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Cycloisomerization of Acetylenic Vinyllithiums: Sequential Anionic Cyclization−Cycloaddition as a Route to Polycyclic Ring Systems

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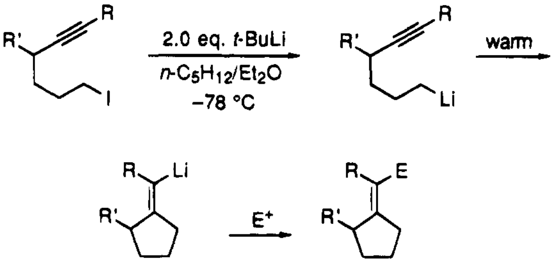
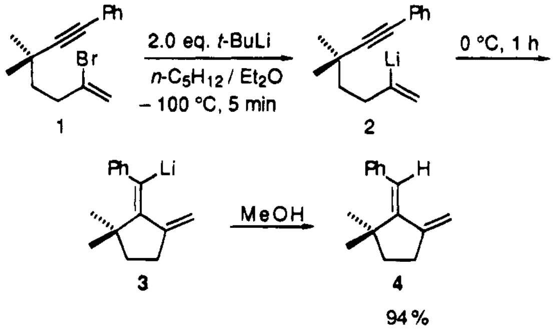
Summary: Acetylenic vinyllithiums, generated by low-temperature metal−halogen exchange, were found to undergo facile 5-*exo-dig* cyclization to afford isomerically pure conjugated 1,3-bis-exocyclic dienes which serve as reactive precursors to complex polycyclic materials through subsequent Diels−Alder methodology.

The construction of ring systems by intramolecular addition of an organolithium to an unactivated olefinic π-bond is now a well-established synthetic transformation.[2−4] As shown in Scheme 1, acetylenic alkyllithiums undergo analogous isomerization via regiospecific and highly syn-stereoselective cyclization to give easily functionalized exocyclic vinyllithium products in good yield.[5] Herein we report extension of this methodology to the preparation of bis-exocyclic 1,3-dienes by 5-*exo-dig* cyclization of acetylenic vinyllithiums.

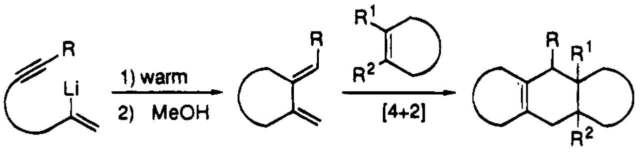
Scheme 1



Scheme 2



Although 1,3-bis-exocyclic dienes may be prepared by classical elimination sequences,[6] recently developed transition-metal-catalyzed routes[7] have largely supplanted other approaches to these useful intermediates. It was anticipated, as shown below, that cycloisomerization of acetylenic vinyllithiums would provide a straightforward route to bis-exocyclic 1,3-dienes which, through subsequent Diels−Alder chemistry,[8] could serve as useful precursors to polycyclic ring systems. As demonstrated by the model studies described below, this expectation was fully realized.



Acetylenic vinyllithiums may be generated in nearly quantitative yield from the corresponding acetylenic vinyl bromides by low-temperature lithium−bromine exchange.[9] The requisite substrates are, in turn, readily prepared by standard acetylide chemistry.[10] Cycloisomerization of an acetylenic vinyllithium to give a five-membered ring is effected simply by warming the reaction mixture to 0 °C. Thus, as illustrated in Scheme 2, vinyllithium **2**, derived from 2-bromo-5,5-dimethyl-7-phenyl-1-hepten-6-yne[11] (**1**) by lithium−bromine exchange with 2 molar equiv of *t*-BuLi at −100 °C in a mixture of *n*-pentane−diethyl ether (4:1 by vol), under-

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[1] (a) Connecticut College. (b) University of Connecticut.

[2] Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, Mechanisms of Importance in Synthesis, p 251−273.

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[11] Satisfactory C and H analyses and/or exact mass spectroscopic molecular weights have been determined for all previously unreported compounds, and their ^{1}H and ^{13}C NMR spectra are fully in accord with the assigned structures.

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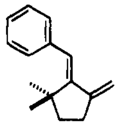
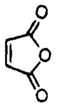
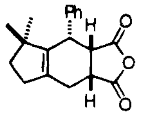
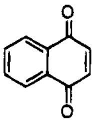
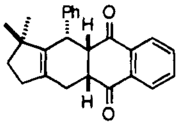
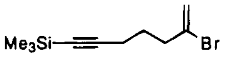
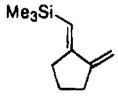
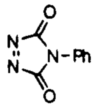
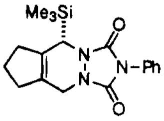
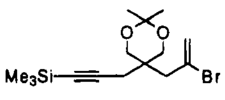
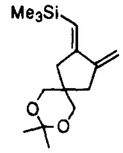
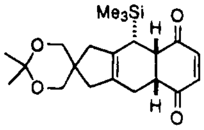
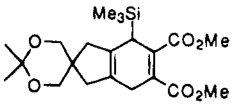
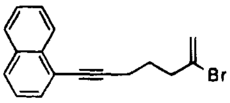
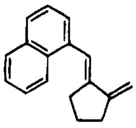
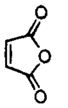
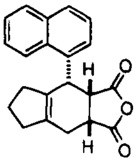
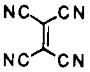
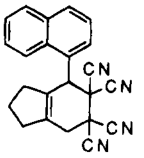
Table 1. Preparation of Polycyclic Ring Systems by Cycloisomerization–Cycloaddition of Acetylenic Vinyllithiums

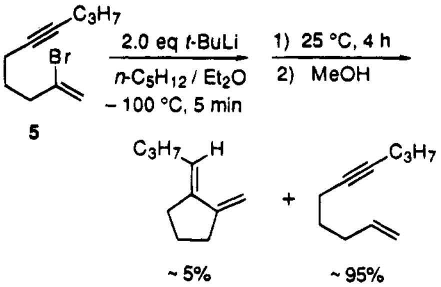
Entry	Substrate	Diene[a]	Yield (%)[b]	Dienophile	Conditions	Cycloadduct	Yield (%)[c]
1			94		$PhCH_3$, refl. 3 h		80
2					$PhCH_3$, refl. 3.5 h		63
3			87		CH_2Cl_2, 0 °C 10 min.		83
4			94		$PhCH_3$, refl. 4 h		89
5					$PhCH_3$, refl. 3 h		91
6			83		$PhCH_3$, refl. 2 h		75
7					$PhCH_3$, refl. 1.5 h		69

[a] Acetylenic vinyllithiums were generated at −100 °C ($MeOH/N_2$ bath) by addition of 2 equiv of *t*-BuLi to a solution of the acetylenic vinyl bromide in *n*-pentane–diethyl ether (4:1 by vol), the cooling bath was removed, and the mixture was allowed to warm and stand at 0 °C for 1 h prior to the addition of an excess of deoxygenated methanol. [b] Isolated yields of crude product. [c] Isolated yields of analytically pure product.

goes facile 5-*exo-dig* cyclization on warming at 0 °C for 1 h. Quench of the reaction mixture with methanol affords the isomerically pure bis-exocyclic 1,3-diene, **4**, in 94% yield.

Analogous results, summarized in Table 1, were obtained with trimethylsilyl- or naphthyl-substituted substrates which cyclize rapidly at 0 °C to give isomerically pure conjugated 1,3-dienes in 89–94% yield. The only byproduct detected from such reactions was typically 4–10% of the enyne.

In contrast to the facile cyclization of aryl- and trimethylsilyl-substituted substrates, alkyl-substituted acetylenic vinyllithiums appear to be more resistant to isomerization. For example, as shown below, the vinyllithium derived from **5** affords the 1,3-diene in low yield after standing at +25 °C for 4 h. This result is consistent with the observation that the rate of 5-*exo* ring closure of acetylenic alkyllithiums is dependent on the nature of substituent on the triple bond: while phenyl and trimethylsilyl groups greatly enhance the rate of cyclization, apparently through stabilization of the incipient exocyclic vinyllithium product,[12] alkyl-substituted analogs cyclize much more slowly.[13]



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The facile cycloisomerization of acetylenic vinyllithiums may be coupled with Diels–Alder methodology to

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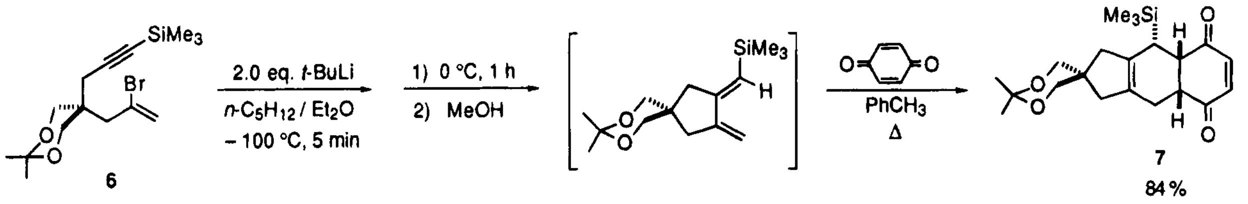
(12) Bailey, W. F.; Ovaska, T. V. *Organometallics* **1990**, *9*, 1694.

(13) An alternative explanation for the low yields of bis-exocyclic 1,3-dienes observed upon attempted cyclization of acetylenic vinyllithiums derived from 7-alkyl-2-bromo-1-hepten-6-ynes would posit that the isomerization of such alkyl-substituted substrates is a reversible process leading to an equilibrium mixture of acetylenic vinyllithium precursor and dienyllithium product. We are currently investigating this possibility.

Scheme 3



provide a simple route to more complex ring systems. Addition of a dienophile (1 equiv) to the bis-exocyclic 1,3-diene product (1.5 equiv) affords the adduct in good to excellent yields (Table 1). The products generated by this cyclization–cycloaddition approach are easily purified by flash chromatography or recrystallization and the entire four-step operation (exchange–cycloisomerization–quench–cycloaddition) may be conducted in one pot without isolation of the intermediate bis-exocyclic 1,3-dienes. The preparation of isomerically pure **7** from the acetylenic vinyllithium **6** in 84% overall yield,[11] which is depicted in Scheme 3, is representative of the utility of the methodology. The expected cis-endo stereochemistry[8] of the Diels–Alder reaction was confirmed by a single-crystal X-ray analysis of **7**.[14] The structures of the remaining Diels–Alder adducts presented in Table 1 were established by analogy with this secure assignment on the basis of NOE difference spectra and phase sensitive NOESY experiments.[11]

We are currently investigating the possibility of generating four- and six-membered bis-exocyclic 1,3-dienes by cyclization of acetylenic vinyllithiums, and we are exploring the utility of sequential cyclization–intramolecular cycloaddition sequences which involve appropriately substituted acetylenic vinyl bromides bearing tethered dienophilic moieties.

Acknowledgment. We are grateful to Dr. Jon Bordner of Pfizer Central Research for performing the X-ray analysis of **7**. This work was supported by a grant from the Connecticut Department of Economic Development.

Supplementary Material Available: Details of preparation and analytical data on all previously unreported compounds (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) Crystallographic data for **7**: $C_{21}H_{30}O_4Si$, $a = 9.224(5)$ Å, $b = 9.931(2)$ Å, $c = 12.549(5)$ Å, $\alpha = 98.17(2)°$, $\beta = 102.01(2)°$, $\gamma = 111.58(2)°$, $V = 1014.9(7)$ Å^3, space group = *P*1bar, molecules/unit cell = 2, ϱ(calcd) = 1.226 g cm^{-3}, linear absorption factor = 1.201 mm^{-1}. The structure was solved by direct methods. The authors have deposited atomic coordinates for **7** with the Cambridge Crystallographic Data Centre. The coordinates may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.