Tandem Lithium−Ene Cyclization and Thiophenoxide Expulsion to Produce Fused Vinylcyclopropanes: First Observation of Allylic Lithium Oxyanion-Induced Reactivity and Stereoselectivity in Intramolecular Carbolithiation

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We reveal herein the first synthetic method based on the rarely used but surprisingly facile lithium−ene cyclization[1] followed by thiophenoxide expulsion to yield fused vinylcyclopropanes. In addition, we present the first observation of the remarkable effect of allylic lithium oxyanion-induced reactivity and stereoselectivity on an intramolecular carbometalation, illustrated by an efficient, highly stereoselective synthesis of a natural bicyclo[3.1.0]hexane.

The lithium−ene cyclization is facile, but the products are usually those formed in a subsequent irreversible process.[1] We now show that the easily prepared substrates used in the prior study[1] can be deprotonated to generate the allyllithiums for the tandem cyclizations. In the present work, the required irreversible step that undoubtedly drives the lithium−ene cyclization to completion is expulsion of a thiophenoxide ion, a process previously revealed in this laboratory as a powerful cyclopropane synthesis.[2,3]

The basic protocol (Scheme 1) involves deprotonation of allylic phenyl thioethers such as **1**[4] by LIC-KOR.[5,6] To obtain high yields of the cyclization product, transmetalation with LiBr is required, presumably because of the high basicity of organopotassiums. Conversion of the resulting allyllithium **2** to the monocyclic intermediate **3** is strikingly efficient, considering the charge localization in the latter and the great stabilization of the anionic group by resonance and by sulfur. Intramolecular displacement of the thiophenoxide ion[2,3] forms the fused vinylcyclopropane **4**.

The yield is quantitative in the formation of the five-membered ring from the substrate in which both alkene functions are monosubstituted (Table 1). Alkyl substituents at all positions of the alkenes except the terminus of the enophile are tolerated well. The formation of fused 6,3-systems was also successful, but attempts to obtain fused 4,3- and 7,3-systems were not.

To provide more functionality and to increase the reactivity so that compounds such as **11** could be induced to react, an allylic hydroxyl group was introduced into the enophile. A number of intermolecular carbolithiations and carbomagnesiations are facilitated by an allylic Li or Mg oxyanionic group, although with limited efficiency and generality.[7] Interestingly, this technique apparently has not been applied to *intramolecular* carbometalations, presumably because of incompatibilities and regiochemical difficulties in generating the dianions.[8] However, successful generation of the requisite dianions by deprotonation could allow, for the first time, allylic lithium oxyanion-facilitated anionic cyclizations.[10]

Scheme 1

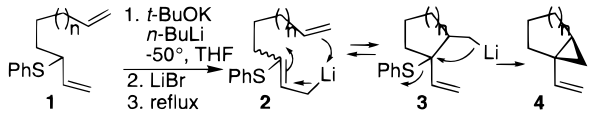
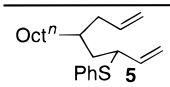
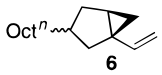
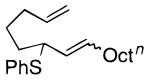
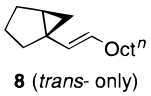
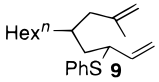
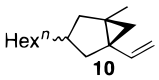
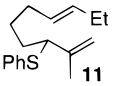
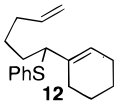
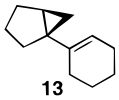
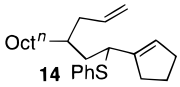
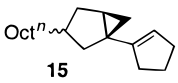
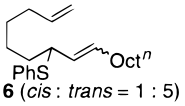
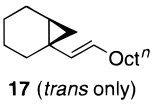
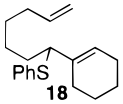
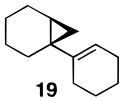


Table 1. Tandem Cyclizations to Fused Vinylcyclopropanes[a]

diene	product	% yield[b]
 **5**	 **6**	99[c]
 **7** (*cis*-: *trans*- = 1:5)	 **8** (*trans*- only)	81
 **9**	 **10**	75[c]
 **11**	decomposition products only	
 **12**	 **13**	89
 **14**	 **15**	73[c]
 **16** (*cis* : *trans* = 1 : 5)	 **17** (*trans* only)	82
 **18**	 **19**	78

[a] See Supporting Information for detailed experimental procedures and compound characterizations. [b] Isolated yields after chromatography. [c] A mixture of two diastereomers.

(1) Cheng, D.; Zhu, S.; Liu, X.; Norton, S. H.; Cohen, T. *J. Am. Chem. Soc.* **1999**, *121*, 10241−42.

(2) Cohen, T.; Matz, J. R. *J. Org. Chem.* **1979**, *44*, 4816−18 and references therein.

(3) The *intermolecular* analogue of this tandem alkene carbolithiation/cyclization requires a more nucleophilic anion and a more active alkene: Cohen, T.; Weisenfeld, R. B.; Gapinski, R. E. *J. Org. Chem.* **1979**, *44*, 4744−46. Cohen, T.; Sherbine, J. P.; Mendelson, S. A.; Myers, M. *Tetrahedron Lett.* **1985**, *26*, 2965−68. Schaumann, E.; Friese, C.; Spanka, C. *Synthesis* **1986**, 1035−1037. Tanaka, K.; Funaki, I.; Kanemasa, S.; Kobayashi, H.; Tanaka, J.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3957−64. Se analogue: Krief, A.; Barbeaux, P.; Guittet, E. *Synlett* **1990**, 509−10. The single *intramolecular* case involves selenide displacement: Krief, A.; Barbeaux, P. *Tetrahedron Lett.* **1991**, *32*, 417−420.

(4) The enophile chain was readily incorporated into the substrate by alkylation of the organolithium generated by deprotonation of an allylic phenyl thioether.[1]

(5) Schlosser, M. In *Modern Synthetic Methods 1992*; Scheffold, R., Ed.; VCH: New York, 1992; pp 227−271, see especially ref 3.

(6) An alkyllithium base deprotonates sluggishly and undergoes some S_N2' displacement of thiophenoxide.

(7) Reviews: Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1−20. Vara Prasad, J. V. N.; Pillai, C. N. *Organometallics* **1983**, *259*, 1−30. Marek, I.; Normant, J.-F. In *Metal Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P., Eds.; Wiley VCH: New York, 1998; pp 269−335.

(8) For example, the organometallic is usually prepared from an alkyl halide[9] which would form a cyclic ether in the presence of the oxyanionic group. In addition, in the case of Mg−ene cyclizations (Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38−52), the allyl halide is produced from an allylic alcohol, thus presenting a regiochemical problem.

(9) Review: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, p 251−273.

(10) Reductive lithiation, another technique that allows the presence of oxyanionic functions, was used in the first examples of intramolecular oxyanion-facilitated addition of unstabilized organolithiums to alkenes; however, the oxyanionic group was in the vicinity of the carbanion rather than the alkene. Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3855−65. Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1994**, *50*, 12793−12810.

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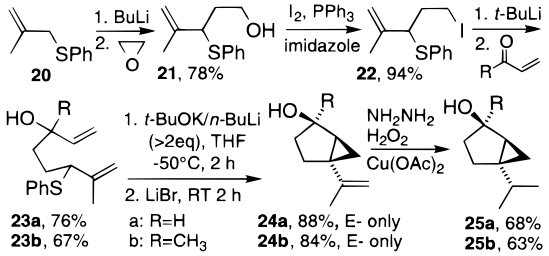
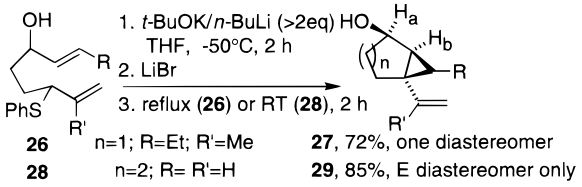
Scheme 2



Scheme 3



Two suitable substrates, **23a**,**b**, were readily prepared as shown in Scheme 2.[11] Happily, not only were the cyclizations of **23a**,**b** to **24a**,**b** greatly facilitated, occurring at room temperature rather than the reflux temperature required in the absence of allylic hydroxy groups (Scheme 1), but they also proceeded in high yields and were completely stereoselective as determined by chromatographic and NMR spectroscopic behavior. Their diimide reduction products **25a**,**b** were shown to have the hydroxyl and cyclopropyl rings cis.[12]

This is the most efficient synthesis of *cis*-sabinene hydrate **25b**, a terpene of the thujane class.[14] It avoids the addition of MeLi to the corresponding ketones, a common strategy of previous syntheses, which results in a mixture of E- and Z-isomers.[14] The flexibility of the method is illustrated by the preparation of **25a** which constitutes a formal synthesis of sabinaketones, sabinene, *cis*- and *trans*-sabinene hydrates, 2-thujene, umbellulone, etc., all of which have been prepared from **25a**.[14a]

The facilitating effect of the lithium oxyanionic group was further demonstrated by the *successful double cyclization of* **26** *(Scheme 3*), an allylically hydroxylated analogue of **11** *which, itself, failed to cyclize*. Impressively, **27** was formed as a single diastereomer.[12] Finally, **28** generated the fused 6,3-system **29** in high yield with the same stereoselectivity.[12]

The first synthetic procedure based on the lithium−ene cyclization has led to a very efficient method for the production of vinylcyclopropanes. The latter constitute a particularly useful class of compounds that includes the large group of pyrethroid insecticides,[15] as well as other natural products, and that can be transformed into still others as illustrated above. Furthermore, they are particularly versatile,[16] undergoing the widely used vinylcyclopropane-to-cyclopentene ring expansion,[17] [2 + 5] and [2 + 3] cycloadditions to alkenes,[18] and ring-opening additions.[19] The present method of generation of fused vinylcyclopropanes is particularly efficient when compared to extant methods,[17b,20] given the ease of preparation of the cyclization substrates. Of great significance is the first use of an allylic lithium oxyanionic group to enhance reactivity and control stereochemistry in an anionic cyclization. Compared with the intermolecular version,[7] the intramolecular version demonstrates remarkably enhanced reactivity and stereoselectivity. For example, the *intermolecular* allyllithiation of an allyl alcohol[21] proceeded with only 2:1 stereoselectivity, in the same sense. If, as appears likely, allylic lithium oxyanionic substituents greatly enhance the scope of anionic cyclizations in general,[9,10] this effect holds considerable potential for new strategies in ring synthesis.

Acknowledgment. We thank the National Science Foundation for support of this work, Professor Fu-Tyan Lin for help in NMR analysis, Ms. Margarete Bower for literature searches, and Professor Peter Wipf and Dr. David A. Mareska for helpful discussions.

Supporting Information Available: Experimental procedures and details of compound characterization are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Epoxide alkylation: Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311−14. Li−I exchange: Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404−06. Diimide reduction: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Plenum Press: New York, 1990; Vol. 2, p 230.

(12) The E-structures were assigned to **25a**,**b**, **27**, and **29** by comparisons with known compounds, NOE studies, and Simmons−Smith cyclopropanation of the corresponding allylic alcohols, a reaction which is cis-selective with regard to the hydroxyl group.[13]

(13) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892−94 and references therein.

(14) (a) Thomas, A. F. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1973; Vol. 2, pp 145−148. (b) Fanta, W. I.; Erman, W. F. *J. Org. Chem.* **1968**, *33*, 1656−58. Gaoni, Y. *Tetrahedron* **1972**, *28*, 5525−31.

(15) Crombie, L. *Pyrethrum Flowers*; Casida, J. E., Quistad, G. B., Ed.; Oxford: New York, 1995; Chapter 8.

(16) Reissig, H.-U. *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1987; Part 1, pp 416−430.

(17) (a) Review: Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 899−970. (b) Rearrangement of fused vinylcyclopropane systems similar to those prepared in the present paper: Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **1999**, *64*, 3567−71.

(18) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348−49 and references therein. Feldman, K. S.; Romanelli, A. L.; Ruckle, J. R. E. *J. Org. Chem.* **1992**, *57*, 100−110 and references therein. Jung, M. E.; Rayle, H. L. *J. Org. Chem.* **1997**, *62*, 4601−09.

(19) One of the more general and useful ones: Alpoim, M. C. M. de C; Morris, A. D.; Motherwell, W. B.; O'Shea, D. M. *Tetrahedron Lett.* **1988**, *29*, 4173−76.

(20) For a summary of synthetic methods for vinylcyclopropanes, see: Schaumann, E.; Kirschning, A.; Narjes, F. *J. Org. Chem.* **1991**, *56*, 717−723 and references 6−10 cited therein. Newer methods of production of fused vinylcyclopropanes based on the transition metal cyclization of enynes: Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424−34. Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. *Helv. Chim. Acta* **1997**, *80*, 623−639. Montchamp, J.-L.; Negishi, E.-I. *J. Am. Chem. Soc.* **1998**, *120*, 5345−46.

(21) Felkin, H.; Swierczewski, G.; Tambuté, A. *Tetrahedron Lett.* **1969**, 707−10.