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Studies of the Generation and Pericyclic Behavior of Cyclic Pentadienyl Carbanions. Alkylation Reactions as an Efficient Route to Functionalized *cis*-Bicyclo[3.3.0]octenes

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Abstract: Carbolithiation has been studied with alkyllithium reagents in a series of six- through nine-membered 3-methylene-1,4-cycloalkadienes, efficiently producing the corresponding cyclic pentadienyl carbanions. These pentadienyl anions display unique reactivity, depending on ring size. Cyclooctadienyl anions readily undergo disrotatory electrocyclization to *cis*-bicyclo[3.3.0]octenyl systems, which are trapped with a variety of electrophiles to stereoselectively provide functionalized *cis*-bicyclo[3.3.0]octenes. The carbolithiation and electrocyclization processes are examined using low-temperature ^{1}H NMR experiments. An expedient synthesis of a linear triquinane illustrates this methodology. Electrocyclization of the corresponding cyclononadienyl anion requires unusually high temperatures (120 °C), and computational studies provide insights into this change in reactivity. Cycloheptadienyl and cyclohexadienyl anions, generated via carbolithiation, provide functionalized cycloheptadienes and cyclohexadienes upon electrophilic capture. Trapping experiments reveal that the cycloheptadienyl anions are transformed to heptatrienyl anions. A series of experiments have been designed to explore evidence for the feasibility of equilibration of open and closed anionic systems, and these studies report the first isolation of a *cis*-bicyclo[3.1.0]hexene derived from electrocyclization of a cyclohexadienyl carbanion.

Introduction

Thermal and photochemical electrocyclizations have played a prominent role in our understanding of both synthetic and physical organic chemistry.[1] An early example of thermal electrocyclization, or “valence tautomerism”, of 1,3,5-cyclooctatriene to *cis*-bicyclo[4.2.0]octa-2,4-diene was first disclosed by Cope[2] in 1950, and the dynamics of the equilibrium were subsequently explored by Winstein.[3] The conservation of orbital symmetry and the stereospecific nature of the electrocyclization were significant components of the Woodward and Hoffmann treatise.[4] Their conclusions regarding electrocyclic reactions predicted that charged species should behave in analogous fashion as the corresponding isoelectronic neutral system.[4a] A pioneering report by Bates and co-workers in 1969 confirmed this prediction for the anionic equivalent of cyclooctatriene, with the observation of the disrotatory conversion of cyclooctadienyllithium to *cis*-bicyclo[3.3.0]octenyllithium.[5] Since this discovery, surprisingly few reports of electrocyclic ring closures of pentadienyl anions have appeared. The low-yield conversion of 1,5-diphenylpentadienyl anion to isomeric diphenylcyclopentenes under harsh reaction conditions was disclosed and remains the only example, to date, of an acyclic, all-carbon pentadienyl anion electrocyclization.[6] Additional reports have described attempts at cyclization of cyclic[7] and acyclic[8] pentadienyl anions. In the context of studies toward new strategies for natural product total synthesis, we proposed to investigate the nature of this anionic electrocyclic ring closure in a cascade reaction in which the requisite pentadienyl system is generated through the initial carbolithiation[9] of triene **1** (Figure 1), inspired by the well-known addition of organometallic reagents to the 6-position of fulvenes to give cyclopentadienyl anions (Eq. 1).[10]

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(2) (a) Cope, A. C.; Hochstein, F. A. *J. Am. Chem. Soc.* **1950**, *72*, 2515−2520. (b) Cope, A. C.; Haven, A. C.; Ramp, F. L.; Trumbull, E. R. *J. Am. Chem. Soc.* **1952**, *74*, 4867−4871.

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(5) Bates, R. B.; McCombs, D. A. *Tetrahedron Lett.* **1969**, *12*, 977−978.

(6) Shoppee, C. W.; Henderson, G. N. *Chem. Commun.* **1974**, 561−562.

(7) Bates, R. B.; Deines, W. H.; McCombs, D. A.; Potter, D. E. *J. Am. Chem. Soc.* **1969**, *91*, 4608.

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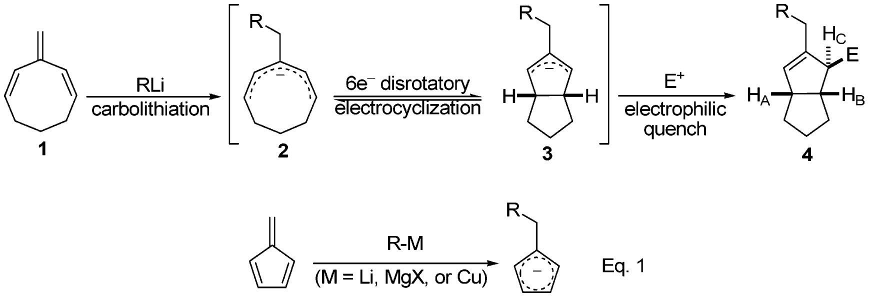

Figure 1. Concept for the carbolithiation/electrocyclization/alkylation cascade.

Disrotatory ring closure of the cyclooctadienyl anion **2** to the *cis*-bicyclo[3.3.0]octenyl anion **3** and subsequent electrophilic capture of **3** would stereoselectively provide the functionalized *cis*-bicyclo[3.3.0]octene **4**. This reaction cascade would allow formation of three C−C bonds and three stereogenic sites in a single operation from simple starting materials. The variation of three reaction components would potentially allow for substantial diversity in product structures. In this account, we report the successful realization of this process, its scope with respect to organolithium reagents and electrophile participation, proton NMR analysis of the reaction, and its application for preparation of a linear triquinane.[11] Our investigations describe the unique reactivity observed upon the extension of this concept to six-, seven-, and nine-membered ring substrates.

Results and Discussion

The triene **1** was prepared by Wittig methylenation ($Ph_3P{=}CH_2$, Et_2O, −78 °C; 67%) of 2,7-cyclooctadienone,[11] which in turn was accessible in one step by *o*-iodoxybenzoic acid (IBX) oxidation of cyclooctanone.[12] For large-scale preparations, the use of a 3-fold excess of IBX became impractical, and the more economical albeit longer procedure of Garbisch[13] was preferred. This three-step sequence involved dibromination of the cyclic ketal, dehydrobromination, and acid-catalyzed hydrolysis to yield the cross-conjugated dienone for subsequent methylenation. With the cyclic triene in hand, an initial screening of reaction conditions for the addition of secondary and tertiary alkyllithium reagents revealed that Et_2O was the optimal solvent, providing for rapid carbolithiation. Reactions of primary alkyllithium reagents required hydrocarbon solvents, typically hexanes, as well as an equivalent of diamine ligand, such as TMEDA or (−)-sparteine, to effect carbolithiation.[14] Typical experimental conditions involve dropwise introduction of a slight excess (10 mol %) of organolithium reagent into a solution (∼0.15 M) of triene **1** at −78 °C. Stirring of the reaction mixture with warming to 22 °C over 1−2 h resulted in complete carbolithiation and electrocyclic ring closure. Quenching of the resultant *cis*-bicyclo[3.3.0]octenyl anion at −78 °C with a solution of electrophile in THF or Et_2O led to the isolation of products. The scope of the reaction was explored as summarized in Table 1. Typical examples of primary, secondary, and tertiary alkyllithium reagents proved to be uniformly effective for the generation of pentadienyl anions, and a wide variety of electrophiles were used as quenching agents. Phenyl-, allyl-, methyl-, and vinyllithium species and Grignard reagents failed to provide for carbometalation. The generation of secondary and primary alkyllithium reagents from the corresponding alkyl iodides by lithium/halogen exchange with *tert*-butyllithium (entries 8 and 11) demonstrates the possibility for broader applications of this reaction component and the compatibility of base-stable functionality. The nucleophilicity of the intermediate bicyclic allyllithium species **3** (Figure 1) enabled efficient trapping with a range of electrophiles. Alkylation reactions with ketones, aldehydes, and CO_2 (entries 1−3 and 7−11) led to formation of a new C−C bond, while heteroatomic electrophiles (entries 4−6) introduced allylic sulfide, alcohol, and silane moieties. Transmetalation of the intermediate *cis*-bicyclo[3.3.0]octenyllithium species **3** using a THF solution of $CuCN{\cdot}2LiCl$ was also possible.[15] The resultant allylcuprates efficiently engaged in C−C bond-forming conjugate additions with α,β-unsaturated ketones and esters in the presence of TMSCl (entries 12 and 13), acylations with acid chlorides (entry 14), and alkylation reactions with alkyl iodide and epoxide electrophiles (entries 15 and 16). The relative stereochemistry of the products was established by ^1H NMR, COSY, and NOESY data. The C-3 allylic methine hydrogen H_C of the major products (see **4**, Figure 1) consistently appears as a broadened singlet upon saturation of vicinal exocyclic neighboring hydrogens. This observation is indicative of the small coupling constant ($J_{BC} < 2$ Hz) which is anticipated from the Karplus correlation of a dihedral angle ($H_B{-}C{-}C{-}H_C$) approximating 106°. The analyses of 2D-NOESY spectra confirmed all assignments and revealed the expected through-space correlations of the *cis* hydrogens for the ring fusion of the bicyclic system. Electrophilic trapping of the allyl carbanions from the more accessible convex face of the *cis*-bicyclo[3.3.0]octenyl system was evident since through-space correlations were observed as cross-peaks between the bridgehead methine hydrogens and methyl, aryl, or methylene hydrogens of C-3 substituents. In all cases, our major isomers did not display through-space NOESY correlations of the hydrogens of the *cis*

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(9) (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988. (b) *Lithium Chemistry: A Theoretical and Experimental Overview*; Sapse, A. M., Schleyer, P. v. R., Eds.; John Wiley & Sons: New York, 1995. (c) Gray, M.; Tinkel, M.; Sniekus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., McKillop, A., Eds.; Pergamon: Oxford, 1995; Vol. 11, pp 1−92. (d) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., 2002; pp 273−335. (e) *Organolithiums in Stereoselective Synthesis*; Hodgson, D. M., Ed.; Springer: Berlin, 2003. (f) *The Chemistry of Organolithium Compounds*; Rapopport, Z., Marek, I., Eds.; John Wiley & Sons: Chichester, 2004.

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(12) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.

(13) Garbisch, E. W. *J. Org. Chem.* **1965**, *30*, 2109−2120.

(14) Norsikian, S.; Baudry, M.; Normant, J. F. *Tetrahedron Lett.* **2000**, *41*, 6575−6578.

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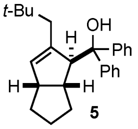
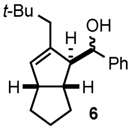
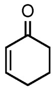
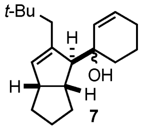
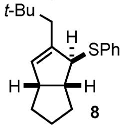
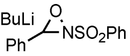
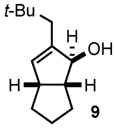
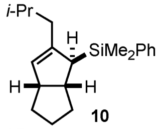
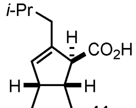
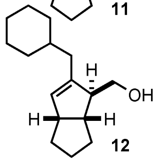
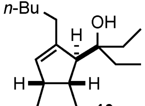
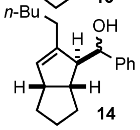
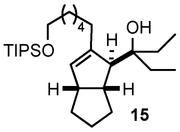
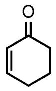
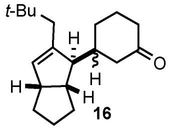
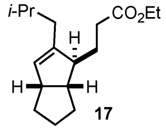
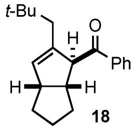
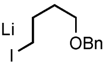
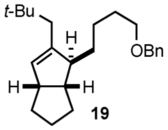
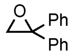
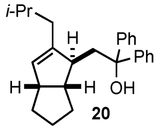
Table 1. Scope of the Cascade Carbolithiation/Electrocyclization/Alkylation Reaction of **1**[a]

Entry	RLi/Electrophile	Major Product	Yield (%)[b]	dr[c]
1	*t*-BuLi Ph_2CO	 **5**	65	>20:1
2	*t*-BuLi PhCHO	 **6**	64	>20:1 [1.6:1][d]
3	*t*-BuLi 	 **7**	61	>20:1 [2.5:1][d]
4	*t*-BuLi PhSSPh	 **8**	71	10:1
5	*t*-BuLi 	 **9**	49	>20:1
6	*i*-PrLi $PhMe_2SiCl$	 **10**	70	>20:1
7	*i*-PrLi CO_2	 **11**	71	6.8:1
8[e]	*c*-HexLi CH_2O	 **12**	48	11.4:1
9	*n*-BuLi Et_2CO	 **13**	77	>20:1
10	*n*-BuLi PhCHO	 **14**	72	>20:1 [1:1][d,f]
11[e]	$TIPSO(CH_2)_5Li$ Et_2CO	 **15**	77	>20:1
12[g]	*t*-BuLi 	 **16**	63	>20:1 [2.5:1][d]
13[g]	*i*-PrLi $H_2C{=}CHCO_2Et$	 **17**	68	7.2:1
14[g]	*t*-BuLi PhCOCl	 **18**	72	>20:1
15[g]	*t*-BuLi 	 **19**	46	4.7:1
16[g]	*i*-PrLi 	 **20**	61	9.7:1

[a] Reactions conducted with **1** in Et_2O (entries 1−7, 12−16) or hexanes/1 equiv of (−)-sparteine (entries 8−11). [b] Isolated yields after purification. [c] Diastereomeric ratios determined from ^1H NMR data of crude product mixtures and refer to the exo (major):endo (minor) ratio of the C-3 substituent with respect to the *cis*-bicyclo[3.3.0]octene. [d] Diastereoselectivity (dr) as measured at the exocyclic stereogenic center in compounds **6**, **7**, **14**, and **16**. [e] Generated from the corresponding iodides by treatment with *t*-BuLi (2.2 equiv) and cannulation away from precipitated LiI. [f] Enantiomeric excesses of 9 and 16% were determined by Mosher ester analysis of each diastereomeric alcohol. [g] A solution of CuCN (1 equiv) and LiCl (2 equiv) in THF was added prior to the electrophile.

ring fusion and the adjacent *trans* C-3 allylic hydrogen. In examples where a fourth exocyclic stereogenic site was formed in the alkylation step (entries 2, 3, 10, and 12), moderate stereoselectivity was observed. Our initial studies to provoke asymmetric induction in the alkylation reactions of the meso allyl anion **3** employed the use of (−)-sparteine as a diamine additive (entry 10). However, low levels of chiral induction were observed for each of the purified diastereomeric alcohols **14** (9−16% ee).

The relative reactivity of the carbolithiation and electrocyclic reactions was investigated by ^1H NMR spectroscopy (Figure 2). Thus, a solution of **1** in Et_2O-d_{10} was treated at −78 °C with 1.1 equiv of *tert*-butyllithium in pentane, and the resultant solution was observed by 400 MHz ^1H NMR spectroscopy as the probe temperature was gradually raised to 25 °C. Carbolithiation was complete within minutes at −78 °C, as evidenced by the absence of signals due to triene **1** and the appearance of signals due to cyclooctadienyl anion **21**. Carbanion **21** is characterized by a doublet at δ 5.69 (H_b, $J = 9.2$ Hz), broad signals at δ 3.03 (H_c) and 2.79 (H_d), and a singlet at δ 1.66 ppm (H_a). A new species, the *cis*-bicyclo[3.3.0]octenyl anion **22**, begins to form at −35 °C at the expense of **21**, with the appearance of a new peak at δ 2.50, and is further characterized by three singlets at δ 2.88 (H_c), δ 2.50 (H_b), and δ 1.85 ppm (H_a), respectively. On warming to +5 °C, signals assigned to cyclooctadienyl **21** are no longer apparent, and **22** is observed as the major species.

The extraordinarily facile carbolithiation of **1** at −78 °C is striking, since carbolithiations of terminal dienes generally require temperatures of 0 °C or higher.[9b,c] Furthermore, the temperature necessary for electrocyclization is notably lower than that observed by Bates and co-workers for the conversion of cyclooctadienyllithium to *cis*-bicyclo[3.3.0]octenyllithium in THF ($t_{1/2} = 80$ min at 35 °C).[5] Our DFT calculations[16] are consistent with these experimental observations and predict the free energy of activation for the cyclization to be 31.96 kcal/

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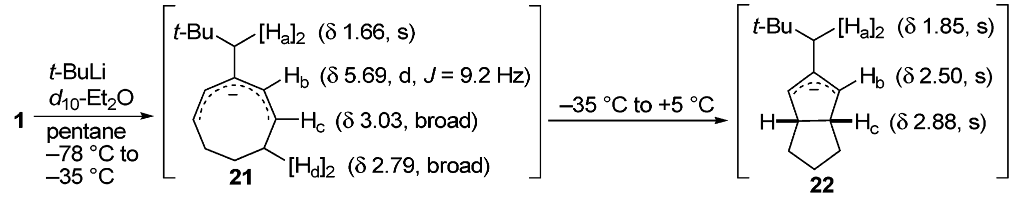
(16) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.



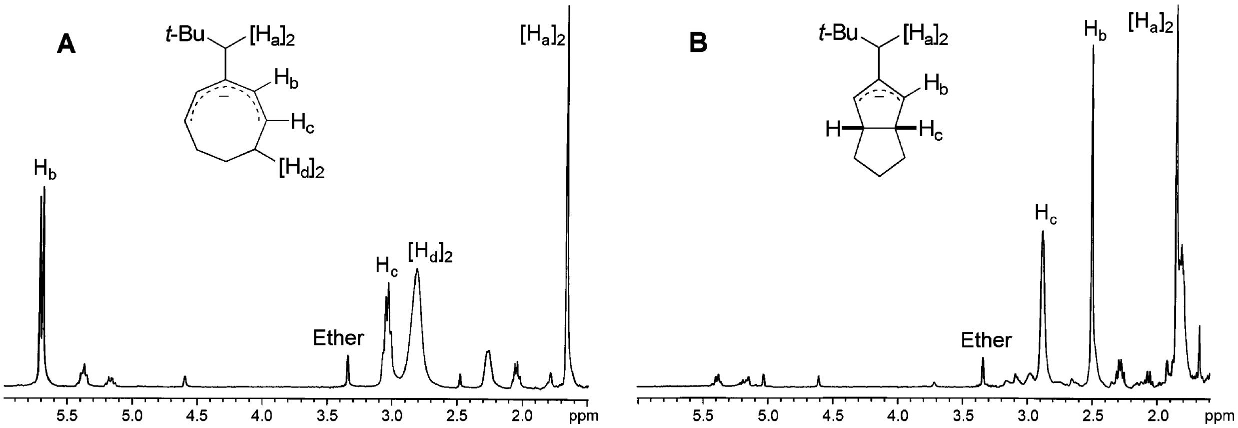
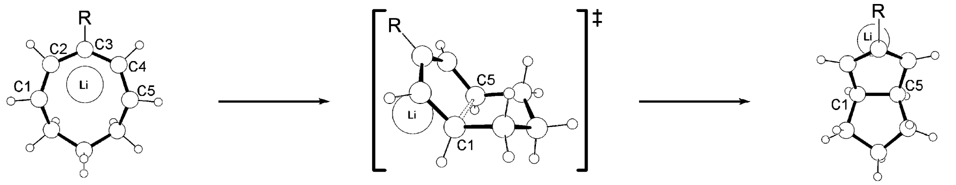


Figure 2. ^{1}H NMR spectra (400 MHz) of cyclooctadienyl anion **21** (A, at −35 °C) and *cis*-bicyclo[3.3.0]octenyl anion **22** (B, at +5 °C).



23 R = H
r(C_1-C_5); 3.442 Å
24 R = -(CH$_2$)$_4$CH$_3$
r(C_1-C_5); 3.381 Å

23-TS $E_a^‡$ = 31.96 kcal/mol
r(C_1-C_5); 2.206 Å
24-TS $E_a^‡$ = 26.30 kcal/mol
r(C_1-C_5); 2.200 Å

25 ΔG° = 1.31 kcal/mol
r(C_1-C_5); 1.595 Å
26 ΔG° = -6.05 kcal/mol
r(C_1-C_5); 1.594 Å

Figure 3. Comparisons of activation energies, Gibbs free energies, and bonding distances calculated for the electrocyclization of cyclooctadienyllithium and its *n*-pentyl derivative.

mol (at 298.15 K) in the case of the cyclooctadienyl ion **23**, whereas 26.3 kcal/mol is predicted for the *n*-pentyl-substituted analogue **24**. Thus, substitution of the eight-membered ring with an alkyl group at C-3 leads to a 4- to 5-fold increase of the rate of electrocyclization. Figure 3 illustrates the computational results for generated structures of the reactants, transition states, and the bicyclic allyl anions. The energy components of these calculations are enumerated in Table S1 (Supporting Information) and describe an energy difference that is mainly electronic in nature. These findings are summarized by the following discussion. The consideration of purely electronic contributions for the cyclizations of cyclooctadienyl ion **23** and *n*-pentyl derivative **24** reveal free energies of activation ($E_a^‡$) of 34.2 and 28.3 kcal/mol, respectively. The inclusion of entropy and solvation terms to account for the role of lithium cation in ether affect each case in a similar fashion, without changing the overall results. Transition state **23-TS** (R = H) lies 31.96 kcal/mol above the ground state of the cyclooctadienyl system **23**, whereas **24-TS** (R = *n*-pentyl) requires 26.30 kcal/mol. The overall change in Gibbs free energy ($\Delta G°$) for conversions to the respective allyllithium species reflects a favorable situation for the *n*-pentyl case **26** ($\Delta G° = -6.05$ kcal/mol) but a more difficult transformation for the unsubstituted cyclooctadienyl **25** ($\Delta G° = +1.31$ kcal/mol). We also have calculated distances (r) between the termini C_1 and C_5 which progress to bond formation. This exercise reveals substantial similiarities in the transition states and bicyclo[3.3.0] species, with a small differential in the respective ground states (Figure 3).

The net decrease in activation energy for the electrocyclic ring closure, which is observed upon alkyl substitution in this system, may be attributed to a destabilization of the ground state or lowering of the energy of the transition state. To evaluate these possibilities, we have calculated the homolytic C_3−C and C_3−H bond dissociation energies for both the ground- and transition-state species. In the starting cyclooctadienyl anion **24**, the bond dissociation energy of the alkyl substituent (C_3−C) is 98.61 kcal/mol, whereas the C_3−H bond dissociation energy in **23** is 111.80 kcal/mol. For the transition states **23-TS** and **24-TS**, homolytic bond dissociation energies are 128.47 (C_3−H) and 121.18 kcal/mol (C_3−C), respectively. These calculations indicate that the *n*-pentyl substituent destabilizes both the ground and the transition state by −13.2 and −7.3 kcal/mol, respectively, compared to the parent cyclooctadienyl system. However, the presence of the inductively donating *n*-pentyl group has a more significant effect in the ground state than in the transition state. Our computational thermodynamic driving force for the solution-phase cyclization is −6.05 kcal/mol, suggesting a highly favored overall conversion. Indeed, these insights effectively corroborate our previous observations stemming from the low-temperature NMR studies.

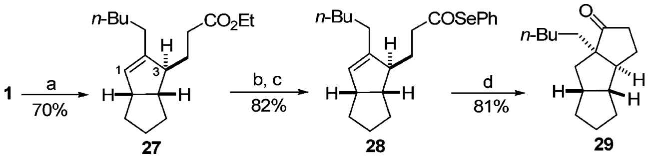


Figure 4. Expedient synthesis of linear triquinane **29**. Conditions: (a) *n*-BuLi, (−)-sparteine, hexanes, −78 °C to room temperature, 1 h; CuCN·2LiCl, THF, −78 °C; ethyl acrylate, TMSCl, −78 °C to room temperature; (b) LiOH, THF/H_2O; (c) *N*-(phenylselenyl)phthalimide, *n*-Bu_3P, THF; (d) *n*-Bu_3SnH, AIBN, PhH, reflux.

The synthetic potential of the carbolithiation/electrocyclization/alkylation cascade was demonstrated by the preparation of linear triquinane **29** (Figure 4).[11] Carbolithiation with *n*-BuLi in the presence of (−)-sparteine, followed by transmetalation with CuCN and treatment with ethyl acrylate/TMSCl, furnished ester **27** in 70% yield (C-3; dr = 8.4:1). Two-step conversion to phenylselenyl ester[17] **28** and subsequent acyl radical cyclization[18] furnished the triquinane **29** in excellent overall yield.

Our fundamental studies of the scope and utility of the carbolithiation/electrocyclization/alkylation cascade for cyclooctadienyl anions subsequently led us to examine the reaction course for both larger and smaller ring systems. Fraenkel and co-workers had reported the addition of alkyllithium reagents to substituted 4-methylene-2,5-cyclohexadienes and had detailed studies of ion-pairing of the resulting conjugated carbanions via NMR.[19] Bates and McCulloch had observed the thermal (120 °C) electrocyclization of cyclononadienyllithium and subsequent formation of a mixture of bicyclo[4.3.0]nonenes.[1e,20] In view of this precedent, the application of our reaction process to the cyclononadienyl anion appeared feasible. In the event, treatment of 3-methylene-1,4-cyclononadiene[21] **30** (Figure 5) with *n*-BuLi in hexanes/TMEDA at −78 °C and subsequent warming to 100−120 °C led to low yields of *cis*-bicyclo[4.3.0]nonene **33** (31%) upon quenching at −78 °C, as well as a complex mixture of unidentified hydrocarbons. While experiments indicated that carbolithiation to **31** occurred rapidly at −78 °C, cyclization to **32** required heating. The addition of various electrophiles upon recooling to −78 °C provided none of the expected alkylation products, suggesting facile proton abstraction at the elevated temperatures necessary for cyclization to **32**.

To understand the physical basis of the different kinetic behavior of the eight- and nine-membered substrates in more detail, we employed computational methods based on density functional theory.[16] Cyclization reactions were considered without and with ion-pairing, to separate purely electronic effects of the cyclization from the perturbation introduced by the formation of the allyllithium complex. The reaction energy profile (Figure 6) of the non-lithiated eight-membered carbanion **24a**, with a rate-determining activation barrier of 24.17 kcal/mol (**24a-TS**), leads to the bicyclic intermediate **26a** (broken line), which is computed to be slightly higher in energy than the starting cyclopentadienyl species **24a**, with a relative free energy of 1.43 kcal/mol. Electrophilic capture of this intermediate upon addition of CO_2 furnishes the carboxylate anion **34a**. Lithium coordination changes the reaction energy profile considerably, as highlighted by the solid line in Figure 6 and further enumerated in Table 2. The ion-pairing energy of the lithiated carbanion **24** in the ground state is computed to be −17.55 kcal/mol but decreases to −15.42 kcal/mol in the transition state. As a result, the activation energy, when one considers lithium cation coordination, increases to 26.3 kcal/mol (**24-TS**). The bicyclo[3.3.0]octenyllithium intermediate **26** is stabilized by 7.48 kcal/mol as compared to the non-lithiated system **26a**, resulting in a relative free energy of −6.05 kcal/mol.

The reason for increased ground-state stabilization in lithiated **24** lies in the compact ion-contact geometry facilitated by the transannular distance of the terminal sp^2 carbons. Streitwieser has shown that pentadienyllithium systems prefer a U-shaped structure, with the lithium cation η^5-bound to the pentadienyl anion.[22] Our calculations indicate an optimized distance of 3.21 Å between these two π-termini. Analysis of the ground state of the eight-membered anion **24** shows a distance of 3.38 Å between the carbon atoms, which approximates the optimum distance anticipated for the unsubstituted system. At this distance, ion-pairing effects are maximized between the lithium cation and the π system. This effect is less pronounced in the transition state **24-TS**, due to the fact that σ bond formation decreases accessible charge and consequently leads to a decrease of ion-pairing energy.

When we examine the observations of Figure 5, the non-lithiated nine-membered carbanion **31a** follows an analogous pathway (Figure 7) and displays an activation energy of 30.3 kcal/mol (**31a-TS**), leading to the 5,6-bicyclic non-lithiated intermediate **32a** (5.6 kcal/mol). Lithium coordination accounts for a slight decrease in the activation barrier to 29.0 kcal/mol (**31-TS**), whereas the bicyclic intermediate **32** is stabilized by nearly 16 kcal/mol, resulting in a relative free energy of −10.4 kcal/mol. For comparison, the calculations evaluated hypothetical reactions with CO_2, leading to the lithium carboxylate **35**, and the energy components are also enumerated in companion Table 3. At a rate-determining activation barrier of 29.0 kcal/mol, elevated temperature is required, as the cyclization of the nine-membered pentadienyl system is approximately 1000 times slower than that of the eight-membered ring. As before, lithium coordination has a pronounced effect on the energy profile. The stabilization of the transition state by ion-pairing in the nine-membered system is essentially identical to that observed in the eight-membered system. Interestingly, ion-pairing does not stabilize the ground state to the same degree as in the eight-membered analogue, and it destabilizes the ground state relative to the transition state by 1.2 kcal/mol. The computed transannular distance of the π-termini in lithiated **31** is 3.59 Å, deviating from the optimal distance of 3.21 Å. The ion-pairing energy for the ground state of the nine-membered system is 4.4 kcal/mol less than that of the eight-membered ring.

The experimental observations and the activation barriers for reactions of the eight- and nine-membered carbocycles offer a stark contrast. The barrier for cyclization of the nine-membered anion is approximately 5 kcal/mol higher than that of the eight-membered system. While ion-pairing is important, it does not

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(21) (a) Mehta, G. *Org. Prep. Proceed. Int.* **1970**, *2*, 245−248. (b) Billups, W. E.; Baker, B. A.; Chow, W. Y.; Leavell, K. H.; Lewis, E. S. *J. Org. Chem.* **1975**, *40*, 1702−1704.

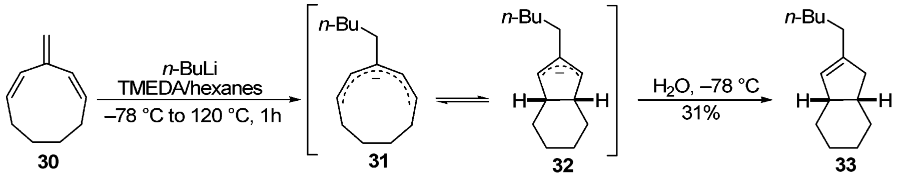

Figure 5. Carbolithiation studies of triene **30**.

Table 2. Energy Components for the Reaction Profile of Non-lithiated and Lithiated Species with Corresponding $\Delta\Delta G$ Values (kcal/mol)

species	ΔH	$-T\Delta S$	ΔG(GP)	ΔG(Solv)	ΔG(Sol)	$\Delta\Delta G$(Sol)
24a	−318 434.99	36.32	−318 471.31	−37.05	−318 508.36	0.00
24a-TS	−318 412.52	35.10	−318 447.63	−36.56	−318 484.19	24.17
26a	−318 433.51	35.27	−318 468.78	−38.15	−318 506.93	1.43
34a	−436 837.49	39.54	−436 877.03	−45.84	−436 922.87	−45.05
24	−323 165.83	37.18	−323 203.01	−8.79	−323 211.80	0.00
24-TS	−323 138.07	35.70	−323 173.77	−11.73	−323 185.50	26.30
26	−323 166.18	36.77	−323 202.96	−14.90	−323 217.86	−6.05
34	−441 567.68	41.05	−441 608.73	−25.53	−441 634.26	−53.00
Li^+	−4 571.41	9.48	−4 580.89	−105.01	−4 685.90	
CO_2	−118 352.27	15.25	−118 367.52	−1.94	−118 369.46	
24a + $Li^+ \rightarrow$ **24**	−159.43	−8.61	−150.82	133.27	−17.55	0.00
24a-TS + $Li^+ \rightarrow$ **24-TS**	−154.14	−8.88	−145.26	129.84	−15.42	2.13

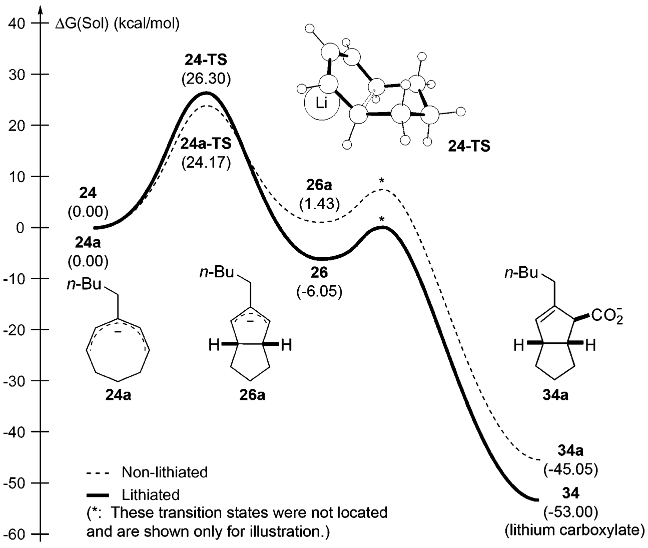

Figure 6. Comparison of energy profiles for non-lithiated **24a** and lithiated cyclooctadienyl **24** pathways.

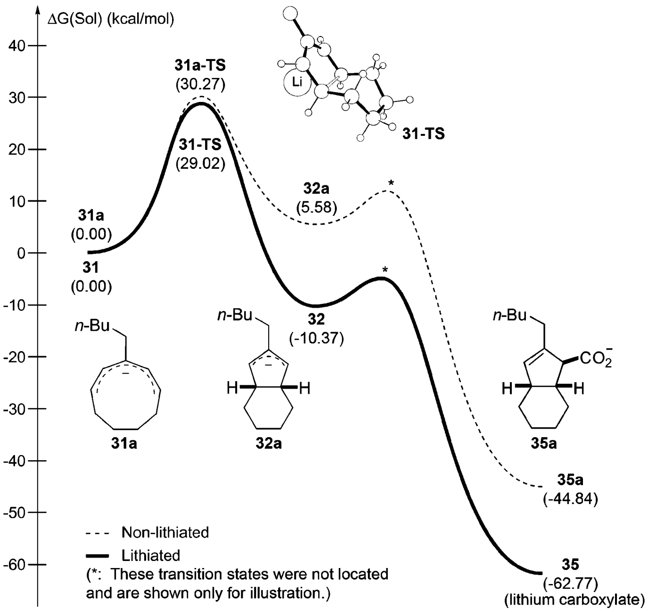

Figure 7. Comparison of energy profiles for non-lithiated **31a** and lithiated cyclononadienyl **31** pathways.

change the trend. Our analysis of **31-TS** recognizes strain in the transition state.

As shown in Figure 7, cyclization provides a planar, five-membered allylic system with a boat-like conformation for the newly formed cyclohexane. While this conformation is strained and less favored than the complementary chair-like conformer, it is required to facilitate the thermal disrotatory ring closure. Thus, substituents located on the π-termini of the pentadienyl system develop eclipsed interactions in the transition state for electrocyclization. This additional factor in the formation of the six-membered ring is alleviated in the cyclopentanyl case (Figure 3 for **24-TS**), which adopts an envelope conformation.

Our evaluation of six- and seven-membered ring substrates recognized the favorable planar orbital alignment of the starting trienes and transannular distances of reacting termini facilitating cyclization. However, we reasoned that the substantial ring strain introduced in the electrocyclic process would favor the conjugated pentadienyl carbanion. Thus, issues of reactivity of these trienes were examined to evaluate the synthetic utility of the reaction and to probe the possibility of an electrocyclic equilibrium of opened and closed anions. The subjection of 3-methylene-1,4-cycloheptadiene[23] **36** to conditions optimized for the eight-membered ring substrates resulted in smooth carbolithiation and, after electrophilic trapping, gave exclusively the 1,3-cycloheptadienes **39** (Figure 8).

No products were observed from alkylation of the *cis*-bicyclo-[3.2.0]heptenyl **38** or trapping of cycloheptadienyl anion **37** at the central carbon. The scope of the reaction was examined with respect to the reactivity of alkyllithium reagents and various electrophiles (Table 4). Application of the solvent systems optimized for the cases of the eight-membered ring triene allowed efficient carbolithiations with primary, secondary, and tertiary alkyllithium reagents. As before, carbolithiation was

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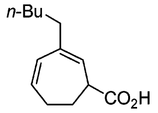
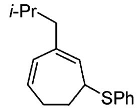
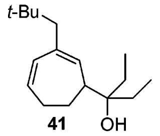
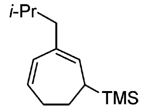
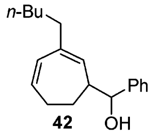
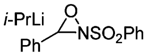
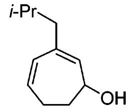
(23) Billups, W. E.; Chow, W. Y.; Leavell, K. H.; Lewis, E. S. *J. Org. Chem.* **1974**, *39*, 274−275.

Table 3. Energy Components for the Reaction Profile of Non-lithiated and Lithiated Cyclononadienyl Species with Corresponding $\Delta\Delta G$ Values (kcal/mol)

species	ΔH	$-T\Delta S$	ΔG(GP)	ΔG(Solv)	ΔG(Sol)	$\Delta\Delta G$(Sol)
31a	−343 074.62	38.12	−343 112.75	−35.22	−343 147.97	0.00
31a-TS	−343 044.74	37.01	−343 081.75	−35.95	−343 117.70	30.27
32a	−343 068.04	37.21	−343 105.25	−37.13	−343 142.38	5.58
35a	−461 474.38	42.20	−461 516.58	−45.69	−461 562.27	−44.84
31	−347 799.15	38.83	−347 837.98	−9.07	−347 847.05	0.00
31-TS	−347 771.11	37.74	−347 808.84	−9.18	−347 818.02	29.02
32	−347 805.26	36.55	−347 841.81	−15.60	−347 857.41	−10.37
35	−466 211.27	42.66	−466 253.93	−25.34	−466 279.27	−62.77
Li^+	−4 571.41	9.48	−4 580.89	−105.01	−4 685.90	
CO_2	−118 352.27	15.25	−118 367.52	−1.94	−118 369.46	
31a + $Li^+ \rightarrow$ **31**	−153.12	−8.77	−144.35	131.16	−13.19	0.00
31a-TS + $Li^+ \rightarrow$ **31-TS**	−154.96	−8.75	−146.21	131.78	−14.43	−1.24

Table 4. Scope of the Carbolithiation/Alkylation of Triene **36**[a]

Entry	RLi/Electrophile	Product	Yield (%)[b]	Entry	RLi/Electrophile	Product	Yield (%)[b]
1	*n*-BuLi CO_2	 **40**	82	4	*i*-PrLi PhSSPh	 **43**	65
2	*t*-BuLi Et_2CO	 **41**	67	5	*i*-PrLi TMSCl	 **44**	65
3	*n*-BuLi PhCHO	 **42**	78[c]	6	*i*-PrLi 	 **45**	37

[a] Reaction conducted in Et_2O (entries 2, 4−6) or hexanes/1 equiv of (−)-sparteine (entries 1 and 3). [b] Isolated yields after purification. [c] Isolated as an inseparable 1:1 mixture of diastereomers.

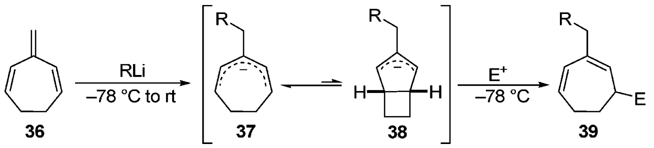


Figure 8. Carbolithiation and alkylation of triene **36**.

complete within minutes at −78 °C. Alkylation of cycloheptadienyl carbanions proved feasible, making this an efficient route for rapid preparation of functionalized 1,3-cycloheptadienes.

Investigations in the six-membered series employed 6,6-dimethyl-3-methylene-1,4-cyclohexadiene **46**, which was prepared as described by Zimmerman and co-workers.[24] Subjection of **46** to the usual conditions for carbolithiation and subsequent trapping with electrophiles furnished functionalized 1,3- or 1,4-cyclohexadienes **49** and **50** as major products (Figure 9). As with the seven-membered derivatives, no products deriving from electrocyclization of the cyclohexadienyl anion **47** were observed. Alkylation at the central carbon of the pentadienyl carbanion led to **50** as a result of significant steric hindrance imposed by the *gem*-dimethyl group.

Examples are summarized in Table 5. Carbolithiation of **46** with primary, secondary, and tertiary alkyllithium reagents proved facile at −78 °C. However, alkylations of the cyclohexadienyl anions were slower than those observed for the cycloheptadienyl cases in Table 4.

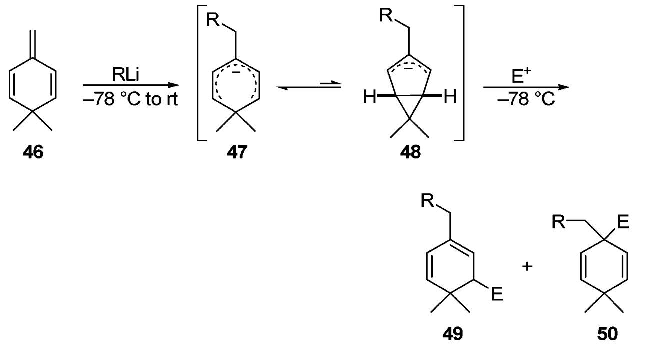


Figure 9. Carbolithiation and alkylation of triene **46**.

The absence of products derived from electrocyclization in the six- and seven-membered ring substrates indicated that these cyclic pentadienyl anions may not support an equilibrium with ring-closed species due to prohibitive strain energy, despite formation of a new carbon−carbon single bond. Experiments were designed in which *cis*-bicyclic allyl intermediates could be trapped via elimination processes to test the possibility of equilibration. Seven-membered triene **57**, containing the *gem*-diphenyl substitution, was prepared in two steps[25a] from 4,4-diphenylcycloheptanone.[25b−d] The seven-membered triene **57** was subjected to carbolithiation with *t*-BuLi at −78 °C, and

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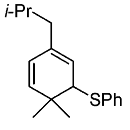
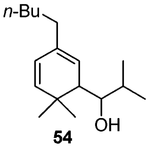
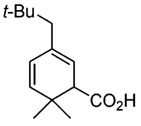
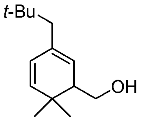
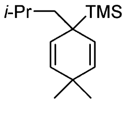
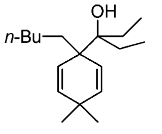
(24) Zimmerman, H. E.; Hackett, P.; Juers, D. F.; McCall, J. M.; Schröder, B. *J. Am. Chem. Soc.* **1973**, *95*, 3653−3662.

(25) (a) See Supporting Information. (b) Zimmerman, H. E.; Keese, R.; Nasielski, J.; Swenton, J. S. *J. Am. Chem. Soc.* **1966**, *88*, 4895−4904. (c) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 2544−2550. (d) Bunce, R. A.; Taylor, V. L.; Holt, E. M. *J. Photochem. Photobiol., A* **1991**, *57*, 317−329.

Table 5. Scope of the Carbolithiation/Alkylation of Triene **46**[a]

Entry	RLi/Electrophile	Product	Yield (%)[b]	Entry	RLi/Electrophile	Products	Yield (%)[b]
1	*i*-PrLi PhSSPh	 **51**	50	4	*n*-BuLi Me_2CHCHO	 **54**	67[c]
2	*t*-BuLi CO_2	 **52**	45	5	*t*-BuLi HCHO	 **55**	46
3	*i*-PrLi TMSCl	 **53**	31	6	*n*-BuLi Et_2CO	 **56**	38

[a] Reaction conducted in Et_2O (entries 1, 2, 4 and 5) or hexanes/1 equiv (−)-sparteine (entries 3 and 6). [b] Isolated yields after purification. [c] Isolated as a separable 3.3:1 mixture of diastereomers.

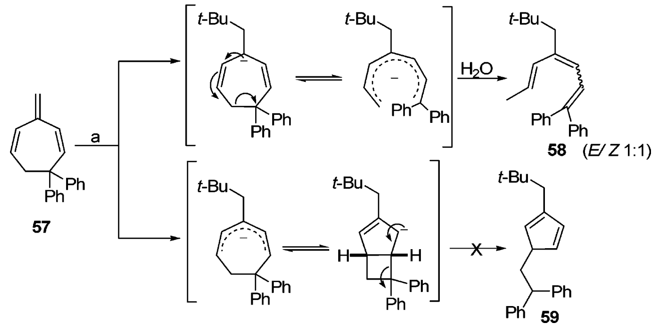


Figure 10. Result of carbolithiation of triene **57**. Conditions: (a) *t*-BuLi, Et_2O, −78 °C to room temperature, 12 h; 50%.

subsequent stirring at room temperature for 12 h gave triene **58** in 50% yield as a 1:1 mixture of *E*:*Z* olefin isomers (Figure 10). None of the cyclopentadiene product **59**, derived from fragmentation of the putative *cis*-bicyclo[3.2.0]heptenyl anion, was observed.[26]

The formation of **58** can be rationalized as a thermal, conrotatory opening of the cycloheptadienyl system, followed by protonation to give the fully conjugated **58**. Interestingly, the low-temperature generation and electrocyclization of heptatrienyl anions to cycloheptadienyl anions has been described by Bates and co-workers.[27] While their observations have shown this conversion to be an extremely facile electrocyclization, our reaction from **57** effectively proceeds in the reverse direction, suggesting a reaction pathway that is impacted by the diphenyl substitution.

A second approach, which was designed to establish the possibility of an equilibrium of six- and seven-membered pentadienyl carbanions with the corresponding *cis*-bicyclic allyl species, proved more rewarding. We rationalized that β-elimination of an alkoxide leaving group could facilitate trapping of strained bicyclic intermediates. To this end, the α-methoxymethyl trienes **61** and **63** were prepared as outlined in Figure 11. After some experimentation, it was found that the Morita−Baylis−Hillman reaction of 4,4-dimethyl-2-cyclohexenone with paraformaldehyde and imidazole in a mixture of THF and aqueous $NaHCO_3$ conveniently provided the hydroxymethyl derivative **60** in good yield (64%).[28] Methylation of the alcohol, and oxidation followed by Wittig olefination, furnished the triene **61**. Similarly, Morita−Baylis−Hillman reaction of cycloheptadienone with formaldehyde and DMAP gave alcohol **62** in 59% yield.[29] Methylation and Wittig olefination furnished the seven-membered triene **63**.

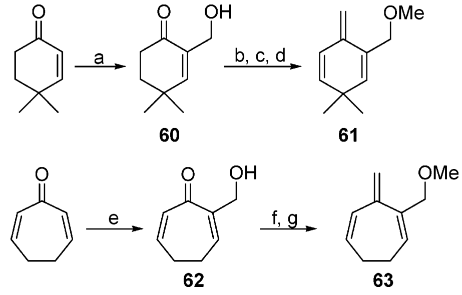


Figure 11. Preparation of α-methoxymethyl trienes **61** and **63**. Conditions: (a) $(CH_2O)_n$, imidazole, THF/1 M aqueous $NaHCO_3$, 64%, brsm; (b) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 °C to room temperature, 69%; (c) i. LDA, THF, −78 °C; PhSeBr, −78 °C to room temperature; ii. 30% aqueous H_2O_2, pyridine, CH_2Cl_2, 56%; (d) *n*-BuLi, Ph_3PCH_3Br, Et_2O, −78 °C to reflux, 52%; (e) DMAP, THF, formalin, room temperature, 48 h, 59%, brsm; (f) Me_3OBF_4, proton sponge, 4 Å MS, CH_2Cl_2, 0 °C to room temperature, 82%; (g) *n*-BuLi, Ph_3PCH_3Br, Et_2O, −78 °C to room temperature, 21%.

Studies of the carbolithiation of **61** proved most gratifying, as the addition of *t*-BuLi occurred rapidly at −78 °C and subsequent warming to 22 °C smoothly produced the *cis*-bicyclo[3.1.0]hexene **66** in 53% isolated yield (Figure 12). The formation of **66** suggests the equilibrium of **64** and **65** via disrotatory processes which result in the trapping of the minor contributor **65**. While the deprotonation of *cis*-bicyclo[3.1.0]-hexenes and subsequent electrocyclic opening to cyclohexadienyl anions is known,[30] this is the first example of the

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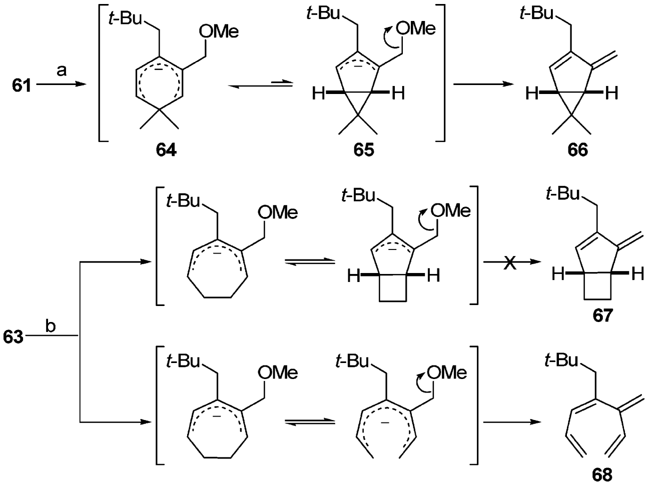

Figure 12. Results of carbolithiations of trienes **61** and **63**. Conditions: (a) *t*-BuLi, Et_2O, −78 °C to room temperature, 15 h; 53%; (b) *t*-BuLi, Et_2O, −78 °C to room temperature, 16 h; 78%.

electrocyclization of a cyclohexadienyl anion in which the product *cis*-bicyclo[3.1.0]hexene has been isolated.

Subjection of **63** to carbolithiation with *t*-BuLi at −78 °C and subsequent stirring at 22 °C for 16 h provided tetraene **68** in 78% yield (Figure 12). None of the desired *cis*-bicyclo[3.2.0]-heptene **67** was observed. Once again, the formation of the cycloheptadienyl anion and the ring-opened heptatrienyl system accounts for the elimination to **68**.[27] The extent to which cycloheptadienyl carbanions are in equilibrium with *cis*-bicyclo-[3.2.0]heptenyl anions is obscured by this dominant pathway.

Conclusion

The carbolithiation of six- through nine-membered 3-methylene-1,4-cycloalkadienes has been investigated and shown to be an exceptionally facile and general process. Primary, secondary, and tertiary organolithium reagents may be employed for carbolithiation of cyclic trienes with uniform efficiency, generating cyclic pentadienyl carbanions. The six-electron pentadienyl systems display unique reactivity as a function of ring size. Cyclooctadienyl anions undergo efficient thermal, disrotatory electrocyclization on warming to 22 °C to provide *cis*-bicyclo-[3.3.0]octenyl anions. The latter species react efficiently with a variety of electrophiles in a stereoselective manner, thus providing one-step access to a diverse array of substituted *cis*-bicyclo[3.3.0]octenes. Transmetalation of the allyllithium intermediates with copper cyanide results in modification of reactivity as organocopper species, which permits expanded possibilities for electrophilic trapping. The potential for further derivatization of the product *cis*-bicyclo[3.3.0]octenes is demonstrated by the expedient stereoselective preparation of a linear triquinane. Electrocyclization of the cyclononadienyl system proved much less favorable and required 120 °C to effect significant formation of the *cis*-bicyclo[4.3.0]nonenyl anion. This species was protonated in situ, precluding its direct functionalization through electrophilic capture. Cycloheptadienyl anions undergo alkylations to provide exclusively 1,3-cycloheptadiene products in good yields, demonstrating a useful entry to functionalized 1,3-cycloheptadienes. Intermediate carbanions of the 6,6-dimethylcyclohexadienyl system yield alkylations which provide six-membered ring products, although the regioselectivity of electrophilic attack is dependent on the nature of the alkyllithium reagent and electrophile. Trapping of putative *cis*-bicyclo[3.2.0]heptenyl anion species has furnished products resulting from the 8e$^-$ conrotatory electrocyclic opening of the initial cycloheptadienyl anion. This process appears to predominate over 6e$^-$ electrocyclic closure to the *cis*-bicyclo[3.2.0]-heptenyl anion. Successful trapping of a *cis*-bicyclo[3.1.0]-hexenyl intermediate via β-elimination suggests the probability of facile disrotatory processes for equilibration of cyclohexadienyl and *cis*-bicyclo[3.1.0]hexenyl carbanions. The nature of these reactions may find utility in strategies for organic synthesis.

Computational Details

All calculations were carried out using density functional theory as implemented in the Jaguar 6.0 suite[31] of ab initio quantum chemistry programs. Geometry optimizations were performed with the B3LYP[32] functional and the 6-31G** basis set. Lithium was always represented using the D95** basis.[33] The energies of the optimized structures were re-evaluated by additional single-point calculations on each optimized geometry using Dunning's correlation-consistent triple-ζ basis set[34] cc-pVTZ++, which includes a double set of polarization functions and diffuse functions. Vibrational frequency calculations based on analytical second derivatives at the B3LYP/6-31G** level of theory were carried out to derive the zero-point energy (ZPE) and entropy corrections at room temperature utilizing unscaled frequencies. Vibrational calculations were also used to confirm proper convergence to local minima or local maxima of the potential energy surface. Note that by "entropy" here we refer specifically to the vibrational/rotational/translational entropy of the solute(s); the entropy of the solvent is implicitly included in the dielectric continuum model.

Solvation energies were evaluated by a self-consistent reaction field (SCRF)[35] approach based on accurate numerical solutions of the Poisson−Boltzmann equation.[36] In the results reported, solvation calculations were carried out at the optimized gas-phase geometry, employing the dielectric constant of $\epsilon = 4.2666$ (diethyl ether). As is the case for all continuum models, the solvation energies are subject to empirical parametrization of the atomic radii that are used to generate the solute surface. We employ the standard set of optimized radii in Jaguar for H (1.150 Å), C (1.900 Å), O (1.600 Å), and Li (1.226 Å).

The energy components have been computed following the standard protocol. The free energy in the solution phase, *G*(sol), was calculated as follows:

$$G(\text{sol}) = G(\text{gas}) + G_{\text{solv}} \tag{1}$$

$$G(\text{gas}) = H(\text{gas}) - TS(\text{gas}) \tag{2}$$

$$H(\text{gas}) = H(\text{SCF}) + \text{ZPE} \tag{3}$$

where *G*(gas) is the free energy in the gas phase, G_{solv} is the free energy of solvation as computed using the continuum solvation model, *H*(gas) is the enthalpy in the gas phase, *T* is the temperature (298.15 K), *S*(gas) is the entropy in the gas phase, *H*(SCF) is the self-consistent field

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energy, i.e., "raw" electronic energy as computed from the SCF procedure, and ZPE is the zero-point energy.

To locate transition states, the potential energy surface was first explored approximately using the linear synchronous transit (LST) method,[37] followed by a quadratic synchronous transit (QST)[38] search using the LST transition state as an initial guess. In QST, the initial part of the transition-state search is restricted to a circular curve connecting the reactant, the initial transition-state guess, and the product, followed by a search along the Hessian eigenvector that is most similar to the tangent of this curve. In certain cases (i.e., when structures were very similar), the QST-optimized transition states were refined by an unrestricted transition-state search.

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Supporting Information Available: Full experimental details, characterization data, ^{1}H and ^{13}C NMR spectra of all new compounds, a tabulation of spectra from variable low-temperature NMR studies of **2** to **3**, Cartesian coordinates of computed structures, vibrational frequencies, and energy components. This material is available free of charge via the Internet at http://pubs.acs.org.

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