one exception. More on this point later.

With a high degree of assurance, the tetraquinanes **13**-**15** arise by 1,4-addition[15] of **11** to **19** (Scheme 7). In this instance the intervention of both trans and cis bis-adducts needs to be taken into account. By analogy with earlier considerations, the formation of **24** can be expected to progress via **25** to **26**. Unlike **22**, the monoprotonation of **26** does not occur uniquely to give cis-fused product, *viz.* **27a**, although this reaction trajectory continues to be dominant as gauged by the preponderance of **13** relative to **15**. While the computational results agree that **27b** is likely more thermodynamically stable than **27a** (see particularly **O** to **R** in Figure 4), it is particularly engaging to consider the modest loss of stereocontrol to be a result of increased reactivity in **26** as a consequence of the juxtapositioning of enolate anions. Whatever the case, it is necessary that the first protonation step be regioselective in the manner shown. Arrival at **27** uniquely allows for ultimate operation of a vinylogous aldol-type cyclization to deliver **13** and **15**.

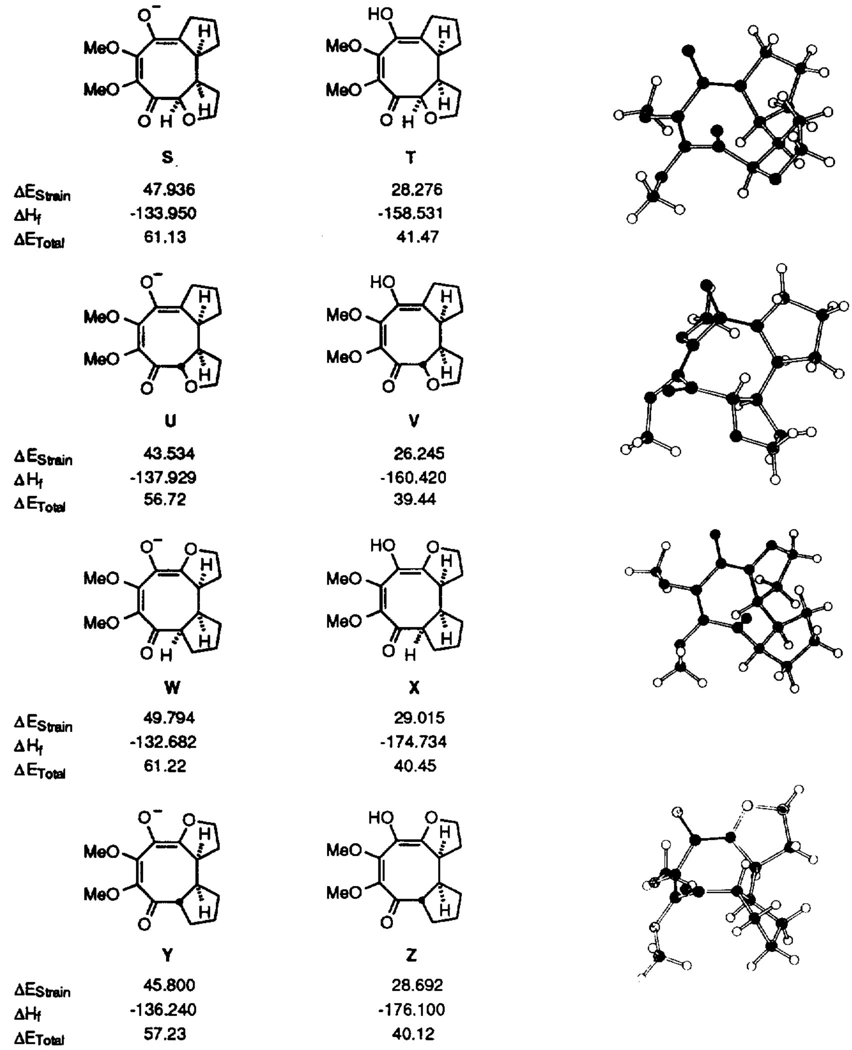
Scheme 7



The geometry of *cis*-1,4-adduct **28** brings the double bonds within the dihydrofuran moieties into close proximity, thereby fostering dianionic oxy-Cope rearrangement. Dianion **29** differs from **26** only in the cis disposition of the tertiary methine protons bonded to the eight-membered ring. Monoprotonation of **29** then leads via **30** to **14**. Although this specific system is not explicitly considered in Figure 5, the stereochemical course of the **29** → **30** reaction is inconsistent with thermodynamic advantage generally resident in cis,trans isomers (see Figure 5).

Once monoprotonation has materialized, the stereochemistry of the final ring closure is expectedly controlled by the requirement that a cis and not a trans bicyclo[3.3.0]octenone core be generated. In this connection, the finding that prolonged stirring at rt after aqueous quench is advantageous to product yields would appear to be compatible with the notion that the neutral enols related to **26**, **30**, and particularly **23** have a reasonable lifetime and that they and their conjugate bases do not necessarily cyclize spontaneously.

At this point, a fascinating divergence in the reactivity of cyclopentenyllithium and 5-lithio-2,3-dihydrofuran (**11**) had become apparent. Exposure of **6** to excess cyclopentenyllithium results in a product



	S	T
ΔE_{Strain}	47.936	28.276
ΔH_f	-133.950	-158.531
ΔE_{Total}	61.13	41.47

	U	V
ΔE_{Strain}	43.534	26.245
ΔH_f	-137.929	-160.420
ΔE_{Total}	56.72	39.44

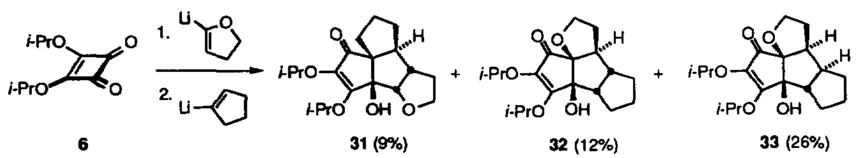
	W	X
ΔE_{Strain}	49.794	29.015
ΔH_f	-132.682	-174.734
ΔE_{Total}	61.22	40.45

	Y	Z
ΔE_{Strain}	45.800	28.692
ΔH_f	-136.240	-176.100
ΔE_{Total}	57.23	40.12

Figure 5. Global minimum energy conformations of monoprotonated cis-fused 1,3,5-cyclooctatriene dienolates as determined by molecular mechanics calculations (Chem 3-D output). All energies are in units of kcal/mol.

distribution accountable mechanistically in terms of trans 1,2-addition (40%), cis 1,2-addition (26%), and trans 1,4-addition (4%).[5] The propensity of this vinyl anion for cis 1,2-addition, which has been encountered frequently,[16] is not shared by **11**. The latter heterocyclic nucleophile displays instead a facility for cis and trans 1,4-addition not exhibited by cyclopentenyllithium. These precedents prompted us to address the stepwise introduction of these two reagents. Both possible addition sequences were probed, the first consisting of leading with **11** (Scheme 8). Coupling occurred uneventfully to afford the tetraquinanes **31** (9%), **32** (12%), and **33** (26%) in order of elution from a silica gel column. Decisive spectral measurements

Scheme 8

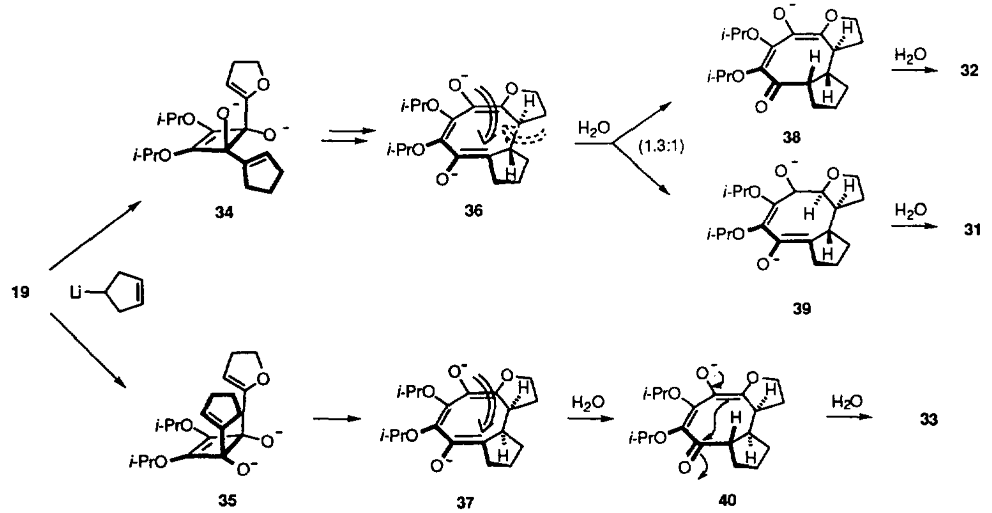


(C-H correlation, ^{13}C DEPT, semiselective INEPT, and NOE) defined the carbon connectivity and stereochemistry in each instance (see Experimental Section).

On the basis of preceding mechanistic considerations, it appears reasonable to conclude that monoadduct **19** experiences reasonably competitive trans and cis 1,2-addition to produce **34** and **35**, respectively (Scheme 9). These reaction trajectories give evidence of being closely balanced kinetically. Curiously, however, **36** and **37** experience initial protonation from the cis and trans directions, respectively. Whereas **37** does so regioselectively at the electronically unperturbed enolate carbon, **36** reacts at both possible sites. The product distribution indicates that **38** is generated about 1.3 times more readily than **39**.

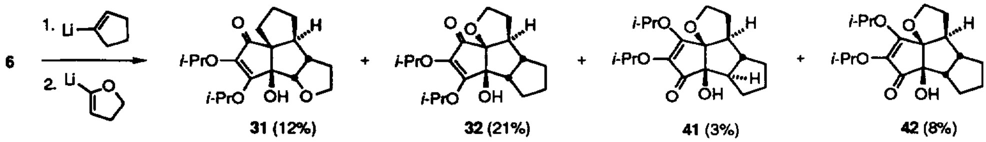
Two important points emerge. First, by judiciously selecting cyclopentyllithium as the second vinyl anion, one can direct a significant portion of the reaction cascade down the cis 1,2-addition pathway. Although the causative factors underlying this stereoselectivity are not clearly understood at this time, the phenomenon is real and should prove to be useful in subsequent synthetic investigations. The second point deals with the regio- and stereoselectivity of the protonation of **36** and **37**. The energy data compiled in Figure 4 for **C** and **G** would implicate that protonation adjacent to oxygen has a 2.7 kcal/mol thermodynamic benefit relative to protonation next to the cyclopentyl ring. The near-equal proportions of **31** and **32** that were isolated contrast with the theoretical output. Analogously, the regioselectivity observed for **37** goes contrary to theory and probably is again dominated by kinetic control. Thus, **Y** is produced to the exclusion of **U**, giving rise ultimately to **33** as the major product.

Scheme 9



We next addressed the introduction of the lithium reagents in the reverse order (Scheme 10). As in the preceding experiment, both **31** (12%) and **32** (21%) were formed. However, no evidence was found for the presence of **33**, the previous major product. Instead, the two new tetraquinanes **41** (3%) and **42** (8%) were

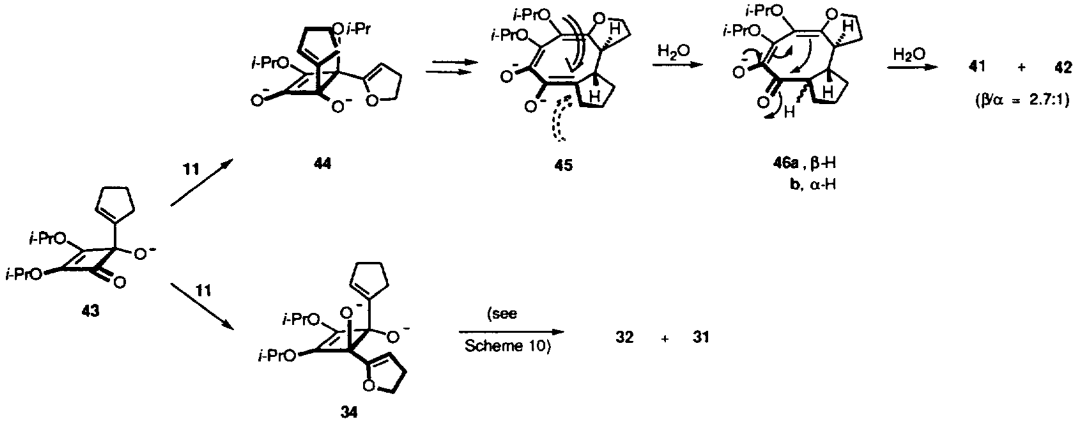
Scheme 10



obtained and identified spectroscopically.

In order to place these data in proper perspective, it is useful to examine Scheme 11. Of the reaction channels available to monoadduct **43**, that involving trans 1,2-addition is most prevalent, amounting to 75% of the total isolated product pool. Bis adduct **34** has been encountered earlier (Scheme 9) and its ensuing conversion to **31** and **32** previously traced. Noteworthily, **11** exhibits no predisposition for cis 1,2-addition as does its cyclopentenyl equivalent. The dihydrofuranyllithium reagent does, however, show once again a marked tendency for trans 1,4-addition. Thus, tacit evidence that **44** does intervene and is converted via two conrotatory electrocyclic events to **45** is found in the structural features of **41** and **42**. Evidently, **45** experiences first-stage protonation at the "conventional" enolate site, with the β trajectory giving **46a** being roughly three times more prevalent than that leading to the α diastereomer **46b**.

Scheme 11



Beyond this, these mixed vinyl anion experiments reveal that **11** very likely undergoes 1,4-addition only after initial 1,2-addition (i.e., **19** → **20** in Scheme 6) when introduced in excess, rather than in the reverse order.

The complex factors that influence the relative efficacies of the several mechanistic pathways are too numerous to discuss here. Conventional wisdom suggests that cis protonation of **45** should be stereochemically preferred for reasons of strain minimization. The responses of **22**, **26**, and **36** lend support to this belief. However, there is mounting evidence that this phenomenon may reflect kinetic rather than thermodynamic control. MM2 calculations on **K-R** (Figure 4) implicate only very modest differences in energy between the two possible sets of isomers. Equally telltale is the fact that little distinction is made between regioisomeric options. In other words, little if any *thermodynamic* preference is associated with the initial protonation of enolates of type **A** or type **B**. *The observations that "conventional" enolates are more reactive may simply implicate the enhanced coordination of lithium cations to A, thus reducing the relative nucleophilicity of such intermediates.* The results detailed herein are therefore considered to delineate the apparent kinetic fate of

1,3,5-cyclooctatetriene diolates, although allowance should be made for the fact that complexities can be obscuring this simplified assertion.

CONCLUSIONS

The rapid assembly of heterocyclic tetraquinanes by means of the addition of 2,3-dihydro-5-furanyllithium either in excess or in combination with cyclopentenyllithium is described. The remarkable scaffolding power of the process is apparent when one considers that three achiral reagents come together to deliver products containing *five* stereogenic centers. Companion computational studies indicate that the observed products are likely formed under kinetic control, since the energies of the several possible intermediates differ almost insignificantly.

The singularly dominant theme is that the twofold addition of vinyl anions to a squarate ester, whether in 1,2- or 1,4-fashion, or via cis or trans trajectories, leads to doubly-charged four-membered ring intermediates which enter into cascade rearrangements that result in the ultimate formation of several carbon-carbon bonds. Trans addition, which is customarily favored, triggers consecutive 4π and 8π electrocyclizations leading to a trans-fused 1,3,5-cyclooctatriene diolate. When cis addition materializes initially, then dianionic oxy-Cope rearrangement occurs to give a structurally related, but cis-fused dianion.

Among the many observations made in the course of generating and quenching these medium-ring intermediates, the following are the more notable:

(a) Relative to non-cyclic vinyl anions,[5-7] cyclopentenyllithium shows an enhanced tendency for cis 1,2-addition; its dihydrofuranyl counterpart, on the other hand, is significantly more prone than usual toward 1,4-addition.

(b) The symmetrical trans dioxa intermediate **22** experiences initial cis protonation, a stereochemical feature also adopted by **29** and **36**. The differences between these three dianions and the less symmetrical analogs **26**, **37**, and **45** are not easily sorted out. Whereas **37** undergoes only trans protonation, the proton transfers to **26** and **45** are not stereocontrolled. These data are not well correlated with molecular mechanics calculations and therefore appear to be of kinetic origin.

(c) In those cases where the option exists for protonation to occur at enolate centers which differ as in **A** and **B**, a decided preference for the protonation of **B** is seen. This is believed to be a direct consequence of a damping effect on the reactivity of **A** resulting from chelation of both oxygens to a lithium cation.

EXPERIMENTAL SECTION[17]

Condensation of 5-Lithio-2,3-dihydrofuran with 6. A. With Workup Following Immediately After Quenching. A cold (-78 °C), argon-blanketed solution of 2,3-dihydrofuran (0.23 mL, 3.07 mmol) in anhydrous THF (15 mL) was treated dropwise with *tert*-butyllithium (1.76 mL of 1.7 M, 3.0 mmol). The reaction mixture was allowed to warm to 0 °C, maintained at this temperature for 20 min, and subsequently returned to -78 °C. A solution of **6** (200 mg, 1.0 mmol) in dry THF (10 mL) was cooled to -78 °C and introduced via cannula. After 10 min at -78 °C, the resulting mixture was stirred at room temperature for 15 h, refluxed for 4 h, cooled to 20 °C, and quenched dropwise with water (5 mL). After further dilution with brine (20 mL), the products were extracted into ethyl acetate (3 x 25 mL), and the combined organic phases were washed with brine (40 mL), dried, and evaporated to a volume of 5-10 mL. On standing, 91 mg of **12** crystallized and was separated by filtration. A second batch of crystals recovered from the filtrate proved to be pure **13** (33 mg). The remaining oil was purified by flash chromatography on silica gel (elution with 60:35:5 petroleum ether-ethyl acetate-acetonitrile) to give an additional 37 mg of **12** (total 38%), more **13** (17 mg, total 15%), 9.3 mg (3%) of **14**, and 5 mg (2%) of **15**.

For **12**: colorless rhombic crystals, mp 116-117 °C; IR ($CHCl_3$, cm^{-1}) 3660, 3475, 1765, 1695, 1600, 1380, 1310; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (hept, J = 6.0 Hz, 1 H), 4.82 (hept, J = 6.0 Hz, 1 H), 4.30 (d, J = 5.7 Hz, 1 H), 4.18 (m, 1 H), 3.94 (m, 1 H), 3.85-3.75 (m, 2 H), 2.68 (m, 1 H), 2.47 (td, J = 7.5, 3.5 Hz, 1 H), 2.26 (ddd, J = 16, 12, 8 Hz, 1 H), 1.98 (m, 1 H), 1.78 (m, 2 H), 1.35 (d, J = 6.1 Hz, 6 H), 1.20 (2d, J = 6.2 Hz, 6 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 195.7, 168.9, 133.7, 93.6, 89.9, 82.2, 75.3, 72.2, 70.9, 68.1, 49.7, 48.8, 33.5, 31.6, 22.8, 22.6, 22.4, 22.2; MS *m/z* (M^+) calcd 338.1729, obsd 338.1743.

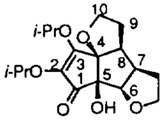
Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.59; H, 7.76.

For **13**: colorless rhombic crystals, mp 136-138 °C (from ether/hexanes); IR ($CHCl_3$, cm^{-1}) 3500, 1700, 1610, 1380, 1310, 1195, 1100, 1070; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (hept, J = 6.0 Hz, 1 H), 5.15 (hept, J = 6.1 Hz, 1 H), 4.30 (d, J = 5.1 Hz, 1 H), 4.10 (m, 1 H), 3.95 (m, 1 H), 3.82 (m, 2 H), 2.74 (m, 1 H), 2.53 (m, 1 H), 2.22 (m, 1 H), 2.05 (m, 1 H), 1.80 (m, 2 H), 1.31-1.15 (series of d, J = 6.1 Hz, 12 H) (OH not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.5, 163.5, 133.4, 94.3, 90.2, 82.1, 73.9, 71.5, 70.4, 68.1, 49.65, 49.60, 33.8, 31.8, 22.7 (2 C), 22.6, 22.0; MS *m/z* (M^+) calcd 338.1729, obsd 338.1760.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.82; H, 7.79.

For **14**: colorless crystals, mp 109-110 °C; IR ($CHCl_3$, cm^{-1}) 3550, 1715, 1620, 1390, 1320, 1110; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (hept, J = 6 Hz, 1 H), 5.06 (hept, J = 6 Hz, 1 H), 4.19-3.98 (m, 4 H), 3.90-3.80 (m, 1 H), 3.22 (s, 1 H), 2.90-2.81 (m, 1 H), 2.61-2.53 (m, 1 H), 2.16-1.81 (m, 4 H), 1.34 (d, J = 6 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.22 (d, J = 6 Hz, 3 H), 1.21 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.0, 166.6, 132.8, 92.6, 86.0, 79.2, 74.3, 72.2, 71.7, 69.5, 47.2, 41.5, 30.5, 28.8, 22.8, 22.7 (2 C), 22.4; MS *m/z* (M^+) calcd 338.1729, obsd 338.1730.

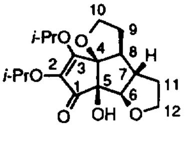
Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.98; H, 7.88.



Semi-selective INEPT:

Irradiate H-8 (δ 2.86): observe C-3 (166.5 ppm), C-4 and C-5 (92.6 ppm and 79.3 ppm), and C-6 (86.1 ppm).

For **15**: colorless crystals, mp 105-107 °C; IR ($CHCl_3$, cm^{-1}) 3550, 1705, 1615, 1385, 1310, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (hept. J = 6 Hz, 1 H), 5.06 (hept, J = 6 Hz, 1 H), 4.34-4.21 (m, 3 H), 3.99 (m, 1 H), 3.45 (d, J = 11 Hz, 1 H), 2.49-2.32 (m, 2 H), 2.15-1.98 (m, 1 H), 1.98-1.88 (m, 1 H), 1.84-1.76 (m, 1 H), 1.75-1.60 (m, 1 H), 1.30 (d, J = 6 Hz, 3 H), 1.28 (d, J = 6 Hz, 3 H), 1.22 (d, J = 6 Hz, 3 H), 1.19 (d, J = 6 Hz, 3 H) (OH not seen); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.2, 163.9, 131.1, 98.8, 89.1, 75.2, 74.8, 74.1, 72.0, 70.3, 50.4, 42.7, 30.3, 26.4, 22.9, 22.6; MS *m/z* (M^+) calcd 338.1729, obsd 338.1730.



Irradiate	Observe	% NOE
H-7	H-10β	4
H-8	H-6	5
	H-9α	2
H-9α	H-8	4

Semi-selective INEPT:
Irradiate H-6 (δ 3.45): observe C-1 (197.2 ppm) and C-4 (75.2 ppm).

B. Storage After Quenching. A second reaction performed on identical scale was stirred at -78 °C for 30 min, maintained at 0 °C for 5 h, and kept at room temperature for 15 h. At this point, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl solution (previously deoxygenated, 6 mL), and stirred at rt under argon for an additional 16 h before being diluted with brine (20 mL) and extracted with ether (3 x 25 mL). Workup in the predescribed manner afforded 174 mg (52%) of **12**, 60 mg (18%) of **13**, 19 mg (6%) of **14**, and 14 mg (4%) of **15**.

X-Ray Data Collection, Structure Determination and Refinement for 12. A transparent single crystal of **12** was mounted on a pin and transferred to the goniometer. The space group was determined to be the centric $P2_1/n$ from the systematic absences. A summary of data collection parameters is given in Table I.

The geometrically constrained hydrogen atoms were placed in calculated positions 0.95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5.5 $Å^2$. The methyl hydrogen atoms were included as a rigid group with rotational freedom at the bonded carbon atom (C-H = 0.95 Å, B = 5.5 $Å^2$). The alcoholic hydrogen atom was located from a difference Fourier map and included with fixed contributions (B = 5.5 $Å^2$). High thermal motion was noted for the isopropyl groups but disorder was not evident. Refinement of nonhydrogen atoms with anisotropic temperature factors led to the final values of R = 0.056 and R_w = 0.056.

X-Ray Data Collection, Structure Determination and Refinement for 13. A transparent single crystal of **13** was mounted on a pin and transferred to the goniometer. The space group was determined to be either the centric C2/c or acentric Cc from the systematic absences. The subsequent solution and successful refinement of the structure were carried out in the centric space group C2/c. A summary of data collection parameters is given in Table I.

Least-squares refinement with isotropic thermal parameters led to R = 0.120. The geometrically constrained hydrogen atoms were placed in calculated positions 0.95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5.5 $Å^2$. The methyl hydrogen atoms were included as a rigid group with rotational freedom at the bonded carbon atom (C-H = 0.95 Å, B = 5.5 $Å^2$). The O(6) hydrogen atom was located from a difference Fourier map and included with fixed contributions (B = 5.5 $Å^2$). Refinement of nonhydrogen atoms with anisotropic temperature factors led to the final values of R = 0.047 and R_w = 0.049.

Coupling with O-Silylation of the 1,3,5-Cyclooctatriene Dienolate. The vinyl anion **11** was generated as before from 0.45 mL (6.0 mmol) of 2,3-dihydrofuran and 6.0 mmol of *tert*-butyllithium in 15 mL of anhydrous THF. This cold (-78 °C) solution was treated dropwise with an equally cold solution of **6** (400 mg, 2.0 mmol) and maintained sequentially at -78 °C for 1 h, 0 °C for 1 h, and at room temperature for 16 h. The reaction mixture was cooled to 0 °C and treated with 20 drops of triethylamine followed by 0.76 mL (6.0 mmol) of chlorotrimethylsilane. After solvent evaporation, the residual solid was slurried in ethyl acetate and filtered through Celite. The filtrate was evaporated to leave an oil, purification of which by chromatography on silica gel (elution with 20% ethyl acetate and 1% triethylamine in petroleum ether) gave 490 mg (51%) of

16, 230 mg (24%) of **17**, and 3% of a third isomer which decomposed before characterization. As a consequence of the dynamic conformational properties of **16** and **17**, their ^{1}H NMR spectra are not well resolved under ordinary conditions.

For **16**: colorless crystals, mp 64-67 °C; IR ($CHCl_3$, cm^{-1}) 1240, 1165, 1100, 1060, 1020, 865, 835; ^{1}H NMR (300 MHz, C_6D_6) δ 4.52-4.40 (br m, 2 H), 3.79-3.67 (m, 4 H), 2.72-2.67 (br m, 2 H), 1.53-1.38 (br m, 2 H), 1.25 (d, J = 6 Hz) and 1.36-1.16 (m, total 14 H), 0.35 (s, 18 H); ^{13}C NMR (75 MHz, C_6D_6) the only well resolved peaks are seen at 71.0, 67.9, 23.5, 22.4, and 0.96 ppm; MS m/z (M^+) calcd 482.2519, obsd 482.2534.

For **17**: colorless crystals, mp 147-150 °C; IR ($CHCl_3$, cm^{-1}) 1245, 1170, 1110, 1070, 1035, 840; ^{1}H NMR (300 MHz, C_6D_6) δ 4.36-4.31 (br, 1 H), 4.19 (hept, J = 6 Hz, 1 H), 3.77-3.68 (m, 4 H), 2.69 (br, 2 H), 1.30 (d, J = 6 Hz) and 1.31-1.06 (m, total 16 H), 0.41 (s, 9 H), 0.35 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) the only well resolved peaks are seen at 71.0, 23.2, 1.4, and 1.3 ppm; MS m/z (M^+) calcd 482.2519, obsd 482.2530.

Regeneration of the Triene Diolates. A. From 16. A cold (-78 °C), magnetically stirred solution of **16** (20 mg, 0.057 mmol) in dry THF (3 mL) was blanketed with argon and treated dropwise with ethereal methyllithium (0.12 mL of 1.4 M, 0.168 mmol). After 15 min, the reaction mixture was allowed to warm to room temperature, quenched with water (3 mL), and extracted three times with ether. The combined organic extracts were dried and evaporated to give 20 mg (100%) of **12**, spectroscopically identical to the compound described above.

B. From 17. By means of an identical procedure, 20 mg (0.057 mmol) of **17** was transformed into 12 mg (86%) of **13**, spectroscopically identical to the compound described above.

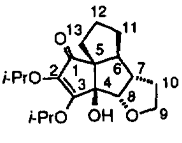
X-Ray Data Collection, Structure Determination and Refinement for 17. A transparent single crystal of **17** was mounted on a pin and transferred to the goniometer. The space group was determined to be either the centric $P\bar{1}$ or acentric P1. The subsequent solution and successful refinement of the structure were carried out in the centric space group $P\bar{1}$. A summary of data collection parameters is given in Table I.

Least-squares refinement with isotropic thermal parameters led to R = 0.141. The geometrically constrained hydrogen atoms were placed in calculated positions 0.95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5.5 Å^2. The methyl hydrogen atoms were included as a rigid group with rotational freedom at the bonded carbon atom (C-H = 0.95 Å, B = 5.5 Å^2). Refinement of nonhydrogen atoms with anisotropic temperature factors led to the final values of R = 0.047 and R_w = 0.060.

Mixed Addition of 5-Lithio-2,3-dihydrofuran and 1-Lithiocyclopentene to 6. A. With 11 as the Lead Nucleophile. 2,3-Dihydrofuran (0.55 mL, 7.5 mmol) dissovled in cold (-78 °C) THF (5 mL) under argon was metalated with *tert*-butyllithium (3.10 mL of 1.7 M, 5.27 mmol) as before. To the resulting cold solution of **11** was added a solution of **6** (1.0 g, 5.0 mmol) in THF (15 mL, precooled to -78 °C). The reaction mixture was stirred for 30 min, during which time 1-lithiocyclopentene was prepared by treating cyclopentenyl iodide (1.0 g, 5.2 mmol) in dry THF (15 mL) dropwise with 6.0 mL of 1.7 M *tert*-butyllithium (10.2 mmol). This solution was stirred for 30 min at -78 °C prior to being transferred by cannula into the reaction mixture, which was stirred at -78 °C for 1 h and at rt for 24 h. After the contents were cooled to 0 °C, water (20 mL) was introduced dropwise followed by further dilution with brine (20 mL). The products were extracted into ether (3 x 25 mL) and the combined organic phases were washed with water (40 mL) and brine (40 mL), dried, and evaporated to leave an orange oil. Flash chromatography of this material on silica gel (elution with 40% ether in petroleum ether) led to the isolation of three fractions. Medium-pressure chromatography (silica gel, elution with 40% ether in petroleum ether) of fraction B gave 152 mg (9%) of pure **31** and 198 mg (12%) of pure **32**. Medium-pressure chromatography of fraction C (silica gel, elution with 35% ethyl acetate in petroleum ether) afforded 436 mg (26%) of **33**. Fraction A contained no relevant products.

For **31**: colorless solid, mp 139-141 °C; IR ($CHCl_3$, cm^{-1}) 3590, 1695, 1625, 1390, 1315; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (hept, J = 6.1 Hz, 1 H), 4.88 (hept, J = 6.2 Hz, 1 H), 4.04 (d, J = 4.7 Hz, 1 H), 3.86-3.72 (m, 2 H), 2.56-2.50 (m, 1 H), 2.33 (s, 1 H), 2.24-2.19 (m, 1 H), 2.08-1.39 (series of m, 8 H), 1.35 (d, J = 6.2 Hz, 3 H), 1.30 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 6.2 Hz, 3 H), 1.19 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.4, 165.0, 131.1, 91.4, 85.4, 74.2, 71.9, 68.1 (2 C), 52.1, 50.9, 34.0, 33.5, 32.1, 26.9, 22.9, 22.6, 22.4 (2 C) (quaternary C not observed); MS m/z (M^+) calcd 336.1937, obsd 336.1940.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.82; H, 8.39. Found: C, 68.15; H, 8.66.

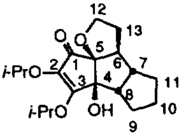


Irradiate	Observe	% NOE
H-6	H-7	1.9
H-8	H-7	6.7
	OH	4.6
H-7	H-6	2.4
	H-8	11

Semi-selective INEPT:
Irradiate H-6 (δ 2.22): observe C-1 (203.4 ppm).
Irradiate H-8 (δ 4.04): no effect at C-3 (165.0 ppm) because of an approximate 90° dihedral angle.

For **32**: colorless solid, mp 67-69 °C; IR ($CHCl_3$, cm^{-1}) 3470, 1680, 1585, 1317, 1295, 1080, 1000, 970; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (hept, J = 6.1 Hz, 1 H), 4.91 (hept, J = 6.2 Hz, 1 H), 4.23-4.17 (m, 1 H), 4.00-3.92 (m, 1 H), 3.27 (s, 1 H), 2.64-2.46 (m, 2 H), 2.41-2.33 (m, 1 H), 2.28-2.14 (m, 1H), 1.86-1.66 (m, 4 H), 1.65-1.47 (m, 2 H), 1.37 (d, J = 6.1 Hz, 3 H), 1.35 (d, J = 6.2 Hz, 3 H), 1.30-1.20 (m, 1 H), 1.24 (d, J = 6.2 Hz, 3 H), 1.20 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.8, 169.1, 132.7, 94.1, 82.5, 74.9, 72.1, 70.6, 54.7, 50.5, 50.3, 32.9, 30.5, 28.0, 25.2, 23.0, 22.8 (2 C), 22.3; MS m/z (M^+) calcd 336.1937, obsd 336.1947.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.82; H, 8.39. Found: C, 68.00; H, 8.52.

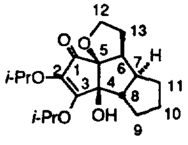


Irradiate	Observe	% NOE
H-7	H-12β	2.9
H-8	H-12β	1.1
H-12β	H-7	5.0
	OH	4.1
H-12α	H-6	2.6

Semi-selective INEPT:
Irradiate H-6 (δ 2.37): observe C-1 (196.8 ppm).
Irradiate H-8 (δ 2.59): no effect at C-3 (169.1 ppm) because of an approximate 90° dihedral angle.

For **33**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3500 (br), 1695, 1610, 1390, 1305, 1100, 1015; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (hept, J = 6.1 Hz, 1 H), 5.00 (hept, J = 6.1 Hz, 1 H), 4.21-4.12 (m, 2 H), 3.0 (br, 1 H), 2.60-2.51 (m, 1 H), 2.05-1.85 (m, 4 H), 1.83-1.38 (series of m, 5 H), 1.34 (d, J = 6.1 Hz, 3 H), 1.33 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 6.1 Hz, 3 H), 1.20 (d, J = 6.1 Hz, 3 H), 1.2-1.1 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 197.6, 166.6, 134.9, 97.7, 75.6, 74.7, 72.9, 71.8, 55.1, 46.1, 44.6, 27.1, 26.2, 22.9, 22.6, 22.5 (2 C), 22.0 (2 C); MS m/z (M^+) calcd 336.1937, obsd 336.1935.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.82; H, 8.39. Found: C, 67.81; H, 8.53.



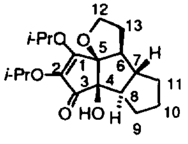
Irradiate	Observe	% NOE
H-6	H-7	6.7
	H-13α	5.9
OH	H-8	2.5

Semi-selective INEPT:
Irradiate H-6 (δ 2.56): observe C-1 (197.6 ppm).

B. With Lithiocyclopentene as the Lead Nucleophile. 1-Iodocyclopentene (1.00 g, 5.0 mmol) was dissolved in anhydrous THF (15 mL), cooled to -78 °C, treated with *tert*-butyllithium (6.0 mL of 1.7 M, 10.2 mmol), and stirred for 30 min, whereupon a solution of **6** (1.0 g, 5.0 mmol) in THF (15 mL, precooled to -78 °C) was introduced via cannula. The reaction mixture was stirred for 30 min at -78 °C, during which time a solution of **11** was prepared at the same temperature from 2,3-dihydrofuran (0.55 mL, 7.5 mmol) and *tert*-butyllithium (3.05 mL of 1.7 M, 4.9 mmol) in THF (15 mL), stirred at 0 °C for 20 min, returned to -78 °C, and transferred into the reaction mixture by means of a cannula. The reaction mixture was stirred at -78 °C for 1 h and at rt for 24 h in advance of cooling to 0 °C, quenching with water (20 mL), dilution with brine (20 mL), and extraction with ether (3 x 25 mL). The combined organic phases were washed with water (40 mL) and brine (40 mL), dried, and evaporated to leave an oil which was subjected to flash chromatography on silica gel (elution with 1:1 ether/petroleum ether) to give a purified four-component mixture. Through a combination of medium-pressure chromatography on silica gel (elution with 40% ether in petroleum ether) or alumina (elution with 6:3:1 petroleum ether/ether/acetone), there was isolated 207 mg (12%) of **31**, 374 mg (21%) of **32**, 50 mg (3%) of **41**, and 142 mg (8%) of **42**.

For **41**: colorless solid, mp 139-141 °C; IR ($CHCl_3$, cm^{-1}) 3510 (br), 1700, 1610, 1380, 1370, 1305, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (hept, J = 6.1 Hz, 1 H), 5.02 (hept, J = 6.1 Hz, 1 H), 4.21 (ddd, J = 8.3, 8.3, 1.4 Hz, 1 H), 3.96-3.90 (m, 1 H), 2.70 (br, 1 H), 2.30-2.24 (m, 1 H), 2.06-1.92 (m, 4 H), 1.77-1.52 (m, 5 H), 1.30 (d, J = 6.1 Hz, 3 H), 1.28 (d, J = 6.1 Hz, 3 H), 1.21 (d, J = 6.1 Hz, 3 H), 1.19 (d, J = 6.1 Hz, 3 H), 1.13-1.05 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.0, 164.0, 130.7, 100.4, 76.2, 73.9, 71.9,70.6, 57.9, 53.6, 47.0, 30.9, 26.9, 25.2, 22.8, 22.7 (2 C), 22.6, 19.4; MS m/z (M^+) calcd 336.1937, obsd 336.1933.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.82; H, 8.39. Found: C, 67.76; H, 8.53.

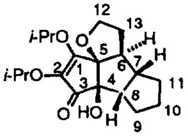


Irradiate	Observe	% NOE
H-6	H-13β	0.9
	H-8	3.5
H-12β	H-7	5.5
	H-13β	3.0
	OH	0.8

Semi-selective INEPT (in C_6D_6 solution):
Irradiate H-6 (δ 2.13): observe C-1 (163.0 ppm).

For **42**: colorless solid, mp 79-81 °C; IR ($CHCl_3$, cm^{-1}) 3500 (br), 1700, 1610, 1380, 1370, 1300, 1290; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (hept, J = 6.1 Hz, 1 H), 5.05 (hept, J = 6.1 Hz, 1 H), 4.13-4.06 (m, 1 H), 3.98-3.90 (m, 1 H), 3.12 (br, 1 H), 2.64-2.41 (m, 3 H), 2.18-2.06 (m, 1 H), 1.81-1.43 (m, 6 H), 1.34-1.20 (m, 1 H), 1.31 (d, J = 6.1 Hz, 3 H), 1.29 (d, J = 6.1 Hz, 3 H), 1.22 (d, J = 6.1 Hz, 3 H), 1.20 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.6, 165.1, 132.8, 94.7, 82.6, 73.9, 72.0, 70.2, 54.1, 50.6, 50.1, 33.3, 30.9, 27.7, 25.6, 22.8, 22.7, 22.6 (2 C); MS m/z (M^+) calcd 336.1937, obsd 336.1940.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.82; H, 8.39. Found: C, 67.89; H, 8.43.



Irradiate	Observe	% NOE
H-7	H-8	5.4
H-8	H-7	5.0
H-6	H-8	< 1

Semi-selective INEPT:
Irradiate H-6 (δ 2.45): observe C-1 (165.1 ppm).
Irradiate H-8 (δ 2.61): no effect at C-3 (198.6 ppm) because of an approximate 90° dihedral angle.

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Supplementary Material Available: Tables of bond distances and angles, final fractional coordinates, thermal parameters, and structure factor data for **12**, **13**, and **17** (27 pages). This information can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

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