aqueous saturated Na_2CO_3 and then aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a residue which was recrystallized from $CHCl_3$ to give (87%) pure olefin **9**, as colorless crystals: 43 mg; mp 410 °C dec; ^1H NMR δ 7.35 (dd, 3-pyH, J = 7.6, 1.2 Hz, 4 H), 7.62 (t, 4-pyH, J = 7.6 Hz, 4 H), 7.96 (dd, 5-pyH, J = 7.6, 1.1 Hz, 4 H), 8.15 (dd, 4'-pyH, $J_{3',4'} = J_{4',5'}$ = 7.8 Hz, 2 H), 8.42 (dd, 3'-pyH, J = 7.8, 1.1 Hz, 4 H); MS m/z 598 (M^+, 3), 597 ($M^+ - H$, 4), 301 ($M^+/2 + 2H$, 100). Anal. Calcd for $C_{36}H_{18}N_6O_4 \cdot {}^1/_2CHCl_3$: C, 66.60; H, 2.83; N, 12.77. Found: C, 67.04; H, 2.55; N, 12.92.

Method B. A stirred solution of dimer **8** (105 mg, 170 μmol) in $CHCl_3$ was aerated for 7 days. The solvent was removed in vacuo to give (99%) pure **9** (103 mg): mp 408 °C dec.

Cu(II) Complexation of Trione 3. To a stirred solution of **3** (15.8 mg, 0.05 mmol) in boiling EtOH (10 mL) was added a solution of anhydrous $CuCl_2$ (0.05 mmol) in EtOH (10 mL). The mixture was refluxed under a N_2 atmosphere for 12 h and then stirred at 25 °C for an additional 12 h, during which time a green precipitate formed. The solid was filtered, washed with EtOH, and recrystallized from EtOH/$CHCl_3$ to afford large dark green crystals. Anal. Calcd for $C_{20}H_{15}N_3O_4 \cdot CuCl_2 \cdot {}^1/_2CHCl_3$: C, 44.32; H, 2.81; N, 7.56. Found: C, 44.09; H, 2.84; N, 7.73.

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Supplementary Material Available: Tables of atomic coordinates, coordinates of hydrogen atoms, bond lengths, and bond angles for **4**, **5**, **6**, **4**·$CuCl_2$·EtOH complex, dimer **8**, and olefin **9** (25 pages). Ordering information is given on any current masthead page.

Synthesis of Pyrrolizidines and Indolizidines by the Intramolecular Cycloaddition of Azides with Electron-Rich 1,3-Dienes. A Synthetic Equivalent of a Nitrene–Diene Cycloaddition

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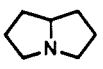
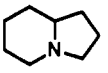
Alkyl azides were found to undergo intramolecular cycloadditions with certain 1,3-dienes to provide 2,3,5,7a-tetrahydro-1*H*-pyrrolizines and 3,5,6,7,8,8a-hexahydroindolizines in one operation (e.g., **12** → **13** and **17** → **18**). The presence of an electron-donating group on the diene (sulfur, selenium, or oxygen) was required to avoid alternative rearrangement processes. The cyclization of chiral azidodienes proceeded with high diastereoselectivity to produce materials that are closely related to several alkaloidal natural products. New methods for the synthesis of the requisite heterosubstituted 1,3-dienes were developed.

Many classes of alkaloids have either a pyrrolizidine (**1**) or indolizidine (**2**) skeleton as a key structural element.[1-3] A general, flexible, and efficient route to such a subunit would obviously be useful.

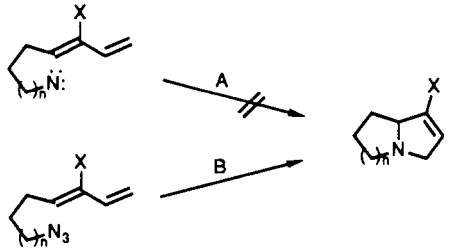


1



2

Perhaps the most efficient ring constructions are those that form more than one bond in a single operation. We have chosen to study a [4 + 1] approach[4] to the pyrroline ring of **1** and **2**. A conceptually simple approach would be an intramolecular nitrene–diene cycloaddition[5] (eq 1, pathway A). Realizing that the use of alkylnitrenes is unsatisfactory,[6] and that more stabilized nitrenes form aziridines with dienes rather than produce the desired 3-pyrrolines,[7-9] we have focused on developing a formal equivalent of this transformation. Herein we report the details of our basic studies on a synthetic equivalent of a nitrene–diene cycloaddition (eq 1, pathway B). The intramolecular cycloaddition of aliphatic azides with certain electron-rich 1,3-dienes directly provides 2,3,5,7a-tetra-



(1)

† Department of Chemistry.
‡ Department of Medicinal Chemistry.

(1) Pyrrolizidine alkaloids: (a) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 31, Chapter 6, pp 193–315. (b) Ikeda, M.; Sato, T.; Ishibashi, H. *Heterocycles* **1988**, *27*, 1465–1487. (c) Robins, D. J. *Nat. Prod. Rep.* **1989**, *6*, 221–230.

(2) Indolizidine alkaloids: (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4. (b) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 523–536. (c) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1, pp 1–54.

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(4) Other formal [4 + 1] approaches to pyrrolidines and 3-pyrrolines have been reported: (a) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (b) Barluenga, J.; Perez-Prieto, J.; Asensio, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1181. (c) Forrest, A. K.; Schmidt, R. R. *Tetrahedron Lett.* **1984**, *25*, 1769. (d) Fugami, K.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 857. (e) Gajda, T.; Zwierzak, A. *Liebigs Ann. Chem.* **1986**, 992–1002. (f) Backvall, J. E.; Renko, Z. D.; Bystrom, S. E. *Tetrahedron Lett.* **1987**, *28*, 4199–4202. (g) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1543–1546. (h) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem Soc.* **1988**, *110*, 2341–2342. (i) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 3041–3044.

(5) A nonconcerted reaction of triplet cyanonitrene with cyclooctatetraene produces a 3-pyrroline by a [4 + 1] cyclization without the intermediacy of a vinylaziridine: (a) Anastassiou, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5512. (b) Anastassiou, A. G. *Ibid.* **1968**, *90*, 1527. (c) Anastassiou, A. G.; Cellura, R. P.; Ciganek, E. *Tetrahedron Lett.* **1970**, 5267–5270. See also reference 13 for a potentially direct nitrene/diene cyclization. Concerted 1,4-additions of carbenes to dienes to give cyclopentenes without the intermediacy of a vinylcyclopropane have been found: (d) Le, N. A.; Jones, M., Jr.; Bickelhaupt, F.; de Wolf, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 8491–8493 and references cited therein. (e) Kraakman, P. A.; de Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1989**, *111*, 8534–8535. (f) Evanseck, J. D.; Mareda, J.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 73–80.

0022-3263/90/1955-5719$02.50/0

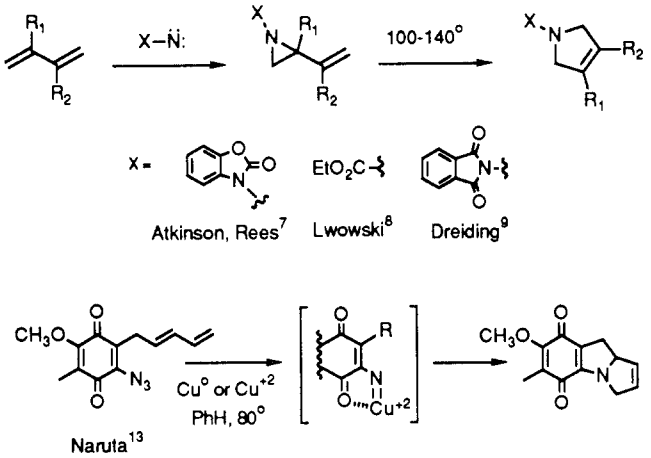


Figure 1. Nitrene–diene reactions.

hydro-1*H*-pyrrolizines and 3,5,6,7,8,8a-hexahydroindolizines, referred to hereafter as pyrrolizidines and indolizidines.[10] Furthermore, these cyclizations generate a heterosubstituted alkene functional group which may facilitate further transformation into alkaloidal natural products.

Background

Other groups have reported transformations related to those shown in eq 1. Atkinson and Rees (1967),[7] Lwowski (1968),[8] and Dreiding (1972)[9] reported the reaction of various "stabilized" nitrenes with 1,3-dienes (Figure 1). As expected, 2-vinylaziridines rather than 3-pyrrolines were produced, but these aziridines could be thermally rearranged to 3-pyrrolines in a separate step. An analogy to the vinylcyclopropane rearrangement may be drawn.[11] However, it is crucial that the nitrogen bear a radical stabilizing group for successful rearrangement. Alkylnitrenes are not useful for the same sequence.[6,12] Naruta[13]

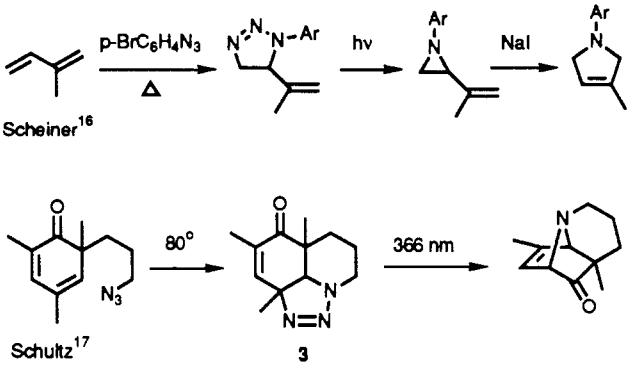
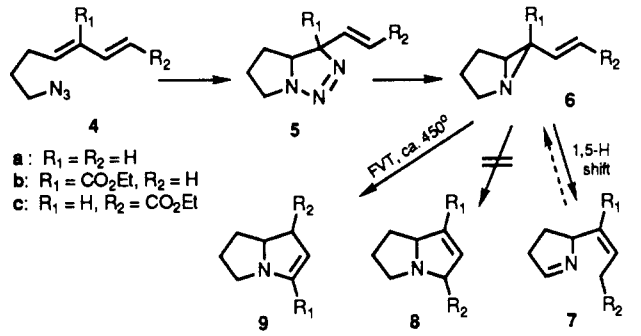


Figure 2. Azide–diene reactions.

Scheme I. Cycloaddition of Simple Azidodienes



has successfully cyclized quinoid azides with dienes via the intermediacy of a copper-nitrenoid species, but this method fails with alkyl or aryl azides.[13d]

A formal equivalent of the nitrene–diene approach to 3-pyrrolines which does not rely on nitrene chemistry is shown in eq 2. Intramolecular 1,3-dipolar cycloaddition[14-18]

(6) (a) Lwowski, W., Ed. *Nitrenes*; Wiley: New York, 1970. (b) Nagata, W. *Lect. Heterocycl. Chem.* **1972**, *1*, 29. (c) Lwowski, W. In *Reactive Intermediates*; Jones, M., Moss, R. A., Eds.; Wiley: New York, 1981; Chapter 8. (d) Deyrup, J. A. In *Heterocyclic Compounds*; Hassner, A., Ed.; Wiley: New York, 1983; Vol. 42, Part 1, Chapter 1, pp. 1–214. (e) Kyba, E. P. In *Azides and Nitrenes–Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: New York, 1984; Chapter 1. (f) Kametani, T.; Honda, T. *Adv. Heterocycl. Chem.* **1986**, *39*, 182–236.

(7) (a) Atkinson, R. S.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1967**, 1232. (b) Atkinson, R. S.; Rees, C. W. *J. Chem. Soc. C* **1969**, 778–782.

(8) Mishra, A.; Rice, S. N.; Lwowski, W. *J. Org. Chem.* **1968**, *33*, 481–486.

(9) (a) Hoesch, L.; Dreiding, A. S. *Chimia* **1972**, *26*, 629. (b) See also: Nelsen, S. F.; Blackstock, S. C.; Steffek, D. J.; Cunkle, G. T.; Kurtzweil, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 6149–6153.

(10) Portions of this work were communicated In: (a) Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527–3530. (b) Pearson, W. H.; Celebuski, J. E.; Poon, Y.-F.; Dixon, B. R.; Glans, J. H. *Tetrahedron Lett.* **1986**, *27*, 6301–6304. For an approach to gephyrotoxin using this methodology, see: (c) Pearson, W. H.; Poon, Y.-F. *Tetrahedron Lett.* **1989**, *30*, 6661–6664. For related work, see ref 18.

(11) Reviews: (a) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3. (b) Salaun, J. R. Y. *Top. Curr. Chem.* **1988**, *144*, 1–71. (c) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (d) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198.

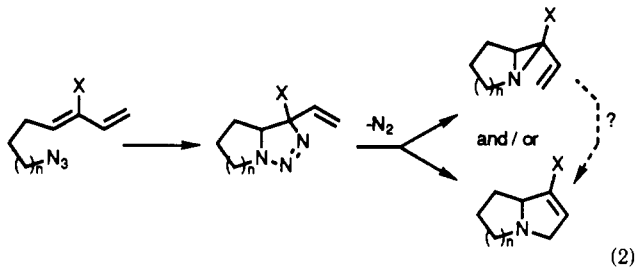
(12) Attempted nitrene generation from azides such as those in Scheme I by photolysis, or from the corresponding amines by oxidation led to complex mixtures in our hands.

(13) (a) Naruta, Y.; Arita, Y.; Nagai, N.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 1859. (b) Naruta, Y.; Nagai, N.; Maruyama, K. *Chem. Lett.* **1983**, 1383. (c) Naruta, Y.; Nagai, N.; Maruyama, K. *Heterocycles* **1984**, *21*, 410. (d) Naruta, Y.; Nagai, N.; Arita, Y.; Maruyama, K. *J. Org. Chem.* **1987**, *52*, 3956.

(14) General references on azide-alkene cycloadditions: (a) Scheiner, P. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley: New York, 1970. (b) Sheradsky, T. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971; Chapter 6. (c) Finley, K.-T. In *The Chemistry of Heterocyclic Compounds*; Montgomery, J. A., Ed.; Wiley: New York, 1980; Vol. 39. (d) Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 5, pp 559–651. (e) Kadaba, P. K.; Stanovnik, B.; Tisler, M. *Adv. Heterocycl. Chem.* **1984**, *37*, 217–361. (f) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

(15) Intramolecular azide-alkene cycloadditions. Reviews: (a) Padwa, A. *Angew. Chem., Int. Ed.* Engl. **1976**, *15*, 123. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (c) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, Chapter 12, pp 277–406. (d) Tsuge, O.; Hatta, T.; Hisano, T. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1989; Vol. 1, Chapter 7, pp 344–475. Selected additional intramolecular examples: (e) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749. (f) Corey, E. J.; Balanson, R. D. *Heterocycles* **1976**, *5*, 445. (g) Bertrand, M.; Dulcere, J. P.; Santell, M. *Tetrahedron Lett.* **1977**, 1783. (h) Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5008. (i) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1982**, *47*, 725. (j) Kozikowski, A. P.; Greco, M. N. *Tetrahedron Lett.* **1982**, *23*, 2005. (k) Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676–1678. (l) Kozikowski, A. P.; Greco, M. N. *J. Org. Chem.* **1984**, *49*, 2310. (m) Pearson, M. J.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, *28*, 1927. (n) Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Chang, R.-C.; Chang, S.-C. *J. Org. Chem.* **1986**, *51*, 1490–1494. (o) Buchanan, J. G.; Edgar, A. R.; Hewitt, B. D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2371–2376. (p) Murthy, K. S. K.; Hassner, A. *Tetrahedron Lett.* **1987**, *28*, 97–100. (q) Tsai, C.-Y.; Sha, C.-K. *Tetrahedron Lett.* **1987**, *28*, 1419–1420 and earlier references. (r) Hassner, A.; Amarasekara, A. S.; Andisik, D. *J. Org. Chem.* **1988**, *53*, 27–30. (s) Taber, D. F.; Deker, P. B.; Fales, H. M.; Jones, T. H.; Lloyd, H. A. *J. Org. Chem.* **1988**, *53*, 2968–2971. (t) Vogel, C.; Delavier, P. *Tetrahedron Lett.* **1989**, *30*, 1789–1792. (u) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303–8304 and earlier references therein. (v) Buchanan, J. G.; Edgar, A. R.; Hewitt, B. D.; Jigajinni, B. B.; Singh, G.; Wightman, R. H. In *Trends in Synthetic Carbohydrate Chemistry*; Horton, D.; Hawkins, L. D., McGarvey, G. J., Eds.; American Chemical Society: Washington, D.C., 1989; Chapter 6, pp 107–116.

of an azide onto the proximal double bond of a 1,3-diene would provide a vinyltriazoline, which may extrude nitrogen[14,19] to produce either a vinylaziridine or the desired bicyclic 3-pyrroline. Should the vinylaziridine be formed, rearrangement to the 3-pyrroline may be possible.

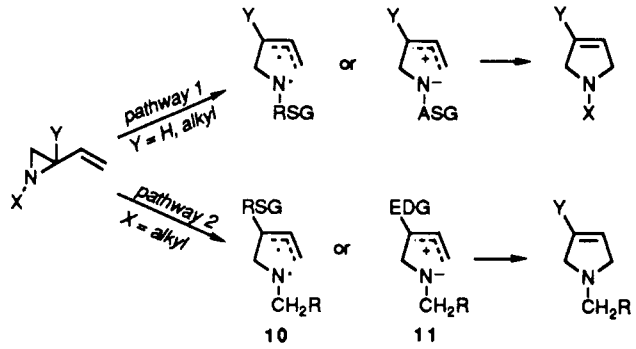


(2)

Scheiner (1960s)[16] pioneered the dipolar 1,3-cycloaddition of azides with dienes (Figure 2). Aryl azides produced vinyltriazolines,[16a] which could be photochemically transformed into vinylaziridines.[16b] These aziridines required sodium iodide to rearrange to the 3-pyrroline, presumably via an S_N2' opening with iodide followed by ring closure of the resultant allylic iodide.[16c,18b,c,20] Schultz (1983)[17] reported a more direct analogy to the desired cyclization. Intramolecular cycloaddition of an alkyl azide with a cyclohexadienone followed by photolysis of the resultant vinyltriazoline produced a bicyclic 3-pyrroline. However, the tricyclic nature of the triazoline **3** is likely a special case since certain side reactions are prevented.[10a,17b] In fact, the outcome of the 1,3-dipolar cycloadditions of azides with dienes is very dependent on the structure of both reaction partners. We have found that the proper choice of diene substituents leads to successful intramolecular cycloadditions with aliphatic azides, as described below.

Initial Studies: The Problem with Vinylaziridines. Our early work involved the investigation of the intramolecular cycloaddition of simple alkyl azides **4** onto 1,3-dienes (Scheme I and supplementary material).[10a,18a] We quickly found that these cyclizations proceeded through vinyltriazolines **5** as desired, but that these materials led to undesired products as a result of further reactions of the subsequently formed vinyl aziridines **6**. In particular, **6** underwent a 1,5-homodienyl shift[21] in nonpolar solvents

Scheme II. Vinylaziridine Reaction Pathways



(benzene, THF) to produce monocyclic 1-pyrrolines **7** in good yield, with little or none of the desired materials **8** being formed. In some cases, vinylaziridines could be isolated, for example **6b** and **6c** (see supplementary material). Attempted rearrangement of these vinylaziridines using Scheiner's sodium iodide method[16c] was not successful.[18b,c,20] Attempts to set up an equilibrium between **7b** or **7c** and **6b** or **6c** at high temperature by an intramolecular ene reaction (the reverse of the 1,5-homodienyl shift) also failed to give **8b** or **8c**. Flash vacuum thermolysis of **6b** or **6c** produced 1-pyrroline isomers **9b,c**. The mechanism of this rearrangement is presumably an electrocyclic ring opening of the aziridine to an azomethine ylide followed by a 1,5-dipolar electrocyclization.[6d,10a,17b,22] Bicyclic 2-pyrrolines **9b** and **9c**, although isomeric with the desired materials **8b** and **8c**, are potentially useful for the synthesis of pyrrolizidine alkaloids (especially **9c**). Hudlicky's group has independently reported success with the high-temperature strategy, resulting in the synthesis of several pyrrolizidine alkaloids.[18b-d] However, this method has so far been limited to ester-substituted dienes and to the production of pyrrolizidines. We were led to consider other methods to facilitate the production of the desired 3-pyrrolines **8** rather than the regioisomers **9** and were particularly interested in methods that would allow the production of the important indolizidine skeleton.

Results

Examination of our initial work reported above, and of earlier work by others, led to the conclusion that the rearrangement of vinylaziridines is quite dependent on substitution (Scheme II). When the nitrogen substituent X is a radical stabilizing group (RSG) or an anion stabilizing group (ASG), for example X = amine,[7,9] carbethoxy,[8] quinone,[13] or electron-poor aromatic ring,[16] cleavage of the allylic C–N bond is favorable (pathway 1) and rearrangement to the desired 3-pyrroline is possible. However, this requirement at the same time diminishes the scope of the reaction by requiring a particular nitrogen substituent X. When X is a simple alkyl group as desired for our work, 1,5-hydrogen shift or azomethine ylide formation becomes

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(17) (a) Schultz, A. G.; Dittami, J. P.; Myong, S. O.; Sha, C.-K. *J. Am. Chem. Soc.* **1983**, *105*, 3273. (b) Schultz, A. G.; Staib, R. R.; Eng, K. K. *J. Org. Chem.* **1987**, *52*, 2968. (c) Schultz, A. G. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, pp 53–85.

(18) For work related to our early studies,[10a] see: (a) Hudlicky, T.; Frazier, J. O.; Kwart, L. D. *Tetrahedron Lett.* **1985**, *26*, 3523–3526. See also: (b) Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755–3762. (c) Hudlicky, T.; Sinai-Zingde, G.; Seoane, G. *Synth. Commun.* **1987**, *17*, 1155. (d) Hudlicky, T.; Seoane, G. Lovelace, T. C. *J. Org. Chem.* **1988**, *53*, 2094–2099.

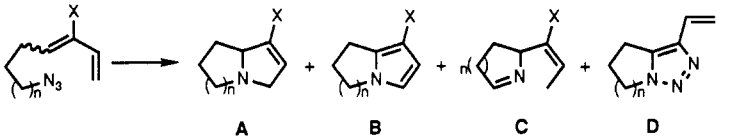
(19) (a) Scheiner, P. *J. Org. Chem.* **1965**, *30*, 7. (b) Scheiner, P. *J. Am. Chem. Soc.* **1966**, *88*, 4759. (e) Stark, B. P.; Duke, A. J. *Extrusion Reactions*; Pergamon Press: New York, 1967. (c) Scheiner, P. *J. Am. Chem. Soc.* **1968**, *90*, 988–992. (d) McDaniel, R. S.; Oehlschlager, A. C. *Tetrahedron* **1969**, *25*, 1381. See also ref 14e.

(20) For related ionic method for vinylaziridine rearrangement, see: (a) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670. (b) Hortmann, A. G.; Koo, J. *J. Org. Chem.* **1974**, *39*, 3781. (c) Expert, J.; Gelas-Mialhe, Y.; Vessiere, R. *J. Heterocycl. Chem.* **1985**, *22*, 1285–1289.

(21) For 1,5-homodienyl shift in vinylaziridines: (a) Reference 6d. (b) Sauleau, A.; Sauleau, A.; Bourget, H.; Huet, J. *C. R. Acad. Sci. Paris, Ser. C* **1974**, *279*, 473. (c) Borel, D.; Gelas-Mialhe, Y.; Vessiere, R. *Can. J. Chem.* **1976**, *54*, 1582, 1590. (d) Sauleau, A.; Sauleau, A.; Huet, J. *Bull. Soc. Chim. Fr.* **1978**, 97. (e) Hassner, A.; D'Costa, R.; McPhail, A. T.; Butler, W. *Tetrahedron Lett.* **1981**, *22*, 3691. (f) Hassner, A.; Chau, W. *Tetrahedron Lett.* **1982**, *23*, 1989. (g) Eberbach, W.; Carre, J. C. *Chem. Ber.* **1983**, *116*, 563. For 1,5-homodienyl shift in vinylcyclopropanes: (h) Daub, J. P.; Berson, J. A. *Tetrahedron Lett.* **1984**, *25*, 4463 and references therein. (i) Loncharich, R. J.; Houck, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 2089 and references therein. (j) Gajewski, J. J.; Squicciarini, M. P. *J. Am. Chem. Soc.* **1989**, *111*, 6717–6728 and references therein.

(22) (a) Borel, D.; Gelas-Mialhe, Y.; Vessiere, R. *Can. J. Chem.* **1976**, *54*, 1590. (b) Pommelet, J. C.; Chuche, J. *Can. J. Chem.* **1976**, *54*, 1571.

Table I. Intramolecular Cyclization of Azides with Heterosubstituted 1,3-Butadienes



A B C D

entry	diene	X	n	geometry	conditions	products[a] A	B	C	D
1	**12**	SPh	1	*Z*	$CHCl_3$, 100 °C, 15 h	**13** (90)	–	–	–
2	**12**	SPh	1	*Z*	$Cl_2CHCHCl_2$, 100 °C, 15 h	**13** (91)	–	–	–
3	**12**	SPh	1	*Z*	diglyme, 100 °C, 15 h	**13** (89)	–	–	–
4	**12**	SPh	1	*Z*	DMSO, 100 °C, 15 h	**13** (63)	–	–	–
5	**12**	SPh	1	*Z*	PhH-d_6, 100 °C, 15 h	**13** (27)[b]	–	**14** (48)[b]	–
6	**12**	SPh	1	*Z*	CD_3CN, 100 °C, 15 h	**13** (22)[b]	–	**14** (45)[b]	–
7	**12**	SPh	1	*Z*	EtOAc, 100 °C, 7 h; 130 °C, 12 h	**13** (28)	–	**14** (70)	–
8	**12**	SPh	1	*Z*	THF, 100 °C, 7 h	**13** (33)	–	**14** (60)	–
9	**12**	SPh	1	*Z*	pyridine-d_5, 100 °C, 7 h	**13** (21)	–	**14** (72)	–
10	**15**	SPh	1	*E*	$CHCl_3$, 100 °C, 15 h	**13** (88)	**16** (10)[c]	–	–
11	**15**	SPh	1	*E*	DMSO, 100 °C, 15 h	**13** (68)	–	–	–
12	**17**	SPh	2	*Z*	$CHCl_3$, 110 °C, 44 h	**18** (87)	**19** (6)[c]	–	–
13	**17**	SPh	2	*Z*	$Cl_2CHCHCl_2$, 110 °C, 44 h	**18** (77)	**19** (10)[c]	–	–
14	**17**	SPh	2	*Z*	CH_2Cl_2, 65 °C, 130 h	**18** (63)	–	–	–
15	**17**	SPh	2	*Z*	diglyme, 110 °C, 44 h	**18** (49)	**19** (50)[c]	–	–
16	**20**	SPh	2	*E*	$CHCl_3$, 110 °C, 44 h	**18** (89)	**19** (7)[c]	–	–
17	**20**	SPh	2	*E*	DMSO-d_6, 90 °C, 46 h	–	–	–	**21** (63)
18	**22**	SCH_3	1	*Z*	$CHCl_3$, 70 °C, 115 h	**23** (28)[d]	–	–	–
19	**24**	S^{t}Bu	1	*Z*	$CDCl_3$, 100 °C, 48 h	**25** (91)	–	–	–
20	**26**	OTBS[e]	1	*Z*	THF, 110 °C, 7 days	**27** (56)	–	**28** (15)	–
21	**29**	OEE[e]	1	*Z*	THF, 120 °C, 7 days	**30** (33)	–	**31** (19)	–
22	**32**	OEE	1	*E*	THF, 110 °C, 7 days	see text			
23	**33**	OEE	2	*E*	THF, 110 °C, 8 days	see text			
24	**34**	OCb[e]	1	*Z*	$CDCl_3$, 110 °C, 71 h	**35** (53)	–	–	–
25	**36**	OCb	1	*E*	$CHCl_3$, 120 °C, 48 h	–[f]	–	–	–
26	**37**	OCb	2	*Z*	$CDCl_3$ or THF, 130 °C, 3 days	–[g]	–	–	–
27	**38**	OCb	2	*E*	THF, 120 °C, 3 days	–	–	–	**21** (50)[h]
28	**39**	Br	1	*Z*	$CDCl_3$, 80 °C, 10 days	**40** (50)[i]	–	–	**41** (50)[i]
29	**42**	SePh	1	*Z*[j]	$Cl_2CHCHCl_2$, 70 °C, 72 h	**43** (54)	–	–	–
30	**42**	SePh	1	*Z*[j]	DMSO, 90 °C, 72 h	**43** (15)	–	–	**41** (15)

[a] Isolated yields unless otherwise noted. [b] Yield determined by ^1H NMR using an internal anisole standard. [c] Determined by ^1H NMR on crude mixture before isolation of major pyrroline component A by chromatography. [d] Although the crude NMR spectrum showed a very clean reaction, chromatography led to considerable decomposition, resulting in a low isolated yield. [e] OTBS = $OSi(tBu)(CH_3)_2$; OEE = $OCH(CH_3)OCH_2CH_3$; OCb = $OCON(iPr)_2$. [f] None of the desired pyrroline was formed. Instead, products assigned as 1,5-hydrogen shift and a bicyclic triazoline analogous to **44** were formed in low yield. [g] Decomposition only. A variety of conditions, with and without additives such as ammonium chloride, failed to produce the desired cycloadducts. [h] By ^1H NMR. In addition, an equal part of a bicyclic triazoline analogous to **45** was formed. [i] Determined by ^1H NMR. Could not be isolated due to the air sensitivity of **40**. Also accompanied by other decomposition products. [j] 70:30 mixture of *Z* and *E* isomers.

competitive, depending on temperature and the nature of Y (see for example Scheme I, **6** → **7** or **9**).[10a,18a] The exception is Schultz's example (Figure 2), where the polycyclic nature of the aziridine presumably prevents 1,5-homodienyl shift.[17a] Our proposed solution is embodied in pathway 2. Placement of a radical stabilizing group (RSG) or an electron-donating group (EDG) at position Y may facilitate the cleavage of the allylic C–N bond via diradical **10** or zwitterion **11**, potentially leading to the desired 3-pyrroline.[23,24] This substitution may also affect the reactivity of the initial triazoline formed by facilitating its ring opening, directly providing **10** or **11** without the intermediacy of vinyl aziridines. Furthermore, if Y were chosen properly, its presence would increase the scope of the reaction, since a potentially useful functional group would be created.

We chose to explore electron-donating groups for Y. To that end, sulfur-substituted diene **12** was prepared (vide infra) and heated in a variety of solvents. In chloroform[25] at 100 °C, smooth cyclization to the desired bicyclic pyrroline **13** was observed in 90% isolated yield (eq 3). The transformation of **12** to **13** is a one-flask synthetic equivalent of a nitrene–diene cycloaddition. Following the reaction by ^1H NMR in $CDCl_3$ provided no evidence for

Table II. Rate Constants and Relative Rates for the Cyclization of Sulfur-Substituted Dienes at 100 °C

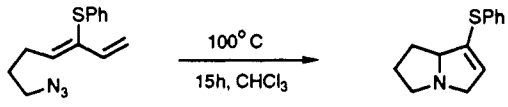
entry	diene	solvent	rate constant 10^5k_{obs}, s^{-1}	k_{rel}
1	**12**	$CDCl_3$	19.00 ± 0.17	1.00
2	**12**	C_6D_6	20.20 ± 0.29	1.06
3	**12**	$(CD_3)_2SO$	34.18 ± 0.75	1.80
4	**12**	CD_3CN	28.88 ± 0.71	1.52
5	**12**	CD_3OD	21.92 ± 0.55	1.15
6	**12**	C_5D_5N	28.05 ± 0.25	1.48
7	**15**	$CDCl_3$	8.14 ± 0.11	0.43
8	**24**	$CDCl_3$	4.55 ± 0.08	0.24

(23) Heteroatoms at a similar position have been shown to increase the rate of the vinylcyclopropane rearrangement,[11] and the cyclopropylimine rearrangement.[24] See also: Danheiser, R. L.; Bronson, J. J.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579–4581 and references therein.

(24) (a) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1982**, *23*, 1413. (b) Wasserman, H. H.; Dion, R. P.; Fukuyama, J. *Tetrahedron* **1989**, *45*, 3203–3216.

(25) Although halogenated solvents are not the first choice for reactions involving amines (such as **13**) at elevated temperatures, chloroform was empirically found to give the cleanest reaction and highest yields of **12** for the sulfur-substitued dienes. For a leading reference on the reaction of amines with halogenated solvents, see: Mills, J. E.; Maryanoff, C. A.; McComsey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857–1859.

intermediates such as a vinyltriazoline or vinylaziridine; only **12** and **13** were seen at partial conversion. Mechanistic considerations will be presented later.



12 **13 (90%)** (3)

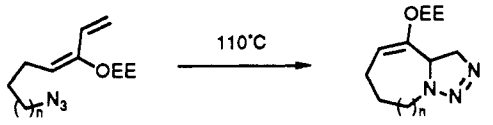
Table I summarizes our basic studies on the intramolecular cycloadditions of azides with heterosubstituted 1,3-dienes, and Table II summarizes some rate measurements.

Changing the substituent X has two primary effects. First, the rate of the initial cycloaddition step varies, and may be qualitatively described by the ranking X = CO_2Et ≫ H > halogen > SR, SeR > OR. This is in accord with the change from a dipole–HOMO controlled reaction with electron poor alkenes to a dipole–LUMO controlled reaction with electron rich alkenes.[26] The observation that sulfur substituted dienes are faster than oxygen substituted dienes (Table I, entries 1, 18, 19–21, and 24) and that a phenylthio substituent leads to an increased rate over an alkylthio substituent (see Table II, entries 1, 18, 19) is expected from a comparison of the HOMO energies of related 2-heterosubstituted 1,3-butadienes.[27]

The second effect of the heteroatom is that product distributions vary widely with X. As discussed previously, 1,5-hydrogen shift to C figures prominently in the cyclizations where X = CO_2Et or H, and this pathway is observed to varying extents with oxygen-substituted dienes (entries 20, 21) as well as sulfur-substituted dienes under certain conditions (entries 5–9, vide infra). Generally, sulfur provides the best results, producing the desired adducts A with little or no contamination (entries 1–4, 10–14, 16, 19). However, in all cases where A is formed, there is the potential for oxidation to pyrrole B. This oxidation may be controlled to a large degree by degassing the reaction mixture thoroughly and by taking reasonable measures to protect the products from air and light during the after isolation. In general, oxygen-substituted dienes are less successful than sulfur, primarily due to their slower cyclization and the competing formation of C by a 1,5-homodienyl shift. While cyclizations of oxygen-substituted dienes are observed to produce pyrrolizidines in moderate yield (entries 20, 21, 24), cyclization to indolizidines is too slow to be effective (see entries 26, 27). Halogen substitution (entry 28) leads to the desired cyclization as judged by ^1H NMR, but the pyrroline A could not be isolated due to its rapid decomposition to an insoluble white precipitate. Selenium-substituted diene **42** has about the same reactivity as the sulfur case, generating a vinyl selenide (entry 29). Examination of dienes where X = SO_2Ph, PPh_2, $P(O)Ph_2$, or NR_2 has not been possible to date due to difficulties encountered in their syntheses or stabilities. To summarize the effects of various heteroatom substituents, sulfur, selenium, and oxygen all provide the desired adduct A, but sulfur substitution is generally the most satisfactory due to the efficiency of the cyclization and the ease of diene synthesis, as will be presented below.

The effect of diene geometry on the cyclization was studied for sulfur and oxygen substituents. With sulfur, the geometry is not crucial to successful cyclization to A (compare entries 1 with 10 and 12 with 16). The rates of cyclization have been measured for dienes **12**, **15** and **24** and are shown in Table II. The *Z* diene **12** cyclizes approximately twice as fast as the *E* isomer **15** at 100 °C (compare Table II, entries 1 and 7), but the yields of A were very similar in each case. Although these phenylthio-substituted dienes are known to isomerize,[28] they do so at rates which are considerably slower than the rate of cyclization. For example, (*E*)- and (*Z*)-3-(phenylthio)-1,3-nonadiene were prepared, which lack an azido group, and each required 3–4 days at 100 °C to isomerize to any large degree, and did not reach an equilibrium mixture in that time frame. Therefore, it is unlikely that the *E* dienes isomerized to *Z* before cyclization, and the rates shown reflect the actual rates of the cyclization rather than the rate of *E* to *Z* isomerization followed by cyclization.

In contrast to sulfur, the geometry of oxygen-substituted dienes must be *Z* for successful cyclization to the desired bicyclic pyrrolines A. For example, whereas entries 20 and 21 illustrate pyrroline A formation from the *Z* dienes **26** and **29**, *E* dienes **32** and **33** (entries 22, 23) produce the medium-ring bicyclic triazolines **44** and **45** (eq 4). This outcome is a result of dipolar cycloaddition onto the distal double bond of the diene, an event which is possible due to the geometry of the *E* dienes.



32: n=1
33: n=2

44: n=1 (62%)
45: n=2 (53%) (4)

Aryl azides are well known to undergo intermolecular cycloadditions with enol ethers and other electron-rich double bonds to provide 1,5-disubstituted triazolines[26,29] rather than the 1,4-isomers that our reactions require, perhaps explaining a lower rate of reaction with the proximal double bond. In addition, it has recently been shown that 2-alkoxybutadienes prefer to react with aryl azides at the vinyl group rather than the enol ether (eq 5).[30] Sterics were proposed to be the operative rationale. It is worth noting here that we have been unsuccessful in bringing about the intermolecular [4 + 1] cyclization of azides with 2-heterosubstituted dienes. In any event, when geometry permits, compounds **44** and **45** are formed and are surprisingly stable at these temperatures. These compounds are sensitive to silica gel, with **44** undergoing a further transformation to the aziridine **46** with loss of nitrogen (eq 6). However, pure samples of either triazoline could be obtained by chromatography on alumina or deactivated silica gel.

(26) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 1, pp 1–176. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(27) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381–7396.

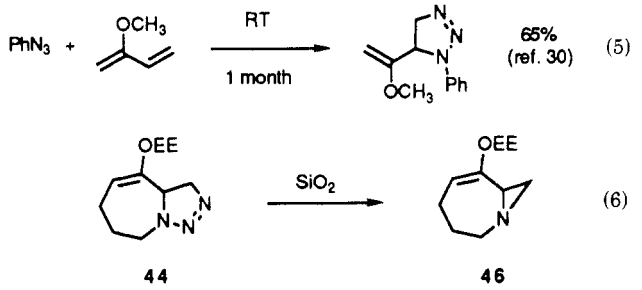
(28) See refs 39, 40, and Chou, S.-S. P.; Liou, S.-Y.; Tsai, C.-Y.; Wang, A.-J. *J. Org. Chem.* **1987**, *52*, 4468–4471.

(29) (a) Uhle, F. C. *J. Org. Chem.* **1967**, *32*, 1596. (b) Scheiner, P. *J. Org. Chem.* **1967**, *32*, 2022–2023. (c) Ito, M. M.; Nomura, Y.; Takeuchi, Y.; Tomada, S. *Heterocycles* **1984**, *21*, 627. (d) Kitane, S.; Berrada, M.; Vebrel, J.; Lande, B. *Bull. Chem. Soc. Belg.* **1985**, *94*, 163–164. (e) Chabala, J. C.; Christensen, B. G.; Ratcliffe, R. W.; Woods, M. F. *Tetrahedron Lett.* **1985**, *26*, 5407–5410. (f) Goldsmith, D.; Soria, J. J. *Tetrahedron Lett.* **1986**, *27*, 4701–4704. (g) DiNunno, L.; Scilimati, A. *Tetrahedron* **1986**, *42*, 3913. (h) Mohrle, H.; Dwuletzi, H. *Chem. Ber.* **1986**, *119*, 3591–3599. (i) Cipollone, A.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **1987**, *52*, 2584–2586.

(30) Kheruze, Y. I.; Galishev, V. A.; Petrov, A. A. *J. Org. Chem. USSR* **1988**, *24*, 852–856.

(31) Nugent, W. A.; Haymore, B. L. *Coord. Chem. Rev.* **1980**, *31*, 123.

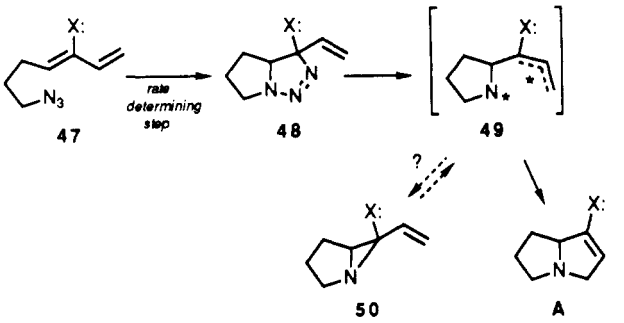
(32) Among the other transition metal catalysts tried were: $PdCl_2$, $NiCl_2$, Rh/Al_2O_3, $RhCl(PPh_3)_3$, Rh(II) acetate, $[(COD)RhCl]_2$, $RuCl_2(PPh_3)_3$, Ag_2O, and $RhCl_3 \cdot 3H_2O$.



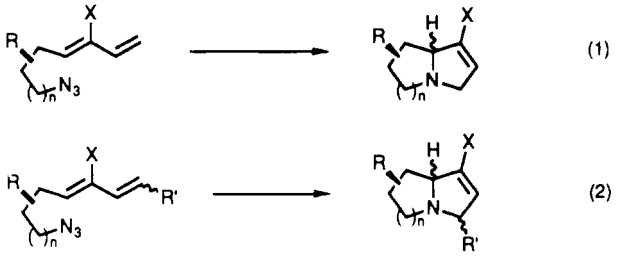
The effect of solvents on the cyclization of heterosubstituted dienes was also studied. Table II provides data from kinetic experiments, which showed smooth first-order kinetics. Changing from chloroform or benzene to the polar solvent dimethyl sulfoxide approximately doubled the rate of the cycloaddition, a small effect. Tenfold rate enhancements have been observed in concerted cycloadditions of phenyl azide with enamines when comparing polar to nonpolar solvents.[26] Other polar solvents (Table II, entries 4–6) led to slight rate enhancements. This small solvent effect combined with the fact that no intermediates are observed kinetically or spectroscopically during the reactions are consistent with a concerted cycloaddition reaction as the rate-determining step. The distribution of products also varied with solvent. In general, the desired production of bicyclic pyrrolines from sulfur-substituted dienes is best accomplished in halogenated solvents ($CHCl_3$, CH_2Cl_2, $Cl_2CHCHCl_2$). Other solvents may lead to substantial amounts of 1,5-hydrogen shift to C (Table I, entries 5–9). There is no clear correlation between solvent polarity and the cyclization outcome. Whereas benzene, acetonitrile, and pyridine lead to C as the major product, DMSO is quite satisfactory for the cyclization of **12** and **15** (Table I, entries 4, 11). However, DMSO leads to the formation of the triazole D with dienes **20**, **38**, **39**, and **42**. It is likely that elimination occurs from the intermediate triazoline **48** (Scheme III) in polar solvents to give the aromatic triazole D, perhaps by an E1-like mechanism. The protic solvent methanol leads to a 1:1.6 ratio of A to C, but aqueous solvents lead to decomposition. Finally, for oxygen-substituted dienes, THF is often preferred.

The role of chloroform in these cyclizations bears some elaboration. When chloroform (or deuteriochloroform) was originally studied as a solvent for the cyclization of dienes **12** and **15**, competitive formation of the 1,5-hydrogen shift product C was observed in some runs but not others. For example, distilled chloroform in KOH-washed glassware led to formation of small amounts of C, whereas neutral or acid washed glassware produced only A. In cases where C was observed, it was produced early in the cyclization but gradually stopped forming as the reaction proceeded. These observations led us to propose that traces of acid were being formed from the chloroform and that this acid was involved in the smooth conversion of triazoline **48** (Scheme III) to product A. Protonation of triazoline **48** may lead to ring opening and formation of A. Alternatively, protonation of aziridine **50** (if formed) may favor cleavage of the allylic C–N bond, leading back to A. Storing **12** or **15** over powdered KOH prior to cyclization led to the formation of a 1:1 mixture of A and C from **12**, and a 4:1 mixture from **15**. Adding 1 equiv of *p*-TsOH·H_2O or NH_4Cl to the KOH treated dienes prior to cyclization led to smooth production of A from either diene, without contamination by C. Ammonium chloride was also successful in improving cyclizations done in nonpolar solvents such as benzene, but was not successful in influencing cyclizations in polar solvents such as DMSO, where triazole

Scheme III



Scheme IV. Stereochemical Issues



was still formed. Ammonium chloride has also proven to be effective in cases where triazole formation is a problem, as in Scheme VI.[10c] Quaternary ammonium salts such as tetra-*n*-butylammonium iodide had no effect on the cyclization of **12**, indicating that it is a protonation which is important, not just a salt effect. Lewis acids such as boron trifluoride etherate did not affect the cyclization of **15**.

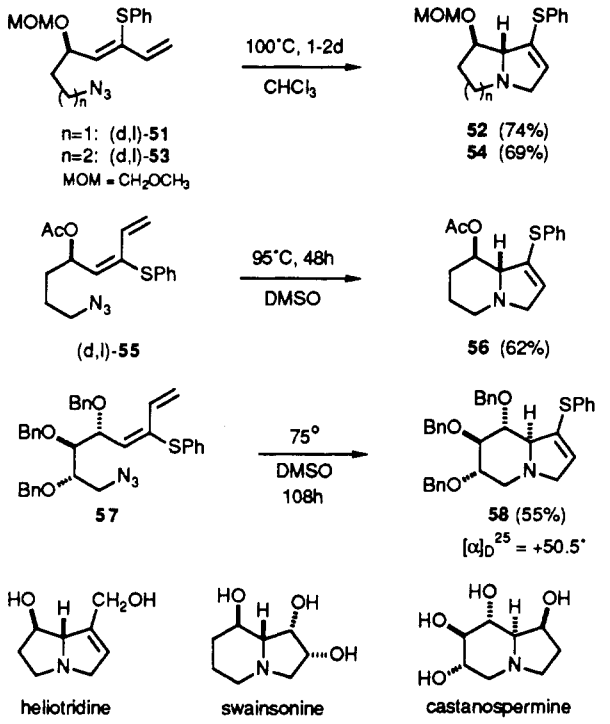
By analogy to the transition metal promoted conversion of diazo compounds into metal carbenoids, we were interested in adding transition metals to our azidodienes in order to facilitate the desired cyclizations. Perhaps a metal nitrenoid species could be formed, which would then react with the diene.[13,31] However, the cyclization of **26** in the presence of several transition-metal catalysts resulted in either decomposition or no effect.[32] The only exceptions were copper powder, cuprous chloride, or $RhCl_3 \cdot 3H_2O$ in THF at 110 °C, which led to a 4- to 5-fold increase in the rate of cyclization of the oxygen-substituted diene **26**, although in decreased yield. However, it is unlikely that a metal nitrene is involved, since the distribution of products does not change appreciably when compared to the thermal reaction (Table I, entry 20). Dienes **17** and **20** were also studied in DMSO at 100 °C, which normally gives triazole. Addition of NH_4Cl or copper catalysts did not change this outcome.

Mechanism. Although the exact details of the mechanism for bicyclic pyrroline formation are not known, some generalizations may be made.

These reactions are likely to proceed through an initial 1,3-dipolar cycloaddition rather than through nitrene intermediates. The temperatures (70–120 °C) are below that normally required for formation of an alkylnitrene from an alkyl azide.[6] The isolation of triazoles D in some cases is good evidence for the intermediacy of triazolines such as **48** in Scheme III. Furthermore, the isolation of the regioisomeric bicyclic triazolines **44** and **45** (eq 4) is consistent with 1,3-dipolar cycloaddition rather than nitrene formation.

Formation of triazoline **48** from **47** is probably the rate-determining step (Scheme III). This triazoline is generally too short lived to be observed, and instead decomposes by a radical or ionic mechanism to intermediate

Scheme V. Diastereoselective Azide-Diene Cyclizations



49. This may close directly to A, or proceed through the vinyl aziridine **50**. Should **50** be a major intermediate, it is likely to be formed reversibly. The heteroatom substituent may be responsible for increasing the persistence of **49** relative to ring closure to **50**, thereby allowing the formation of A by a 5-*endo-trig* cyclization.[33]

The observation of 1,5-homodienyl shift products C supports the intermediacy of vinylaziridines in some cases. However, this does not prove that the entire reaction proceeds through a vinylaziridine. A reasonable alternative is that an intermediate such as **49** (Scheme III) is formed, which partitions between two different pathways, i.e., direct cyclization to the bicyclic pyrroline A and cyclization to vinylaziridine **50**. The formation of the vinylaziridine may be reversible or may go on to the 1,5-homodienyl shift products C.

Stereoselective Cyclizations. If the tether connecting the diene and the azide contains one or more chiral centers, the diastereoselectivity of the cyclization must be considered (process 1, Scheme IV). If the diene bears a substituent on the terminal carbon, the relative stereochemistry of the newly formed chiral center relative to the bridgehead chiral center (as well as any preexisting chiral center) must be considered (process 2, Scheme IV). A related question is whether the geometry of the diene at the terminal alkene relates to the relative stereochemistry at this center. Our studies on these issues are described below. A third stereochemical issue is the possibility of enantioselective cyclizations in cases where the electron-donating group X also doubles as a chiral auxilliary. This work is still underway and will be reported separately.

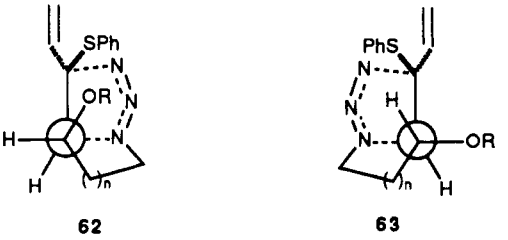


Figure 3. Stereochemical rationale.

The diastereoselectivity of process (1) will depend on the diastereoselectivity of the initial 1,3-dipolar cycloaddition of the azide with the proximal double bond of the diene. In contrast to other 1,3-dipolar cycloadditions,[34] the diastereoselectivity of azide cyclizations with chiral alkenes has seen less activity.[10c,13,15d-f,k,m,o,p,r,u,v,17,18c,d] We chose to study this question in systems which may be useful for natural products synthesis (Scheme V). Azidodienes **51**, **53**, **55**, and **57** were prepared (vide infra) and cyclized. A common feature in each is the presence of an alkoxy group at the allylic position of the diene. These cyclizations were very smooth, providing the pyrrolizidine **52** and the indolizidines **54**, **56**, and **58** in good to moderate yields. Of particular note is the stereoselectivity of these cyclizations, which proceeded to give only one detectable isomer in each case by examination of high-field ^{1}H NMR and ^{13}C NMR spectra. The assignments were made by examining the coupling constant between the bridgehead methine hydrogen and the neighboring ether-substituted methine hydrogen. In **54**, **56**, and **58**, respective couplings of 10, 9.2, and 8.5 Hz indicated a trans relationship of these two methine hydrogens. The stereochemistry of **52** is assigned by analogy to **54**, **56**, and **58**, since direct assignment by NMR was not possible. The similarity of **52** to heliotridine, **54**/**56** to swainsonine,[2c] and **58** to castanospermine[2c] should be noted, and efforts to synthesize these materials will be reported elsewhere.

The cyclization of racemic dienes **59**[35] and **61**[36] were attempted, since the transformation of these cycloadducts to heliotridine and swainsonine would require less effort. However, none of the desired materials were obtained. Triazole **60** was the major product from **59**, and **61** led to decomposition, again pointing out the reluctance of oxygen-substituted dienes to participate in cyclizations to indolizidines (see also Table I, entries 23, 26, 27).

The stereoselectivity of these cyclizations is readily understood by consideration of nonbonded steric interactions in the two likely diastereomeric transition states as shown in Figure 3. Allylic strain[37] between the SPh or vinyl group (depending on geometry) and the allylic ether is apparent in transition state **62** and absent in **63**. These same concerns have been well documented in studies

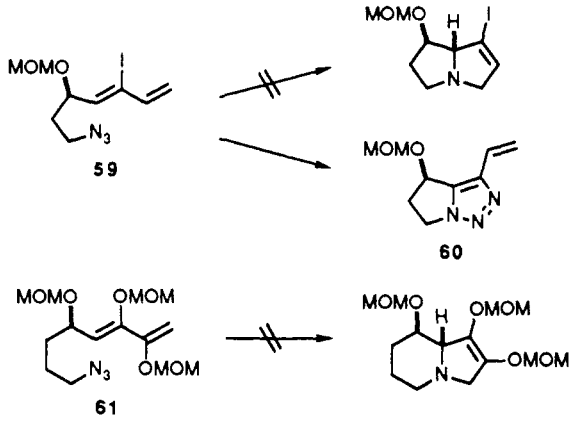
(33) Increasing evidence suggests that such closures are reasonable: (a) Duboudin, J.-G.; Jousseaume, B. *Synth. Commun.* **1979**, *9*, 53–56. (b) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778–1781. (c) Knochel, P. A.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455–4458. (d) Tanaka, K.; Yoda, H.; Kaji, A. *Tetrahedron Lett.* **1985**, *26*, 4747–4750, 4751–4754. (e) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1986**, *51*, 4627–4639 and references therein. (f) Tarnchompoo, B.; Thebtaranonth, C.; Thebtarononth, Y. *Tetrahedron Lett.* **1987**, *28*, 6675–6678. (g) Padwa, A. Yeske, P. E. *J. am. Chem. Soc.* **1988**, *110*, 1617–1618. (h) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 3041–3044. (i) Beak, P.; Burg, D. A. *J. Org. Chem.* **1989**, *54*, 1647–1654.

(34) (a) Annunziana, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253–269. (b) Curran, D. P.; Gothe, S. A. *Tetrahedron* **1988**, *44*, 3945–3952 and earlier references. (c) Confalone, P. N. *Org. React.* **1988**, *36*, 1. (d) Pearson, W. H. In *Studies in Natural Products Chemistry: Volume 1, Stereoselective Synthesis (Part A)*, Rahman, A., Ed.; Elsevier: New York, 1988; pp 323–328.

(35) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236–1245. Compound **59** was made in a fashion similar to the preparation of **53**, except iodine was used to quench the vinyl alanate rather that PhSCl.

(36) Prepared using the chemistry of McDougal: McDougal, P. G.; Rico, J. G. *J. Org. Chem.* **1987**, *52*, 4817–4819. 1-Lithio-2,3-bis(methoxymethoxy)-1,3-butadiene was added to 4-azidobutanal and the resultant alcohol was protected with MOM-Cl/iPr$_2$NEt to provide **61**. We thank Professor McDougal for providing the procedure for generating the metalated butadiene.

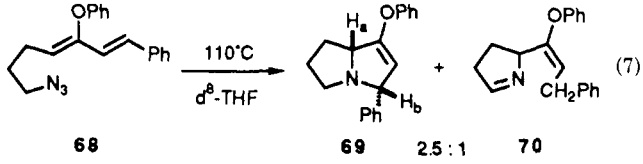
(37) Review on allylic 1,3-strain in controlling stereochemistry: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.



on intramolecular Diels–Alder cycloadditions with similar dienes,[38] where allylic strain rather than electronic rationalizations best fit the data.

An additional example of diastereoselectivity in an azidodiene with preexisting chiral centers is illustrated by the cyclization of **64**,[10c] a model cyclization for gephyrotoxin **67** (Scheme VI). The cyclization produces one stereoisomer of **66** and is presumed to arise from the chair/chair transition state **65**. Other groups in place of the ketal functionality produced mixtures of diastereomers.[10c]

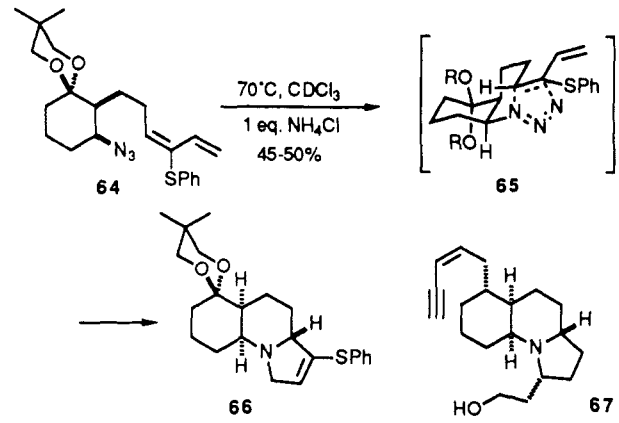
Dienes bearing a terminal substituent have also been examined. For example, upon heating **68** in a sealed tube, a single stereoisomer **69** is produced, accompanied by the 1,5-homodienyl shift product **70** in a 2.5:1 ratio (eq 7).



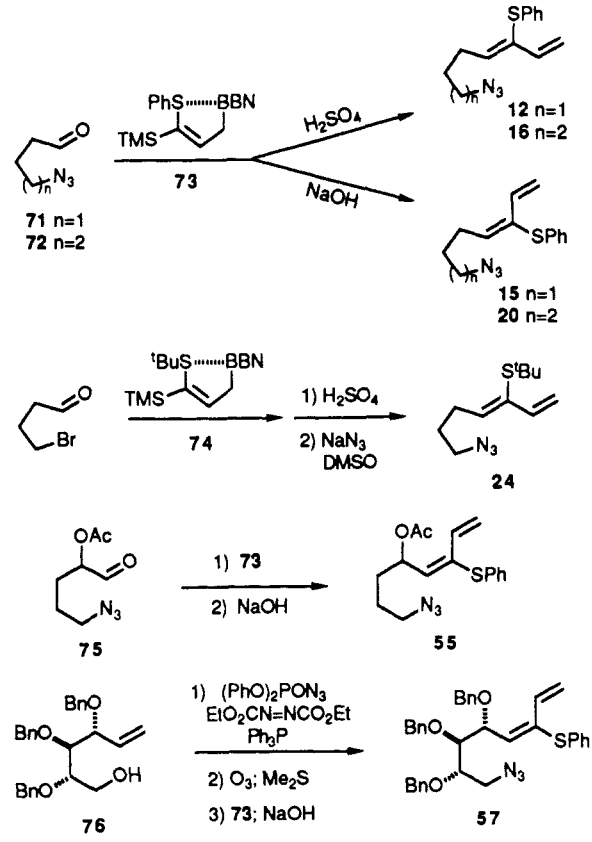
Although the crude reaction mixture was very clean by ^1H NMR, the sensitive nature of **69** led to an isolated yield of only 27% after chromatography. Direct ^1H NMR experiments on the reaction mixture confirmed the stereochemical assignment. An NOE enhancement at H_a of 4% was observed when H_b was irradiated. In order to study the nature of this stereoselection, the opposite stereoisomer of **68** is desired, where the terminal alkene is *Z*. Whereas the *E,Z* isomer of **68** gives **69**, it would be interesting to cyclize the *Z,Z* isomer to see if the same product were obtained, or whether a diastereomer is produced, thereby providing some insight into the mechanism of the rearrangement. Unfortunately, attempted cyclization of the *Z,Z* isomer of **68** resulted in isomerization of the diene to the *E,Z* isomer. Efforts to prepare other complementary pairs of diene stereoisomers are underway.

Diene Synthesis. If these azide–diene cyclizations are to be useful, the requisite heteroatom substituted dienes must be readily available. A combination of literature methods and new techniques were used in their preparation, as reported in Schemes VII–IX.

Scheme VI. Gephyrotoxin Model Cyclization[10c]



Scheme VII. Synthesis of Dienes via Allylborane Chemistry



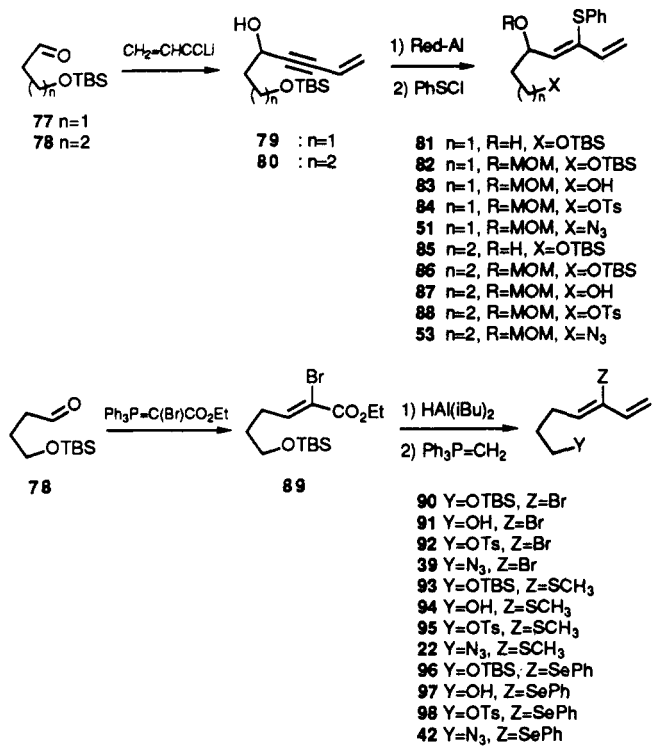
Scheme VII shows our recently reported[39,40] method with allylborane **73**, which allows efficient and stereoselective access to either the *E* or *Z* sulfur-substituted dienes **12**, **15**, **16**, **20**, **55**, and **57**. This work has now been extended to the preparation of *tert*-butylthio dienes such as **24** using the analogous allylborane **74**. Dienes **51** and **53** were conveniently prepared using a variation of Marshall's method involving Red-Al (Aldrich) reduction of propargyl alcohols (Scheme VIII),[35] modified in our case by quenching the intermediate vinyl alanate with phenylsulfenyl chloride. Dienes **22**, **39**, and **42** were synthesized

(38) (a) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541–3544. (b) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710. (c) Boeckman, R. K., Jr.; Barta, T. E. *Ibid.* **1985**, *50*, 3421. (d) McDougal, P. G.; Rico, J. G.; VanDerveer, D. *J. Org. Chem.* **1986**, *51*, 4492–4494. Intermolecular examples with dienes bearing allylic ethers: (e) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257–3262 and references therein. (f) Reitz, A. B.; Jordon, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800–4802. (g) Gupta, R. C.; Raynor, C. M.; Stoodley, R. J.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1773–1785.

(39) Pearson, W. H.; Lin, K.-C.; Poon, Y.-F. *J. Org. Chem.* **1989**, *54*, 5814–5819.

(40) We had originally used the titanium based method reported by Yamamoto, but have found that the allyl borane **73** is more convenient and also provides access to either diene geometry. The titanium analogue produces the *E* geometry: Furuta, K.; Ikeda, Y.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781–2790.

Scheme VIII. Synthesis of Sulfur-, Selenium-, and Bromine-Substituted Dienes



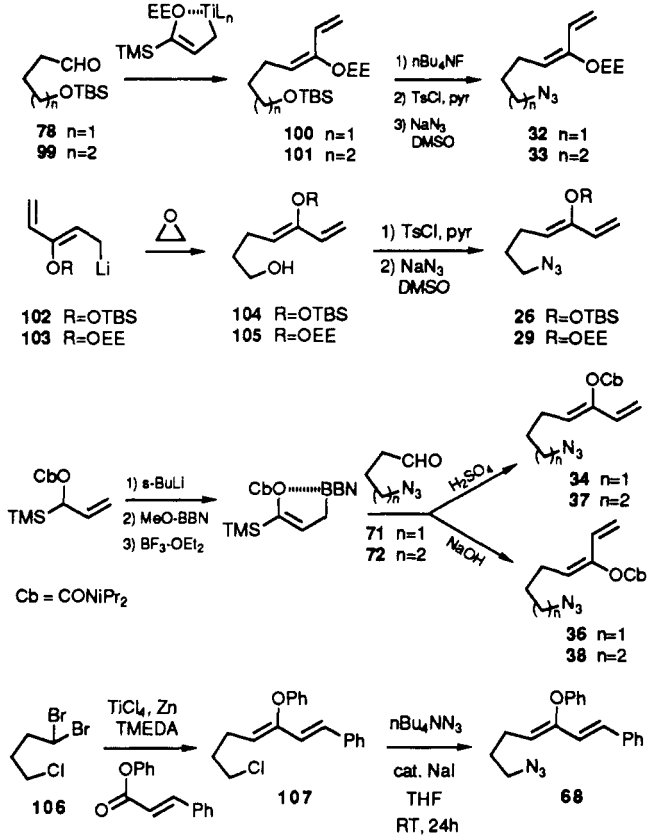
from the dienyl bromide **90** by standard methods involving metal–halogen exchange.

Scheme IX shows the various methods used to prepare oxygen substituted dienes. Murai's titanium-based method[41] was used for the preparation of dienes **32** and **33**. Oppolzer's (3-alkoxypentadienyl)lithium reagents **101** and **102** were used to prepare dienes **26** and **29**.[42] We have recently developed a new and convenient method for the stereoselective synthesis of carbamoyloxy-substituted dienes such as **34**, **36**, **37**, and **38**, based on allyl borane chemistry similar to that shown above in Scheme VII.[43] Finally, Takai's recent method[44] was ideal for the preparation of the terminally substituted diene **68**. Alkylation of (dibromomethyl)lithium with 3-chlorobromopropane gave the geminal dibromide **105**, which condensed with phenyl cinnamate under Takai's conditions to give **106** and hence **68** after azide displacement.

Conclusions

An effective [4 + 1] cyclization has been developed to produce pyrrolizidines and indolizidines. The cyclization involves an initial intramolecular 1,3-dipolar cycloaddition of an azide with the proximal double bond of a tethered 1,3-diene. The chemistry of the resultant triazoline depends strongly on the nature of the substituents present. A heteroatom at the 4-position of the triazoline is crucial to the desired rearrangement of this material to a bicyclic 3-pyrroline. A qualitative preference for sulfur substitution over oxygen, selenium and halogen was indicated by the milder conditions, higher yields, and ease of synthesis. Diastereoselective cyclizations were observed. Overall, this

Scheme IX. Synthesis of Oxygen-Substituted Dienes



one-flask "nitrene–diene" cyclization equivalent is cosmetically similar to an intramolecular Diels–Alder process, and quickly assembles pyrrolizidines and indolizidines, which are common structural features in naturally occurring compounds.

Experimental Section

General. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane, chloroform, pyridine, hexane, benzene, toluene, acetonitrile, ethyl acetate, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and triethylamine were distilled from calcium hydride immediately before use. All reactions were conducted under an atmosphere of dry nitrogen. Chromatography refers to liquid chromatography on silica gel (230–400 mesh) according to the method of Still[45] unless otherwise noted. ^{13}C NMR assignments were made with SEFT experiments. The preparation of **12**,[39] **15**,[39] **16**,[39] **20**,[39] **55**,[39] **71**,[18b] **72**,[39] **73**,[39] **77**,[46] **78**,[47] and **102**[42] have been previously reported. The preparation and thermolysis of azides **4a–c** and the production of **5b**, **6b,c**, **7a–c**, **8b**, and **9b** are described in the supplementary material.

Cyclization Reactions. General Procedure for the Cyclization of Azides. The thermolyses were carried out in freshly distilled solvents or were used directly from sealed vials in the case of deuterated solvents unless otherwise noted. All reaction vessels were soaked in a base bath (methanol–potassium hydroxide) for 24 h, rinsed thoroughly with distilled water, and oven-dried prior to introduction of the reactants. The dienes were dissolved in the desired solvent (ca. 0.1 M) and then introduced into the reaction vessel. For exploratory reactions, this vessel consisted of a 5-mm NMR tube. Otherwise, a thick-walled glass tube with or without a resealable Teflon valve was used. In cases

(41) Murai, A.; Abiko, A.; Shimada, N; Masamune, T. *Tetrahedron Lett.* **1984**, *25*, 4951.
(42) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002. Oppolzer has reported the synthesis of silyloxy dienes from **104**. We have extended this methodology to 2-(ethoxyethoxy) dienes from **105**.
(43) Schkeryantz, J., unpublished results.
(44) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4412.
(45) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(46) Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603.
(47) (a) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865. (b) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *Ibid.* **1986**, *51*, 3388.

where rigorous exclusion of oxygen is required, an all-glass sealed system was used. The sample was thoroughly degassed by five freeze/thaw cycles, and the reaction vessel was sealed under vacuum. The vessel was then introduced into an oil bath and heated for the desired time period. On completion of the reaction, the vessel was opened, the solvent removed in vacuo, and the mixture was purified by chromatography on silica gel (unless otherwise noted) to yield the pure cycloadduct.

2,3,5,7a-Tetrahydro-7-(phenylthio)-1*H*-pyrrolizine (13). Table I, entry 1. A solution of the diene **12**[39] (95.6 mg, 0.39 mmol) in $CHCl_3$ (4 mL) was placed in a resealable glass tube with a Teflon valve and was degassed by five freeze/thaw cycles. The tube was heated in an oil bath to 100 °C for 15 h. The tube was then cooled and opened, and the solvent was removed under reduced pressure. ^1H NMR indicated **13** to be the sole product. Gradient chromatography (0–10% $CH_3OH/CHCl_3$) provided **13** (77 mg, 90.2%) as a pale yellow oil: R_f 0.10 (5% $CH_3OH/CHCl_3$); IR (neat) 1524 (m), 1442 (s), 1420 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5–7.2 (m, 5 H), 5.43 (m, 1 H), 4.41 (m, 1 H), 4.18 (m, 1 H), 3.3–3.5 (m, 2 H), 2.62 (m, 1 H), 1.8–2.0 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 132.7, 132.5, 129.1, 128.0, 122.8, 72.7, 61.5, 56.9, 29.8, 25.2; MS *m/e* (rel int) 217 (M^+, 100.0), 188 (29.9), 184 (28.9), 108 (33.6), 107 (25.6), 106 (29.0), 80 (53.8), 71 (33.1), 39 (20.3); HRMS calcd for $C_{13}H_{15}NS$ 217.0925, found 217.0921.

Table I, entry 2. As above, **12** (114.3 mg, 0.46 mmol) in $Cl_2CHCHCl_2$ (4 mL) at 100 °C for 15 h gave 92 mg (90.9%) of **13** as a pale yellow oil after chromatography.

Table I, entry 3. As above, **12** (104 mg, 0.42 mmol) in diglyme (4 mL) at 100 °C for 15 h gave 82 mg (89.1%) of **13** as a pale yellow oil after chromatography.

Table I, entry 4. As above, **12** (96.8 mg, 0.40 mmol) in DMSO (4 mL) was heated at 100 °C for 15 h. The reaction mixture was poured into brine (20 mL) and extracted six times with 10-mL portions of a mixture of ether/petroleum ether (1:1). The extracts were dried (Na_2SO_4) and concentrated. Chromatography as above gave 54 mg (63%) of **13** as a pale yellow oil.

Table I, entry 5. As above, **12** (17.2 mg, 0.071 mmol) in benzene-d_6 (0.7 mL) containing anisole (20 mg, 0.019 mmol) as an internal standard at 100 °C for 15 h indicated 27% of **13** and 48% of **5-[(*E*)-1-(phenylthio)-1-propenyl]-1-pyrroline (14)** by integration of the ^1H NMR spectrum. (See entry 7 for spectral data of **14**.)

Table I, entry 6. As above, **12** (16.5 mg, 0.067 mmol) in CD_3CN (0.7 mL) containing anisole (2.0 mg, 0.019 mmol) as an internal standard at 100 °C for 15 h indicated 22% of **13** and 45% of **14** by integration of the ^1H NMR spectrum.

Table I, entry 7. As above, **12** (106.3 mg, 0.43 mmol) in ethyl acetate (EtOAc) (4 mL) at 100 °C for 7 h and 130 °C for 12 h gave 25.7 mg (28%) of **13** and 65.4 mg (70%) of **14** after chromatography (0–10% $CH_3OH/CHCl_3$). R_f for **14**, 0.60 (10% $CH_3OH/CHCl_3$). Spectral data for **14**: IR (neat) 1582 (m), 1476 (s), 1438 (s), 1302 (s), 1223 (m), 1024 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.63 (br s, 1 H), 7.37–7.14 (m, 5 H), 5.87 (q, J = 7.1 Hz, 1 H), 5.17 (m, 1 H), 2.69 (m, 1 H), 2.53 (m, 1 H), 2.05 (m, 1 H), 1.88 (d, J = 7.1 Hz, 3 H), 1.78 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.1, 136.7, 136.0, 132.9, 130.1, 128.8, 126.2, 72.6, 37.7, 26.1, 14.8; MS *m/e* (rel int) 217 (M^+, 99.1), 184 (37.7), 146 (26.7), 144 (83.1), 125 (30.3), 119 (34.0), 109 (34.8), 108 (100), 93 (61.4), 53 (47.7), 41 (59.1); HRMS calcd for $C_{13}H_{15}NS$ 217.0925, found 217.0923.

Table I, entry 8. As above, **12** (47 mg, 0.19 mmol) in THF (2 mL) at 100 °C for 16 h gave 13.6 mg (33%) of **13** and 25 mg (60%) of **14** after chromatography.

Table I, entry 9. As above, **12** (32 mg, 0.13 mmol) in pyridine-d_5 (1.4 mL) at 100 °C for 7 h gave 6 mg (21%) of **13** and 20.3 mg (72%) of **14** after chromatography.

Table I, entry 10. Under the procedure as above, diene **15** (104 mg, 0.42 mmol) in $CHCl_3$ (4 mL) at 100 °C for 15 h gave a mixture of **13** and **2,3-dihydro-7-(phenylthio)-1*H*-pyrrolizine (16)** in a 9:1 ratio by ^1H NMR. Gradient chromatography (0–10% $CH_3OH/CHCl_3$) gave 81 mg (87.9%) of **13** and 4 mg (4.4%) of **16** as pale yellow oils: R_f of **13**, 0.18 (5% $CH_3OH/CHCl_3$); R_f of **16**, 0.4 (5% EtOAc/hexane). ^1H NMR for **16**: (360 MHz, $CDCl_3$) δ 7.2–7.5 (m, 5 H), 6.67 (d, J = 2.7 Hz, 1 H), 6.31 (d, J = 2.7 Hz, 1 H), 4.01 (t, J = 7.3 Hz, 2 H), 3.25 (t, J = 7.1 Hz, 2 H), 1.8–1.9 (m, 2 H).

Table I, entry 11. As for entry 4, **15** (99 mg, 0.40 mmol) in DMSO (4 mL) at 100 °C for 15 h gave 60 mg (68%) of **13** after aqueous workup and chromatography.

3,5,6,7,8,8a-Hexahydro-1-(phenylthio)indolizine (18). Table I, entry 12. Using the procedure above, a solution of **17** (102.1 mg, 0.39 mmol) in $CHCl_3$ (4 mL) was heated to 110 °C for 44 h. The solution was concentrated, and the ^1H NMR of the crude material indicated a 16:1 mixture of **18** and **5,6,7,8-tetrahydro-1-(phenylthio)indolizine (19)**. Gradient chromatography (0–5% $CH_3OH/CHCl_3$) provided 78.2 mg (86.6%) of **18**, R_f 0.35 (5% $CH_3OH/CHCl_3$), and 5.3 mg (6%) of **19**, R_f 0.5 (5% EtOAc/hexane), both as pale yellow oils. For **18**: IR (neat) 1582 (m), 1476 (m), 1439 (s), 1372 (s), 1320 (s), 1196 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.2–7.5 (m, 5 H), 5.67 (m, 1 H), 3.62 (m, 1 H), 3.2 (m, 1 H), 3.0–3.1 (m, 2 H), 2.49 (m, 1 H), 1.7–1.9 (m, 2 H), 1.5–1.6 (s, 2 H), 1.2–1.3 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 133.3, 131.8, 129.0, 127.4, 126.8, 69.1, 57.4, 50.5, 28.3, 24.5, 23.9; MS *m/e* (rel int) 231 (M^+, 100), 198 (48), 189 (33), 174 (22), 156 (15), 147 (15), 122 (49), 121 (48), 120 (50), 80 (83); HRMS calcd for $C_{14}H_{17}NS$ 231.1081, found 231.1080. For **19**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.0–7.4 (m, 5 H), 6.61 (d, J = 1.1 Hz, 1 H), 6.25 (d, J = 1.1 Hz, 1 H), 3.96 (t, J = 6.9 Hz, 2 H), 2.77 (t, J = 7.1 Hz, 2 H), 1.7–1.85 (m, 2 H), 1.85–2.0 (m, 2 H).

Table I, entry 13. As above, **17** (130 mg, 0.50 mmol) in $Cl_2CHCHCl_2$ (4 mL) at 110 °C for 44 h provided a 9:1 mixture of **16** and **17** by crude ^1H NMR. Gradient chromatography (0–5% $CH_3OH/CHCl_3$) gave 89 mg (77%) of **18** as a pale yellow oil.

Table I, entry 14. As above, **17** (31 mg, 0.126 mmol) in CD_2Cl_2 (0.75 mL) was heated to 65 °C for 130 h to yield **18** (63%) as the sole product. The yield was determined by GC using decane as an internal standard.

Table I, entry 15. As above, **17** (140 mg, 0.54 mmol) in diglyme (4 mL) at 110 °C for 44 h provided a 1:1 mixture of **18** and **19** by ^1H NMR. Gradient chromatography (0–5% $CH_3OH/CHCl_3$) gave 61 mg (48.9%) of **18** as a pale yellow oil.

Table I, entry 16. As above, diene **20** (121 mg, 0.46 mmol) in $CHCl_3$ (4 mL) provided a 13:1 mixture of **18** and **19** by ^1H NMR. Gradient chromatography (0–5% $CH_3OH/CHCl_3$) gave 96 mg (89.2%) of **18** as a pale yellow oil.

3-Vinyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine (21). Table I, entry 17. A solution of the diene **20** (44.3 mg, 0.17 mmol) in 1 mL of DMSO-d_6 in a sealable NMR tube was degassed using five freeze/thaw cycles and then sealed. The tube was heated to 90 °C for 46 h. The tube was then opened, and the solvent was removed at reduced pressure. Chromatography of the residue (50% EtOAc/hexane) gave 16 mg (63%) of the triazole **21** as a light brown oil, R_f 0.2 (50% EtOAc/hexane): IR (neat) 1630 (w), 1475 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (dd, J =11.4, 17.9 Hz, 1 H), 5.73 (d, J = 17.9 Hz, 1 H), 5.31 (d, J = 11.4 Hz, 1 H), 4.36 (t, J = 6.0 Hz, 2 H), 2.85 (t, J = 6.4 Hz, 2 H), 2.06 (m, 2 H), 1.96 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 130.2, 126.2, 114.5, 46.2, 22.6, 20.9, 20.1; MS *m/e* (rel int) 149 (29, M^+), 121 (15), 120 (39), 109 (2), 106 (13), 93 (30), 80 (100); HRMS calcd for $C_8H_{11}N_3$ 149.0953, found 149.0958.

2,3,5,7a-Tetrahydro-7-(methylthio)-1*H*-pyrrolizine (23). Table I, entry 18. A solution of the diene **22** (0.125 g, 0.68 mmol) in $CHCl_3$ (12 mL) was degassed using five freeze/thaw cycles, sealed, and heated to 70 °C for 115 h. The tube was opened, and the solution was concentrated. The residue was chromatographed (grade III neutral alumina, 10% EtOAc/hexane) to give 29.6 mg (28%) of the amine **23** as a dark, air-sensitive oil, R_f 0.4 (10% EtOAc/hexane): IR (neat) 1602 (w), 1436 (w), 1085 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (br s, 1 H), 4.12 (m, 1 H), 3.90 (br d, J = 15.0 Hz, 1 H), 3.39 (br d, J = 15.0 Hz, 1 H), 3.09 (m, 1 H), 2.48 (q, J = 9.4 Hz, 1 H), 2.30 (s, 3 H), 1.96 (m, 1 H), 1.70 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 115.5, 73.1, 62.1, 56.9, 30.3, 29.7, 25.7; MS *m/e* (rel int) 155 (M^+, 13), 149 (2), 140 (8), 125 (5), 111 (11), 97 (18), 83 (26), 43 (100); HRMS calcd for $C_8H_{13}NS$ 155.0769, found 155.0764.

2,3,5,7a-Tetrahydro-7-(*tert*-butylthio)-1*H*-pyrrolizine (25). Table I, entry 19. A solution of the diene **24** (29.2 mg, 0.13 mmol) in $CDCl_3$ (1.4 mL) was degassed with five freeze/thaw cycles. After sealing, the tube was heated to 100 °C for 48 h and then opened, and the solvent was evaporated. ^1H NMR indicated **25** to be the sole product in the reaction mixture. Gradient chromatography (0–10% $CH_3OH/CHCl_3$) provided **25** (23.2 mg, 90.7%) as a light

brown oil, R_f 0.23 (5% $CH_3OH/CHCl_3$): IR (neat) 1446 (s), 1364 (s), 1215 (m), 1153 (m), 1041 (w), 1010 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.71 (m, 1 H), 4.84 (m, 1 H), 4.55 (dt, J = 16, 2 Hz, 1 H), 3.72–3.79 (m, 1 H), 3.67 (dt, J = 16, 3 Hz, 1 H), 2.87 (m, 1 H), 1.92–2.27 (m, 4 H), 1.38 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 124.4, 75.0, 60.2, 56.9, 47.3, 31.2, 29.2, 24.7; MS m/e (rel int) 197 (M^+, 21.4), 141 (38.5), 140 (61.8), 113 (10.5), 96 (11.8), 71 (60.2), 70 (100.0), 57 (25.6), 45 (18.37), 41 (57.6), 36 (69.0); HRMS calcd for $C_{11}H_{19}NS$ 197.1238, found 197.1230.

2,3,5,7a-Tetrahydro-7-[(*tert*-butyldimethylsilyl)oxy]-1*H*-pyrrolizine (27) and (*E*)-5-[1-[(*tert*-Butyldimethylsilyl)-oxy]-1-propenyl]-1-pyrroline (28). Table I, entry 20. A solution of **26** (138.8 mg, 0.52 mmol) in THF (3 mL) was degassed by five freeze/thaw cycles. The tube was sealed and heated to 110 °C for 7 days. The reaction mixture was concentrated, and the residue was chromatographed on deactivated silica gel. The column had been packed with silica gel containing 20% by weight of HMDS, which was then washed with 50% EtOAc/hexane (200 mL) followed by straight hexane (100 mL). Elution with 5% EtOAc/hexane gave 19 mg (15.3%) of the homodienyl shift product **28**, R_f 0.45 (EtOAc): IR (neat) 1662 (w), 1257 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (br s, 1 H), 4.90 (m, 1 H), 4.60 (q, J = 7 Hz, 1 H), 2.51 (m, 2 H), 1.77 (q, J = 7 Hz, 2 H), 1.61 (d, J = 7 Hz, 3 H), 0.78 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.5, 150.9, 101.4, 70.8, 37.8, 25.8, 25.7, 23.6, 18.0, 11.8, −3.6; MS m/e (rel int) 240 (M + 1, 1), 239 (M^+, 1), 182 (100), 124 (19), 84 (38), 75 (74); HRMS calcd for $C_{13}H_{25}NOSi$ 239.1705, found 239.1703. Further elution with 30% EtOAc/hexane gave 70 mg (56%) of **27**: IR (GC-FTIR) 1654 (m), 1257 (s), 1234 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.48 (br s, 1 H), 3.82–3.90 (m, 2 H), 3.16–3.22 (m, 1 H), 2.99–3.06 (m, 1 H), 2.50–2.57 (m, 1 H), 1.64–1.88 (m, 4 H), 0.92 (s, 9 H), 0.17 and 0.16 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 97.1, 69.2, 59.2, 57.5, 29.3, 25.6, 25.1, 18.1, −4.7, −4.9; MS m/e (rel int) 240 (M^+ + 1, 11), 239 (M^+, 52), 183 (54), 154 (63), 108 (36), 86 (40), 84 (65), 80 (23), 75 (55), 73 (100), 59 (64), 55 (22), 47 (33), 41 (75); HRMS calcd for $C_{13}H_{25}NOSi$ 239.1705, found 239.1703.

2,3,5,7a-Tetrahydro-7-(1-ethoxyethoxy)-1*H*-pyrrolizine (30) and 5-[(*Z*)-1-(1-Ethoxyethoxy)-1-propenyl]-1-pyrroline (31). Table I, entry 21. A solution of diene **29** (35 mg, 0.155 mmol) in THF (2.5 mL) in a resealable tube was degassed by five freeze/thaw cycles, and the vessel was sealed and heated to 120 °C for 7 days. Concentration and chromatography on deactivated silica gel (prepared as for **27** above) with 5% EtOAc/hexane gave 5.8 mg (19%) of **31** as a colorless liquid, R_f 0.24 (EtOAc): IR (neat) 2976 (m), 2933 (m), 2869 (w), 1662 (w), 1379 (w), 1128 (s), 1081 (vs), 1050 (s), 1032 (s), 950 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), mixture of diastereomers, δ 7.64 (m, 1 H), 4.97–5.10 (m, 2 H), 4.79 and 4.64 (q, J = 7.0 Hz, 1 H), 3.34–3.70 (m, 2 H), 2.63–2.77 (m, 1 H), 2.45–2.58 (m, 1 H), 1.84–1.94 (m, 2 H), 1.74 (d, J = 7.0 Hz, 3 H), 1.29 and 1.31 (d, J = 5.0 Hz, 3 H), 1.13 and 1.18 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.00, 153.69, 98.60, 98.34, 98.20, 96.97, 70.60, 62.08, 61.19, 38.02, 24.46, 20.52, 20.16, 15.52, 15.37, 11.90; MS m/e (rel int) 198 (M + 1, 0.6), 197 (M^+, 0.2), 152 (1), 125 (9), 108 (1), 97 (3), 73 (15), 69 (12), 45 (100); HRMS calcd for $C_{11}H_{19}O_2NH^+$ (MH^+) 198.1494, found 198.1490. Further elution with 30% EtOAc/hexane gave 10 mg (33%) of pyrroline **30** as a colorless liquid that turned a pale yellow on standing at room temperature: IR (neat) 1652 (s), 1381 (w), 1344 (w), 1225 (m), 1180 (m), 1140 (vs), 1103 (s), 1076 (s), 1048 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) mixture of diastereomers, δ 5.08 (q, J = 5.0 Hz, 1 H), 4.40 (s, 1 H), 3.99 (br s, 1 H), 3.87 (m, J = 13.0, 2.0 Hz, 1 H), 3.68–3.81 (m, 1 H), 3.42–3.53 (m, 1 H), 3.25 (dquint, J = 13.0, 2.0 Hz, 1 H), 2.80–3.06 (m, 1 H), 2.47–2.57 (m, 1 H), 1.63–1.97 (m, 4 H), 1.39 (t, J = 5.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.45, 155.23, 100.29, 100.15, 91.89, 91.81, 68.68, 68.48, 62.68, 62.39, 59.65, 59.59, 57.20, 29.80, 25.27, 25.20, 19.73, 15.14, 15.07; MS m/e (rel int) 198 (M^+ + 1, 0.1), 197 (M^+, 0.5), 152 (0.5), 97 (4), 73 (18), 70 (10), 55 (5), 45 (100); HRMS calcd for $C_{11}H_{19}O_2N$ 197.1415, found 197.1414.

6-(1-Ethoxyethoxy)-1,9,10-triazabicyclo[5.3.0]deca-5,9-diene (44). Table I, entry 22. A solution of diene **32** (170 mg, 0.75 mmol) in THF (5 mL) was degassed by five freeze/thaw cycles and heated to 110 °C for 7 days. Concentration and chromatography on deactivated silica gel (prepared as for **27** above) with 5% EtOAc/hexane gave 104 mg (62.3%) of **44** as a colorless liquid: R_f 0.63 (50% EtOAc/hexane, alumina TLC plate): IR (neat) 1658 (s), 1175 (s), 1136 (s), 1101 (s), 1047 (s), 1013 (s), 972 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) mixture of diastereomers, δ 4.97–5.11 (m, 2 H), 4.35–4.51 (m, 2 H), 4.18–4.30 (m, 1 H), 3.92–4.02 (m, 1 H), 3.60–3.70 (m, 1 H), 3.39–3.50 (m, 1 H), 3.27–3.35 (m, 1 H), 1.73–2.34 (m, 4 H), 1.40–1.43 (m, 3 H), 1.17–1.38 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 152.4, 103.6, 103.0, 99.0, 98.3, 69.4, 69.3, 61.8, 61.2, 59.9, 59.8, 50.5, 27.3, 22.9, 20.0, 19.8, 15.2; MS m/e (rel int) 226 (M^+ + 1, 3), 225 (M^+, 5), 153 (37), 125 (12), 96 (9), 73 (57), 45 (100); HRMS calcd for $C_{11}H_{19}O_2N_3$ 225.1477, found 225.1471.

7-(1-Ethoxyethoxy)-1,10,11-triazabicyclo[6.3.0]undeca-6,10-diene (45). Table I, entry 23. A solution of **33** (60 mg, 0.25 mmol) in THF (2 mL) was degassed by five freeze/thaw cycles, sealed, and heated to 110 °C for 8 days. Concentration and chromatography on deactivated silica gel (prepared as for **27** above) with 5% EtOAc/hexane gave 28 mg (53%) of **45** as a colorless oil, R_f 0.7 (5% $CH_3OH/CHCl_3$, alumina TLC plate): IR (neat) 2977 (s), 2931 (s), 2868 (s), 1657 (s), 1498 (s), 1446 (s), 1380 (s), 1208 (s), 1156 (s), 1135 (s), 1111 (s), 1077 (s), 1050 (s), 937 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers: δ 5.08–5.14 (m, 1 H), 4.75–4.88 (m, 1 H), 3.93–4.49 (m, 4 H), 3.33–3.71 (m, 3 H), 2.46–2.62 (m, 1 H), 1.46–2.06 (m, 5 H), 1.35–1.39 (m, 3 H), 1.16–1.28 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.90, 151.70, 101.22, 100.94, 98.50, 98.26, 69.65, 69.17, 61.56, 61.15, 58.14, 57.79, 49.65, 49.45, 27.75, 27.54, 25.25, 24.95, 22.86, 22.58, 20.11, 19.93, 15.27, 15.18; MS m/e (rel int) 240 (M^+, 15), 167 (4), 138 (4), 110 (9), 84 (8), 73 (85), 55 (20), 45 (100); HRMS calcd for $C_{12}H_{22}O_2N_3$ 240.1712, found 240.1700.

6-(1-Ethoxyethoxy)-1-azabicyclo[5.1.0]oct-5-ene (46). A solution of **44** (25 mg, 0.11 mmol) in pentane (2 mL) was stirred with silica gel (ca. 100 mg) at room temperature for 1 h. After filtration to remove the silica gel, the solution was concentrated and purified by preparative TLC on an alumina plate with 50% EtOAc/hexane to give 3 mg (14%) of aziridine **46**, R_f 0.52 (50% EtOAc/hexane, alumina TLC plate): IR (neat) 2958 (vs), 2930 (vs), 2872 (m), 2860 (m), 1733 (w), 1447 (w), 1178 (m), 1134 (m), 1048 (m), 1020 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) mixture of stereoisomers, δ 5.14 (m, 1 H), 4.72–4.85 (m, 1 H), 3.66–3.81 (m, 1 H), 3.43–3.54 (m, 1 H), 3.29–3.36 (m, 1 H), 2.63–2.69 (m, 1 H), 2.44–2.57 (m, 1 H), 1.79–2.11 (m, 4 H), 1.19–1.50 (m, 8 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 150.38, 150.08, 100.19, 100.10, 98.74, 97.92, 62.16, 61.05, 53.39, 53.32, 35.28, 25.23, 32.97, 32.65, 23.28, 23.16, 21.82, 21.56, 20.30, 19.88, 15.24, 15.15; MS m/e (rel int) 198 (M^+ + 1, 0.11), 197 (M^+, 1), 152 (1), 108 (5), 125 (16), 97 (14), 73 (48), 45 (100); HRMS calcd for $C_{11}H_{19}O_2NH^+$ 198.1494, found 198.1504.

2,3,5,7a-Tetrahydro-7-(diisopropylcarbamoyl)-1*H*-pyrrolizine (35). Table I, entry 24. A solution of diene **34** (31.0 mg, 0.11 mmol) in $CDCl_3$ (2 mL) was degassed with six freeze/thaw cycles, sealed in an NMR tube, and heated for 71 h at 110 °C. Concentration and chromatography (5% $CH_3OH/CHCl_3$) gave 14.7 mg (53%) of **35**, R_f 0.30 (10% $CH_3OH/CHCl_3$): IR (neat) 1657 (m), 1456 (m), 1437 (s), 1370 (m), 1328 (m), 1289 (s), 1254 (m), 1198 (s), 1154 (s), 1044 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.44 (dd, J = 4, 2 Hz, 1 H), 4.23 (m, 1 H), 4.09 (m, 1 H) 3.95 (m, 1 H), 3.74 (m, 1 H), 3.33 (ddd, J = 12, 4, 2 Hz, 1 H), 3.11 (m, 1 H), 2.55 (m, 1 H), 1.94 (m, 1 H), 1.74 (m, 3 H), 1.22 (d, J = 7 Hz, 12 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 152.6, 148.9, 104.9, 68.0, 59.0, 57.2, 46.9, 46.0, 29.4, 25.2, 21.5, 20.4; MS m/e (rel int) 253 (M + 1, 3), 252 (M^+, 12), 128 (22), 125 (31), 124 (100), 108 (12), 97 (17), 86 (88), 70 (14), 43 (79); HRMS calcd for $C_{14}H_{24}N_2O_2$ 252.1838, found 252.1831. Entries 25–27 in Table I were run in a similar fashion on approximately the same scales, resulting in no bicyclic pyrroline formation.

2,3,5,7a-Tetrahydro-7-bromo-1*H*-pyrrolizine (40) and 3-Vinyl-5,6-dihydro-4*H*-pyrrolo[1,2-*e*][1,2,3]triazole (41). Table I, entry 28. A solution of bromo diene **39** (30 mg, 0.14 mmol) in $CDCl_3$ (1 mL) was degassed by five freeze/thaw cycles, sealed, and heated at 80 °C for 10 days. The reaction was monitored by ^1H NMR spectroscopy. After consumption of **39**, NMR indicated an approximately equal amount of **40** and **41**, accompanied by another material showing diene resonances. Partial spectrum of **40**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.95 (m, 1 H, vinylic), 4.3–4.4 (m, 1 H, bridgehead). Upon opening the tube and exposure to air, a white solid rapidly formed which was insoluble in several

organic solvents, but a trace amount of triazole **41** could be isolated by chromatography. See below (entry 30) for spectral data on **41**.

2,3,5,7a-Tetrahydro-7-(phenylseleno)-1*H*-pyrrolizine (43). Table I, entry 29. A solution of the diene **42** (0.31 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was degassed using five freeze/thaw cycles and then heated to 70 °C for 72 h. The reaction mixture was concentrated, and the residue was chromatographed (silica gel, 10% $CH_3OH/CHCl_3$) to give 0.15 g (54%) of the pyrroline **43** as a dark oil, R_f 0.3: IR (NaCl, neat) 2960 (w), 2841 (w), 1576 (w), 1476 (w), 1437 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2 H), 7.27 (m, 3 H), 5.63 (m, 1 H), 4.22 (m, 1 H), 3.99 (br d, J = 15.7 Hz, 1 H), 3.40 (dq, J = 15.7, 2.2 Hz, 1 H), 3.16 (m, 1 H), 2.55 (m, 1 H), 1.88 (m, 1 H), 1.74 (m, 3 H); MS m/e (rel int) 265 (M^+, 52), 263 (66), 236 (10), 185 (100), 184 (54), 157 (23), 156 (26), 143 (18), 106 (45); HRMS calcd for $C_{13}H_{15}NSe$ 265.0370, found 265.0359.

2,3,5,7a-Tetrahydro-7-(phenylseleno)-1*H*-pyrrolizine (43) and 3-Vinyl-5,6-dihydro-4*H*-pyrrolo[1,2-*e*][1,2,3]triazole (41). Table I, entry 30. A solution of the diene **42** (0.15 g, 0.50 mmol) in 5 mL of DMSO was degassed with five freeze/thaw cycles, then sealed and heated at 90 °C for 72 h. The reaction mixture was concentrated and chromatographed (50% EtOAc/hexane) to give 10 mg (15%) of the triazole **41** as a light brown oil. Further elution with 10% $CH_3OH/CHCl_3$ gave 20 mg (15%) of the pyrroline **43**. See above for the spectral data for **43**. For **41**: R_f 0.2 (50% EtOAc/hexane); IR (neat) 2959 (w), 2875 (w), 1630 (w), 1475 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.75 (dd, J = 11.2, 17.9 Hz, 1 H), 5.57 (d, J = 17.9 Hz, 1 H), 5.30 (d, J = 11.2 Hz, 1 H), 4.31 (t, J = 7.6 Hz, 2 H), 2.96 (t, J = 6.7 Hz, 2 H), 2.83 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.8, 126.8, 114.9, 46.1, 28.3, 21.1; MS m/e (rel int) 135 (29, M^+), 106 (54), 92 (29), 79 (100), 65 (20), 52 (64), 41 (33); HRMS calcd for $C_7H_9N_3$ 135.0796, found 135.0804.

Table II: Kinetic Runs. Standard solutions of the dienes **12** and **15** (0.1 M) were prepared in $CDCl_3$ with anisole (0.03M) as an internal standard. An aliquot (700 μL, 0.07 mmol) was transferred to an NMR tube, degassed by five freeze/thaw cycles, and sealed under vacuum. The samples were introduced into an oil bath at the desired temperature. The temperature gradient and fluctuations in the working region of the bath did not vary more than 0.5 °C. Upon removal from the temperature bath, the NMR tube was cooled in a liquid nitrogen bath until the ^1H NMR spectrum could be measured (300 MHz, relaxation delay of 20 s). After acquisition of the ^1H NMR spectrum the sample was reintroduced into the oil bath and heated for the next determination. All kinetic runs were made on at least two sample tubes. Peak areas were determined by integration of starting material (azide) peaks versus the internal standard anisole and compared to a calibration curve obtained by integration of the peaks of authentic mixtures of products and starting materials versus anisole.

(1*R,7a*R**)-2,3,5,7a-Tetrahydro-1-(methoxymethoxy)-7-(phenylthio)-1*H*-pyrrolizine (52).** Diene **51** (0.28 g, 0.91 mmol) was dissolved in $CHCl_3$ (9 mL) and degassed by the freeze/thaw method. After sealing, the mixture was heated to 100 °C for 1 day. Evaporation of the solvent and chromatography (5% $CH_3OH/CHCl_3$) provided 0.19 g of **48** (47%) as a yellow liquid, R_f 0.27 (5% $CH_3OH/CHCl_3$): IR (neat) 1476 (s), 1440 (s), 1151 (s), 1113 (s), 1093 (s), 1041 (s), 748 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4 (m, 2 H), 7.3 (m, 3 H), 5.54 (dd, J = 4, 1 Hz, 1 H), 4.56 (d, part of AB, J = 7 Hz, 1 H), 4.52 (d, part of AB, J = 7 Hz, 1 H), 4.17 (m, 1 H), 4.09 (ddd, J = 7, 2, 1 Hz, 1 H), 3.95 (ddd, J = 16, 2, 1 Hz, 1 H), 3.33 (m, 1 H), 3.32 (s, 3 H), 3.2 (m, 1 H), 2.71 (m, 1 H), 1.86 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 134.7, 132.9, 131.9, 129.2, 127.6, 127.3, 95.4, 80.1, 79.2, 62.2, 55.4, 54.8, 31.4; MS m/e (rel int) 277 (M^+, 26), 189 (38), 188 (48), 106 (17), 95 (33), 82 (20), 80 (98), 71 (18), 45 (100); HRMS calcd for $C_{15}H_{19}NO_2S$ (M^+) 277.1137, found 277.1134.

(8*R,8a*R**)-3,5,6,7,8,8a-Hexahydro-8-(methoxymethoxy)-1-(phenylthio)indolizine (54).** Diene **53** (0.12 g, 0.38 mmol) was dissolved in $CHCl_3$ (2 mL) and degassed by the freeze/thaw technique. The mixture was heated to 110 °C for 2 days. Evaporation of solvent and gradient chromatography (0–5% $CH_3OH/CHCl_3$) provided 76 mg of **54** (69%) as a yellow liquid, R_f 0.18 (5% $CH_3OH/CHCl_3$): IR (neat) 1477 (m), 1440 (m), 1144 (s), 1039 (s) cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 7.51 (m, 2 H), 7.0 (m, 3 H), 5.11 (dd, J = 2, 1 Hz, 1 H), 4.83 (d, part of AB, J = 8 Hz, 1 H), 4.75 (d, part of AB, J = 8 Hz, 1 H), 3.68 (ddd, J = 10, 9, 4 Hz, 1 H), 3.35 (m, 2 H), 3.32 (s, 3 H), 3.04 (m, 1 H), 2.62 (m, 1 H), 2.23 (m, 2 H), 1.5 (m, 1 H), 1.3 (m, 2 H). ^{13}C NMR (360 MHz, $CDCl_3$) δ 140.4, 133.9, 129.0, 128.3, 121.5, 96.7, 77.8, 77.2, 72.3, 57.2, 55.8, 49.2, 31.7, 23.6; MS m/e (rel int) 291 (M^+, 22), 120 (27), 109 (28), 85 (29), 83 (44), 81 (30), 80 (35), 71 (26), 45 (100), 41 (23); HRMS calcd for $C_{16}H_{21}NO_2S$ 291.1293, found 291.1295.

(8*R,8a*R**)-3,5,6,7,8,8a-Hexahydro-1-(phenylthio)-8-acetoxyindolizine (56).** Diene **55** (200 mg, 0.63 mmol) was dissolved in freshly distilled DMSO (20 mL) in a 100-mL, round-bottomed flask. The contents were degassed five times then sealed under vacuum (0.02 mm). After heating at 95 °C for 48 h, the reaction mixture was cooled to room temperature, diluted with water (120 mL), and extracted with 3:1 ether/petroleum ether (5 × 20 mL). The extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by chromatography (5:1 then 3:1 hexane/EtOAc) gave 113 mg (62%) of **56** as a pale-yellow oil, R_f 0.25 (2:1 hexane/EtOAc): IR (neat)) 1733 (s), 1652 (w), 1584 (m), 1476 (m), 1439 (m), 1437 (s), 1323 (m), 1240 (vs), 1198 (m), 1043 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 2 H), 7.30 (m, 3 H), 5.34 (m, 1 H), 4.77 (ddd, J = 10.7, 9.2, 4.5 Hz, 1 H), 3.61 (m, 1 H), 3.32 (m, 1 H), 3.29 (m, 1 H), 2.93 (dm, J = 11.9 Hz, 1 H), 2.54 (app td, J = 11.9, 3.4 Hz, 1 H), 2.11 (m, 1 H), 2.04 (s, 3 H), 1.68 (m, 2 H), 1.27 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.20, 138.90, 132.82, 132.72, 129.20, 127.96, 124.78, 72.42, 69.97, 56.89, 48.59, 30.08, 22.84, 21.32; MS m/e (rel int) 289 (M^+, 10), 229 (32), 196 (15), 188 (7), 174 (7), 147 (4), 137 (9), 120 (100), 109 (19), 93 (5), 80 (36), 71 (17), 67 (10), 53 (9), 43 (67); HRMS calcd for $C_{16}H_{19}NO_2S$ (M^+) 289.1137, found 289.1144.

(+)-(6*S*,7*R*,8*R*,8a*S*)-3,5,6,7,8,8a-Hexahydro-1-(phenylthio)-6,7,8-tris(benzyloxy)indolizine (58). Following the procedure for the preparation of **56**, diene **57** (3.3 g, 5.72 mmol) was heated at 75 °C for 108 h in DMSO (300 mL). Purification of the residue by gradient chromatography (10:1 to 5:1 hexane/EtOAc) afforded 1.48 g (55% based on 85% conversion) of **58** as a white solid: mp 93–94 °C; $[\alpha]^{25}_D$ = +50.5° (*c* 1.16, $CHCl_3$), R_f 0.30 (3:1 hexane/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5 (m, 1 H), 7.41–7.18 (m, 19 H), 5.08 (dd, J = 4.0, 2.0 Hz, 1 H), 4.96 (AB q, J = 10.3 Hz, $\Delta\nu$ = 17.4 Hz, 2 H), 4.90 (AB q, J = 10.9 Hz, $\Delta\nu$ = 56.2 Hz, 2 H), 4.68 (AB q, J = 11.6 Hz, $\Delta\nu$ = 12.7 Hz, 2 H), 3.74 (m, 1 H), 3.59 (dd, J = 8.5 Hz, 8.5 Hz, 1 H), 3.56 (dd, J = 8.9 Hz, 1 H), 3.51 (m, 1 H), 3.40 (m, 1 H), 3.3 (ddd, J = 6.7, 4.8, 1.9 Hz, 1 H), 3.22 (dd, J = 11.5, 5.3 Hz, 1 H), 2.54 (dd, J = 11.5, 10.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.40, 138.93, 138.76, 138.55, 134.20, 132.25, 129.29, 128.45, 128.38, 128.4, 127.98, 127.92, 127.81, 127.71, 127.53, 127.37, 127.29, 121.29, 87.83, 81.78, 78.92, 75.72, 74.73, 72.80, 70.61, 57.13, 51.53. IR (KBr) 1950 (w), 1877 (w), 1807 (w), 1754 (m), 1584 (m), 1496 (s), 1476 (m), 1453 (s), 1359 (s), 1303 (m), 1207 (s), 1167 (s) cm^{-1}; MS m/e (rel int) 550 (M + 1, 15), 549 (M^+, 32), 547 (22), 441 (11), 352 (5), 348 (7), 337 (6), 246 (6), 228 (6), 189 (13), 188 (12), 175 (8), 92 (13), 91 (100), 80 (11), 77 (8), 43 (24); HRMS (EI) calcd for $C_{35}H_{35}NO_3S$ (M^+) 549.2338, found 549.2327. Anal. Calcd for $C_{35}H_{35}NO_3S$: C, 76.47; H, 6.42; N, 2.55. Found: C, 76.39; H, 6.36; N, 2.55.

(5*R,7a*R**)-2,3,5,7a-Tetrahydro-5-phenyl-7-phenoxy-1*H*-pyrrolizine (69) and (*E*)-5-(1-Phenoxy-3-phenyl-1-propenyl)-1-pyrroline (70).** A solution of **68** (36 mg, 0.12 mmol) in THF-d_8 (1 mL) in an NMR tube was degassed by five freeze/thaw cycles, and the tube was sealed and heated at 110 °C for 13 days. The progress of the reaction was monitored by ^1H NMR spectroscopy, and the reaction was stopped after ca. 90% of the starting material had been consumed. The ratio of **69** to **70** was determined by NMR to be 2.5 to 1. An NOE experiment was performed on the crude mixture in the sealed NMR tube after a homodecoupling experiment to confirm the crucial proton assignments. Irradiation of H_8 (4.25 ppm) caused an NOE enhancement at H_3 (5.14 ppm) of 4%. The tube was opened, and the solution was concentrated and chromatographed on grade III basic alumina to give 8.7 mg (29%) of **69**, which was very sensitive to decomposition and could not be isolated without contamination by a small amount (ca. 10%) of the corresponding pyrrole. For **69**, R_f 0.05 (EtOAc, SiO_2 TLC plate): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14–7.43 (m, 10 H), 5.26 (dd, J = 3.5, 1.5 Hz, 1 H, H_3), 4.65 (t, J = 1.5 Hz, 1 H, H_2), 4.39 (m, 1 H, $w_{1/2}$ = 20 Hz, H_8), 3.33 (t, J = 6.5 Hz, 2 H), 1.86–2.12 (m, 2 H), 1.61–1.71 (m, 2 H) ppm. Note

that the shifts for H_3 and H_8 are slightly different in $CDCl_3$ as compared to THF-d_8. Partial ^1H NMR spectrum for **70** (300 MHz, THF-d_8): δ 7.57 (s, 1 H), 5.24 (br s, 1 H), 4.87 (t, J = 7 Hz, 1 H), 3.75 (m, 2 H), 2.2–2.7 (m, 4 H).

Preparation of Dienes. See ref 39 for the preparation of **12**, **15**, **16**, **20**, and **55** by the allylborane method.

1-(Trimethylsilyl)-1-(*tert*-butylthio)-1,2-propadiene. To a solution of lithium diisopropylamide (LDA, 66 mmol) in THF (300 mL) was added 1-(*tert*-butylthio)-1-propyne[48] (8.37 g, 65.3 mmol) at −78 °C. After 30 min, chlorotrimethylsilane (7.17 g, 66 mmol) was added quickly, and the mixture was allowed to warm to room temperature. Saturated NH_4Cl solution was added, and the mixture was extracted twice with petroleum ether. The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was distilled (69–72 °C at 4 mmHg) to provide 8.4 g (64%) of the title compound. Gas chromatography showed this material to be 89% pure: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.58 (s, 2 H), 1.42 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 208, 89.9, 72.5, 47.1, 30.7, −1.7; IR (neat) 2960 (s), 1920 (s), 1363 (s), 1248 (s) cm^{-1}.

(*Z*)-7-Bromo-3-(*tert*-butylthio)hepta-1,3-diene. To 1-(trimethylsilyl)-1-(*tert*-butylthio)-1,2-propadiene (500 mg, 2.5 mmol) in a resealable tube with a Teflon valve was added 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 5 mL, 2.5 mmol). The tube was sealed, and the mixture was heated for 24 h at 66 °C to generate the allylborane **74**, cooled, and added to a solution of 4-bromobutanal[18b] (380 mg, 2.5 mmol) in THF (1 mL) at 0 °C via syringe. After being warmed to room temperature for 2.5 h, the mixture was cooled to 0 °C and treated with 4 drops of concentrated H_2SO_4. After being stirred at room temperature for 4 h, the mixture was carefully poured into saturated $NaHCO_3$ and extracted with petroleum ether (3 × 20 mL). The organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexane) gave 254 mg (38.4%) of the title compound as a pale light yellow oil, R_f 0.29 (2% EtOAc/hexane): IR (neat) 2960 (s), 2896 (s), 1652 (w), 1558 (m), 1471 (s), 1456 (s), 1393 (m), 1363 (s), 1248 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.45 (dd, J = 17.0, 10.5 Hz, 1 H), 6.18 (t, J = 7.3 Hz, 1 H), 5.71 (br d, J = 17.0 Hz, 1 H), 5.11 (d, J = 10.6 Hz, 1 H), 3.41 (t, J = 7.0 Hz, 2 H), 2.65 (q, J = 7.0 Hz, 2 H), 1.96 (m, 2 H), 1.85 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.38, 140.57, 134.48, 115.82, 47.37, 32.98, 32.27, 31.97, 29.65; MS (CI/NH_3) m/e (rel intensity) 264 (M + 1, 7), 263 (M^+, 1), 262 (7), 208 (20), 206 (20), 127 (24), 99 (35), 93 (44), 71 (29), 65 (22), 57 (100), 45 (21), 41 (73), 39 (43); HRMS calcd for $C_{11}H_{19}BrS$ 262.0384, found 262.0388.

(*Z*)-7-Azido-3-(*tert*-butylthio)hepta-1,3-diene (24). Sodium azide (195 mg, 3 mmol) was added to a solution of (*Z*)-7-bromo-3-(*tert*-butylthio)hepta-1,3-diene (254 mg, 0.95 mmol) in DMSO (3 mL). The mixture was stirred at room temperature for 16 h, poured into brine/petroleum ether (1:1, 20 mL), and extracted with petroleum ether (3 × 20 mL). The extracts were dried ($MgSO_4$) and concentrated. Chromatography (hexane) gave **24** (144 mg, 66.8%) as a pale yellow oil, R_f 0.2 (2% EtOAc/hexane): IR (neat) 2095 (s), 1614 (s) 1477 (w), 1456 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.46 (dd, J = 17.0, 10.5 Hz, 1 H), 6.18 (t, J = 7.4 Hz, 1 H), 5.71 (br d, J = 17.0 Hz, 1 H), 5.1 (d, J = 10.6 Hz, 1 H), 3.29 (t, J = 7.0 Hz, 2 H), 2.58 (q, J = 7.4 Hz, 2 H), 1.69 (m, 2 H), 1.30 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.81, 140.57, 134.00, 115.82, 51.03, 47.41, 31.94, 28.32, 28.11; MS (CI/NH_3) m/e (rel intensity) 226 (M^+, 6), 198 (20), 142 (77), 136 (66), 110 (100), 89 (27), 77 (2); HRMS calcd 226.1378, found 226.1372.

(−)-(*E*)-(5*R*,6*S*,7*S*)-8-Azido-3-(phenylthio)-5,6,7-tris(benzyloxy)-1,3-octadiene (57). The conversion of (2*S*,3*S*,4*R*)-2,3,4-tris(benzyloxy)-5-hexen-1-ol (**76**)[49] to (3*R*,4*S*,5*S*)-6-azido-3,4,5-tris(benzyloxy)hex-1-ene followed the procedure of Bose.[50] To a well-stirred mixture of diethyl azodicarboxylate (11.7 g, 67.24 mmol) and triphenylphosphine (17.62 g, 67.24 mmol) in THF (80 mL) was added a solution of alcohol **79** (21 g, 52 mmol) in THF (20 mL) at room temperature. To this red solution was added diphenylphosphoryl azide (18.5 g, 67.24 mmol). After 1 h, the solvent was removed in vacuo, and the residue was filtered through a plug of silica gel (50:1 hexane/EtOAc) to afford 18.9 g (84.8%) of (3*R*,4*S*,5*S*)-6-azido-3,4,5-tris(benzyloxy)-1-hexene as a colorless oil: $[\alpha]^{25}_D$ = −4.1° (*c* 1.15, MeOH); IR (neat) 2097 (s, N_3) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 15 H), 5.95 (ddd, J = 16.8, 10.9, 7.4 Hz, 1 H), 5.40 (br s, 1 H), 5.35 (br d, J = 8.4 Hz, 1 H), 4.78 (AB q, J = 11.4 Hz, $\Delta\nu$ = 15.1 Hz, 2 H), 4.70 (AB q, J = 11.4 Hz, $\Delta\nu$ = 17.2 Hz, 2 H), 4.55 (AB q, J = 11.8 Hz, $\Delta\nu$ = 80.1 Hz, 2 H), 4.08 (dd, J = 7.4, 4.8 Hz, 1 H), 3.82 (ddd, J = 6.0, 5.9, 4.1 Hz, 1 H), 3.64 (dd, J = 5.5, 4.8 Hz, 1 H), 3.44 (dd, J = 12.9, 4.1 Hz, 1 H), 3.31 (J = 12.9, 6.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.34, 138.22, 138.13, 135.31, 128.42, 128.35, 128.12, 127.99, 127.76, 118.84, 81.21, 80.07, 78.95, 75.00, 73.43, 70.60, 51.62; HRMS (CI,NH_3) calcd for $C_{27}H_{30}N_3O_3$ (MH^+) 444.2287, found 444.2281.

Ozone was passed through the above azide (3.0 g, 6.96 mmol) in CH_3OH (100 mL) at −78 °C until the solution turned blue. After a stream of nitrogen was passed through to remove the excess ozone, dimethyl sulfide (1 mL, 1.36 mmol) was added, and the mixture was stirred at −78 °C for 2 h, 0 °C for 2 h, and room temperature overnight. After evaporation of the solvent in vacuo, ether (35 mL) was added, and the organic phase was washed with brine (10 mL) and dried (Na_2SO_4) to afford (2*S*,3*R*,4*S*)-5-azido-2,3,4-tris(benzyloxy)pentanal (2.7 g, 90%) as a pale yellow oil. This aldehyde was used immediately in the next step without further purification: IR (neat)) 2097 (s, N_3), 1729 (vs, C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (d, J = 0.6 Hz, 1 H), 7.38–7.22 (m, 15 H), 4.66 (AB q, J = 11.9 Hz, $\Delta\nu$ = 84.9 Hz, 2 H), 4.56 (d, J = 10.8 Hz, 4 H), 3.94 (dd, J = 5.4, 0.6 Hz, 1 H), 3.90 (dd, J = 4.4, 4.4 Hz, 1 H), 3.77 (m, 1 H), 3.38 (dd, J = 11.8, 5.4 Hz, 1 H), 3.27 (dd, J = 11.8, 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.08, 137.44, 137.24, 137.00, 128.66, 128.57, 128.49, 128.43, 128.35, 128.32, 126.27, 128.13, 28.03, 81.21, 78.81, 77.18, 74.13, 74.43, 73.26, 51.11.

To 1-(phenylthio)-1-(trimethylsilyl)-1,2-propadiene[39] (1.52 g, 95% purity, 6.5 mmol) was added 9-borabicyclo[3.3.1]nonane (9-BBN, 0.50 M in THF, 13 mL, 6.5 mmol) at room temperature. The mixture was stirred at 35 °C for 2 h to complete the formation of the allylborane **73**. After cooling to room temperature, a solution of the above aldehyde (2.3 g, 5.31 mmol) in THF (2 mL) was added at 0 °C. The ice bath was removed, and the reaction mixture was allowed to stir for 10 h and then quenched by the addition of 4 N NaOH (1 mL). After 2 h at room temperature, the mixture was diluted with petroleum ether, and the organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. Chromatography (hexane followed by 50:1 hexane/EtOAc) afforded 2.2 g (74%) of the title diene **57** as a clear, colorless oil: R_f 0.40 (10:1 hexane/EtOAc); $[\alpha]^{25}_D$ = −40.0° (*c* 1.5, CH_3OH); IR (neat) 2867 (br s), 2100 (s), 1951 (w), 1875 (w), 1808 (w), 1621 (m), 1605 (w), 1582 (m), 1496 (s), 1478 (s), 1454 (s), 1440 (s), 1068 (br s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.26 (m, 20 H), 6.71 (dd, J = 16.8, 10.7 Hz, 1 H), 5.97 d, J = 9.4 Hz, 1 H), 5.90 (d, J = 16.8 Hz, 1 H), 5.36 (d, J = 10.7, 1 H), 4.76 (AB q, J = 11.3 Hz, $\Delta\nu$ = 11.4 Hz, 2 H), 4.72 (m, 1 H), 4.69 (AB q, J = 11.5 Hz, $\Delta\nu$ = 20.0 Hz, 2 H), 4.57 (AB q, J = 11.8 Hz, $\Delta\nu$ = 79.54 Hz, 2 H), 3.76 (ddd, 6.0, 5.3, 4.0 Hz, 1 H), 3.69 (dd, J = 5.3, 4.4 Hz, 1 H), 3.48 (dd, J = 13.0, 4.0 Hz, 1 H), 3.32 (dd, J = 13.0, 6.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.97, 137.67, 137.11, 132.86, 131.46, 130.29, 129.13, 128.39, 128.33, 128.29, 128.23, 127.79, 127.74, 127.69, 127.23, 120.20, 81.18, 79.05, 75.7, 74.34, 73.26, 70.60, 51.47; MS m/e (rel intensity) 549 (0.4), 458 (2), 439 (1), 430 (1), 350 (1), 348 (1), 280 (1), 240 (0.9), 218 (2), 190 (1), 189 (1), 110 (7), 109 (4), 107 (6), 91 (100); HRMS (CI-NH_3) calcd for $C_{35}H_{36}N_3O_3S$ (MH^+) 578.2477, found 578.2459.

1-[(*tert*-Butyldimethylsilyl)oxy]hept-6-en-4-yn-3-ol (79). To vinylacetylene[51] (10 mL of a 2.5 M solution in toluene, 25 mmol) in THF (56 mL) at −78 °C was added *n*-butyllithium (10 mL of a 2.5 M solution in hexane, 25 mmol), which was stirred for 30 min. A solution of 3-[(*tert*-butyldimethylsilyl)oxy]propanal (**77**)[46] (2.74 g, 14.5 mmol) in THF (15 mL) was then slowly added, and the mixture was stirred for 45 min, warmed to room temperature, and poured into saturated $NaHCO_3$. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated

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in vacuo. Chromatography (10% EtOAc/hexane) provided **79** (3.18 g, 91%) as a colorless oil: R_f 0.36 (10% EtOAc/hexane): IR (neat) 3418 (br s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17, 11, 2 Hz, 1 H), 5.64 (dd, J = 17, 2 Hz, 1 H), 5.48 (dd, J = 11, 2 Hz, 1 H), 4.75 (dd, J = 10, 5 Hz, 1 H), 4.05 (m, 1 H), 3.86 (m, 1 H), 3.5 (d, J = 6 Hz, 1 H), 2.02 (m, 1 H), 1.9 (m, 1 H), 0.91 (s, 9 H), 0.11 (s, 6 H); MS m/e (rel int) 241 (M^+, 43), 224 (13), 223 (67), 190 (16), 189 (100), 145 (24), 131 (14), 89 (14); HRMS calcd for $C_{13}H_{24}O_2SiH$ ($M + H^+$) 241.1624, found 241.1632. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.94; H, 10.06. Found: C, 64.65; H, 10.06.

(*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-(phenylthio)-4,6-heptadien-3-ol (81). To a solution of Red-Al (2.9 mL of a 3.4 M solution in toluene, 9.8 mmol) in ether (6 mL) at 0 °C was added **79** (1.4 g, 5.7 mmol) in ether (6 mL). The resultant mixture was stirred for 1 h before EtOAc (1.8 mL) was added to quench the excess Red-Al. The mixture was then cooled to −78 °C, and phenylsulfenyl chloride[52] (0.83 g, 5.7 mmol) was added. After being warmed to room temperature, the mixture was poured into water and extracted with $CHCl_3$. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (10% EtOAc/hexane) provided **81** (1.3 g, 64%) as a colorless oil: R_f 0.28 (10% EtOAc/hexane); IR (neat) 3429 (br s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 5 H), 6.4 (dd, J = 16, 10 Hz, 1 H), 6.35 (d, J = 8 Hz, 1 H), 5.58 (d, J = 16 Hz, 1 H), 5.13 (d, J = 10 Hz, 1 H), 5.1 (m, 1 H), 3.37 (m, 2 H), 3.62 (d, J = 3 Hz, 1 H), 1.75 (m, 2 H), 0.89 (s, 9 H), 0.1 (s, 6 H); MS m/e (rel int) 350 (M^+, 29), 332 (26), 201 (17), 183 (14), 123 (12), 105 (29), 91 (24), 77 (11), 75 (100), 73 (34); HRMS calcd for $C_{19}H_{30}O_2SSi$ (M^+) 350.1736, found 350.1740.

(*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-(methoxymethoxy)-3-(phenylthio)-1,3-heptadiene (82). Chloromethyl methyl ether (2.1 mL, 27 mmol) was added to a solution of **81** (7.9 g, 22 mmol) and *N,N*-diisopropylethylamine (4.7 mL, 27 mmol) in CH_2Cl_2 (90 mL) at 0 °C. The resultant mixture was then warmed to room temperature for 16 h, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (5% EtOAc/hexane) provided **82** (7.4 g, 84%) as a colorless oil: R_f 0.34 (5% EtOAc/hexane): IR (neat) 1479 (s), 1472 (s), 1256 (s), 1153 (s), 1095 (s), 1034 (s), 837 (s), 775 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06–7.26 (m, 5 H), 6.37 (dd, J = 17, 10 Hz, 1 H), 6.18 (d, J = 8 Hz, 1 H), 5.57 (d, J = 17 Hz, 1 H), 5.13 (d, J = 10 Hz, 1 H), 5.04 (m, 1 H), 4.65 (d, part of AB, J = 7 Hz, 1 H), 4.57 (d, part of AB, J = 7 Hz, 1 H), 3.7 (t, J = 6 Hz, 1 H), 3.36 (s, 3 H), 1.65–1.94 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H). MS m/e (rel int) 394 (M^+, 2), 349 (40), 307 (33), 275 (95), 235 (23), 201 (19), 119 (22), 89 (69), 73 (34), 45 (100). Anal. Calcd for $C_{21}H_{34}O_3SSi$: C, 63.91; H, 8.68. Found: C, 63.76; H, 8.76.

(*Z*)-3-(Methoxymethoxy)-5-(phenylthio)-4,6-heptadien-1-ol (83). Tetrabutylammonium fluoride (33 mL of a 1 M solution in THF, 33 mmol) was added to a solution of **82** (4.3 g, 11 mmol) in THF (55 mL) at room temperature. After 2 h, the mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (50% EtOAc/hexane) provided **83** (3.0 g, 97%) as a colorless oil, R_f 0.47 (50% EtOAc/hexane): IR (neat) 3424 (br s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.1–7.4 (m, 5 H), 6.38 (dd, J = 17, 11 Hz, 1 H), 6.19 (d, J = 8 Hz, 1 H), 5.62 (d, J = 17 Hz, 1 H), 5.17 (d, J = 11 Hz, 1 H), 5.1 (dt, J = 12, 5 Hz, 1 H), 4.66 (d, part of AB, J = 7 Hz, 1 H), 4.58 (d, part of AB, J = 7 Hz, 1 H), 3.75 (m, 2 H), 3.37 (s, 3 H), 2.25 (t, J = 5 Hz, 1 H), 1.69–2.0 (m, 2 H); MS m/e (rel int) 280 (M^+, 2), 175 (10), 73 (23), 45 (100); HRMS calcd for $C_{15}H_{20}O_3S$ (M^+) 280.1133, found 280.1135. Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19. Found: C, 64.22; H, 7.02.

(*Z*)-3-(Phenylthio)-5-(methoxymethoxy)-7-[(*p*-tolylsulfonyl)oxy]-1,3-heptadiene (84). To a solution of **83** (3.0 g, 11 mmol) and pyridine (1.8 g, 22 mmol) in $CHCl_3$ (14 mL) at 0 °C was added *p*-toluenesulfonyl chloride (TsCl, 3.1 g, 17 mmol). After being stirred overnight at room temperature, the mixture was poured into saturated NH_4Cl. The organic phase was washed with saturated Na_2CO_3, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (20% EtOAc/hexane) provided **84** (4.8 g, 96%) as a colorless oil, R_f 0.46 (20% EtOAc/hexane): IR (neat) 1598 (m), 1479 (m), 1440 (s), 1361 (s), 1189 (s), 1179 (s), 1153 (s), 1097 (s), 1032 (s), 918 (m), 740 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2 H), 7.09–7.37 (m, 7 H), 6.33 (dd, J = 17, 10 Hz, 1 H), 6.06 (d, J = 9 Hz, 1 H), 5.6 (d, J = 17 Hz, 1 H), 5.15 (d, J = 10 Hz, 1 H), 4.92 (m, 1 H), 4.54 (d, part of AB, J = 7 Hz, 1 H), 4.46 (d, part of AB, J = 7 Hz, 1 H), 4.5 (m, 2 H), 3.28 (s, 3 H), 2.45 (s, 3 H), 1.9 (m, 2 H); MS m/e (rel int) 434 (M^+, 10), 373 (54), 201 (100), 93 (32), 91 (54), 77 (23); HRMS calcd for $C_{22}H_{26}O_5S_2$ (M^+) 434.1222, found 434.1217. Anal. Calcd for $C_{22}H_{26}O_5S_2$: C, 59.69; H, 6.20. Found: C, 59.55; H, 6.09.

(*Z*)-7-Azido-5-(methoxymethoxy)-3-(phenylthio)-1,3-heptadiene (51). To a solution of **84** (3.2 g, 7.0 mmol) in DMSO (23 mL) at room temperature was added sodium azide (2.3 g, 35 mmol). The resultant slurry was then stirred for 3 h, poured into saturated $NaHCO_3$, and extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (10% EtOAc/hexane) provided **51** (1.8 g, 83%) as a colorless oil, R_f 0.34 (10% EtOAc/hexane): IR (neat) 2098 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 5 H), 6.39 (dd, J = 17, 10 Hz, 1 H), 6.14 (d, J = 9 Hz, 1 H), 5.63 (d, J = 17 Hz, 1 H), 5.18 (d, J = 10 Hz, 1 H), 4.99 (dt, J = 12, 5 Hz, 1 H), 4.66 (d, part of AB, J = 7 Hz, 1 H), 4.57 (d, part of AB, J = 7 Hz, 1 H), 3.37 (m, 5 H), 1.7–1.98 (m, 2 H); MS (CI, NH_3) m/e (rel int) 323 ($M + NH_4^+$, 6), 278 (60), 244 (100), 203 (33), 153 (25), 108 (37); HRMS calcd for $C_{15}H_{19}N_3O_2SNH_4$ ($M + NH_4^+$) 323.1542, found 323.1535. Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 59.19; H, 6.29; N, 13.80. Found: C, 59.56; H, 6.41; N, 13.65.

1-[(*tert*-Butyldimethylsilyl)oxy]oct-7-en-5-yn-4-ol (80). *n*-Butyllithium (58 mL) of a 1.9 M solution in hexane, 110 mmol) was added to diisopropylamine (11.6 g, 110 mmol) in THF (70 mL) at −23 °C. After the mixture was stirred for 15 min, 1,4-dichloro-2-butene (4.3 g, 34 mmol) was added, and the resultant mixture was allowed to stir for 15 min and then cooled to −78 °C. The aldehyde **78**[45] (4.1 g, 20 mmol) was added, and the solution was stirred for 1 h at −78 °C, warmed to room temperature, and added to saturated NH_4Cl. The organic phase was washed with brine, and the aqueous phase was back-extracted with ether. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (15% EtOAc/hexane) provided **80** (84%) as a colorless oil, R_f 0.39 (15% EtOAc/hexane): IR (neat) 3392 (br s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddd, J = 18, 11, 2 Hz, 1 H), 5.61 (dd, J = 18, 2 Hz, 1 H), 5.45 (dd, J = 11, 2 Hz, 1 H), 4.53 (m, 1 H), 3.66 (m, 2 H), 1.84 (m, 2 H), 1.53 (m, 1 H), 1.38 (m, 1 H), 0.92 (s, 9 H), 0.08 (s, 6 H); MS m/e (rel int) 255 (M^+, 4), 237 (12), 123 (11), 105 (100); HRMS calcd for $C_{14}H_{27}O_2Si$ (M^+) 255.1780, found 255.1789. Anal. Calcd for $C_{14}H_{27}O_2Si$: C, 66.07; H, 10.32. Found: C, 66.10; H, 10.16.

(*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-(phenylthio)-5,7-octadien-4-ol (85). A solution of **80** (4.02 g, 15.8 mmol) in ether (4 mL) was added to a solution of Red-Al (7.9 mL of a 3.4 M solution in toluene, 27 mmol) in ether (16 mL) at 0 °C. After the mixture was stirred for 1 h, EtOAc (8 mL) was added to quench excess Red-Al. Upon cooling to −78 °C, phenylsulfenyl chloride (2.3 g, 16 mmol) was added and the resultant mixture was allowed to stir for 15 min, warmed to room temperature, and washed with saturated NaOAc and brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (20% EtOAc/hexane) provided **85** (95%) as a colorless oil, R_f 0.21 (10% EtOAc/hexane): IR (neat) 3398 (br s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 6.39 (dd, J = 17, 10 Hz, 1 H), 6.28 (d, J = 8 Hz, 1 H), 5.59 (d, J = 17 Hz, 1 H), 5.11 (d, J = 10 Hz, 1 H), 4.86 (m, 1 H), 3.64 (m, 2 H), 3.16 (d, J = 4 Hz, 1 H), 1.61 (m, 4 H), 0.91 (s, 9 H), 0.09 (s, 6 H); MS m/e (rel int) 364 (M^+, 1), 215 (29), 123 (32), 105 (52), 91 (23), 79 (25), 77 (36), 75 (100), 73 (47), 71 (24), 45 (28), 41 (29); HRMS calcd for $C_{20}H_{32}O_2SSi$ (M^+) 364.1892, found 364.1892. Anal. Calcd for $C_{20}H_{32}O_2SSi$: C, 65.87; H, 8.85. Found: C, 65.51; H, 8.87.

(*Z*)-8-[(*tert*-Butyldimethylsilyl)oxy]-5-(methoxymethoxy)-3-(phenylthio)-1,3-octadiene (86). Chloromethyl methyl ether (1.5 g, 19 mmol) was slowly added to a solution of **85** (5.8 g, 16 mmol) and *N,N*-diisopropylethylamine (2.4 g, 19 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature, stirred overnight, and then washed with saturated NH_4Cl and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Chromatography

(52) Harpp, D. N.; Mathiaparanam, P. *J. Org. Chem.* **1972**, *37*, 1367.

(10% EtOAc/hexane) provided **86** (87%) as a colorless oil, R_f 0.42 (10% EtOAc/hexane): IR (neat) 1476 (m), 1265 (m), 1099 (s), 1038 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 5 H), 6.35 (dd, J = 17, 10 Hz, 1 H), 6.11 (d, J = 9 Hz, 1 H), 5.55 (d, J = 17 Hz, 1 H), 5.11 (d, J = 10 Hz, 1 H), 4.85 (m, 1 H), 4.63 (d, part of AB, J = 7 Hz, 1 H), 4.54 (d, part of AB, J = 7 Hz, 1 H), 3.56 (m, 2 H), 3.33 (s, 3 H), 1.56 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 142.9, 136.3, 135.9, 133.8, 128.9, 125.7, 118.2, 95.0, 74.6, 63.0, 55.5, 31.8, 28.6, 26.0, 18.3, -5.3; MS m/e (rel int) 408 (M^+, 1), 201 (31), 117 (30), 107 (26), 105 (30), 91 (20), 89 (44), 79 (27), 75 (55), 73 (47), 49 (24), 45 (100); HRMS calcd for $C_{22}H_{36}O_3SSi$ (M^+) 408.2154, found 408.2152.

(*Z*)-4-(Methoxymethoxy)-6-(phenylthio)-5,7-octadien-1-ol (87). To a solution of **86** (2.7 g, 6.8 mmol) in THF (33 mL) was added tetrabutylammonium fluoride (20 mL of a 1 M solution in THF, 20 mmol) at room temperature. The mixture was allowed to stire for 2 h, poured into water, and extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (50% EtOAc/hexane) provided **87** (91%) as a colorless oil, R_f 0.46 (50% EtOAc/hexane): IR (neat) 3420 (br s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 5 H), 6.38 (dd, J = 17, 11 Hz, 1 H), 6.17 (d, J = 9 Hz, 1 H), 5.6 (d, J = 17 Hz, 1 H), 5.15 (d, J = 11 Hz, 1 H), 4.92 (m, 1 H), 4.66 (d, part of AB, J = 7 Hz, 1 H), 4.57 (d, part of AB, J = 7 Hz, 1 H), 3.63 (m, 2 H), 3.38 (s, 3 H), 2.4 (t, J = 8 Hz, 1 H), 1.65 (m, 4 H). Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.26; H, 7.55. Found: C, 65.29; H, 7.54.

(*Z*)-5-(Methoxymethoxy)-3-(phenylthio)-8-[(*p*-tolylsulfonyl)oxy]-1,3-octadiene (88). TsCl (2.8 g, 15 mmol) was added to a solution of **87** (2.9 g, 9.8 mmol) and pyridine (1.6 g, 20 mmol) in chloroform (13 mL) at 0 °C. The resultant mixture was warmed to room temperature for 5 h and then washed with saturated NH4Cl, saturated $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (25% EtOAc/hexane) afforded **88** (98%) as a colorless oil, R_f 0.49 (20% EtOAc/hexane): IR (neat) 1361 (s), 1189 (s), 1177 (s), 1097 (s), 1034 (s), 935 (m), 919 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2 H), 7.23 (m, 5 H), 6.34 (dd, J = 17, 10 Hz, 1 H), 6.05 (d, J = 9 Hz, 1 H), 5.56 (d, J = 17 Hz, 1 H), 5.15 (d, J = 10 Hz, 1 H), 4.78 (m, 1 H), 4.6 (d, part of AB, J = 7 Hz, 1 H), 4.5 (d, part of AB, J = 7 Hz, 1 H), 4.02 (t, J = 7 Hz, 2 H), 3.31 (s, 3 H), 2.45 (s, 3 H), 1.4-1.8 (m, 4 H); MS (CI, NH_3) m/e (rel int) 466 ($M + NH_4^+$, 11), 362 (56), 358 (48), 296 (48), 234 (43), 233 (70), 215 (44), 154 (30), 124 (100), 107 (32), 94 (22), 75 (31); HRMS calcd for $C_{23}H_{28}O_5S_2NH_4$ ($M + NH_4^+$) 466.1722, found 466.1694.

(*Z*)-8-Azido-5-(methoxymethoxy)-3-(phenylthio)-1,3-octadiene (53). Sodium azide (2.6 g, 39 mmol) was added to **88** (3.6 g, 7.9 mmol) in DMSO (30 mL) at room temperature. After 6 h, the slurry was poured saturated $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was then washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (10% EtOAc/hexane) provided **53** (84%) as a colorless oil, R_f 0.33 (10% EtOAc/hexane): IR (neat) 2097 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.1-7.4 (m, 5 H), 6.49 (dd, J = 17, 10 Hz, 1 H), 6.33 (d, J = 9 Hz, 1 H), 5.45 (d, J = 17 Hz, 1 H), 5.13 (d, J = 10 Hz, 1 H), 4.75 (m, 1 H), 4.54 (d, part of AB, J = 5 Hz, 1 H), 4.51 (d, part of AB, J = 5 Hz, 1 H), 3.32 (s, 3 H), 3.26 (t, J = 6 Hz, 1 H), 1.55 (m, 4 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 142.2, 136.2, 135.7, 134.3, 128.9, 128.0, 125.8, 118.6, 95.0, 74.1, 55.6, 51.3, 32.5, 24.9; MS m/e (rel int) 291 (M^+, 9), 259 (14), 258 (81), 230 (100), 120 (12); HRMS calcd for $C_{16}H_{21}NO_2S$ ($M^+ - N_2$) 291.1293, found 291.1311. Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16. Found: C, 60.25; H, 6.52; N, 12.81.

Ethyl (*E*)- and (*Z*)-2-Bromo-6-[(*tert*-butyldimethylsilyl)oxy]-2-hexenoate (89). A solution of aldehyde **78**[47] (2.0 g, 11.7 mmol) in benzene (10 mL) was added to a stirred solution of (carbethoxybromomethylene)triphenylphosphorane[53] (5 g, 11.7 mmol) in benzene (40 mL) at room temperature. The reaction mixture was heated at 80 °C for 8.5 h, cooled, and evaporated. The residue was dissolved in hexane (25 mL), cooled to -78 °C, and then quickly filtered. After evaporation of the filtrate, ^1H NMR indicated an 87:13 mixture of (*Z*)-**89** and (*E*)-**89** by integration the signal at δ 7.33 for the *Z* isomer and at δ 6.71 for the *E* isomer. The crude material was chromatographed with 5% EtOAc/hexane to give 2.33 g (57%) of pure (*Z*)-**89** as a colorless liquid and 1.2 g (29%) of material enriched in (*E*)-**89**. The combined yield was 86%. (*Z*)-**89** had the following properties: R_f 0.27 (5% EtOAc/hexane); IR (neat) 2955 (s), 2930 (s), 1731 (vs), 1255 (vs), 836 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33 (t, J = 7 Hz, 1 H), 4.26 (q, J = 7 Hz, 2 H), 3.65 (t, J = 7 Hz, 2 H), 2.41 (q, J = 7 Hz, 2 H), 1.71 (qn, J = 7 Hz, 2 H), 1.32 (t, J = 7 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 162.39, 145.88, 116.41, 62.36, 62.25, 30.62, 28.98, 25.98, 14.15, -5.37 ppm; MS m/e (rel int) 353 (M^+, 88), 351 (M^+, 84), 337 (12), 295 (100), 307 (17), 265 (15), 249 (16), 247 (17); HRMS calcd for $C_{14}H_{27}BrO_3Si^{79}H^+$ 351.0991, found 351.0991. Anal. Calcd for $C_{14}H_{27}BrO_3Si$: C, 47.86; H, 7.75. Found: C, 47.96; H, 7.81.

(*E*)-**89** had the following properties: R_f 0.24, (5% EtOAc/hexane); IR (neat) 1731 (s), 1718 (shoulder), 1255 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.71 (t, J = 7.8 Hz, 1 H), 4.28 (q, J = Hz, 2 H), 3.63 (t, J = 6 Hz, 2 H), 2.56 (q, J = 7 Hz, 2 H), 1.67 (br, qn, J = 7 Hz, 2 H), 1.34 (t, J = 7 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.81, 148.13, 111.21, 62.35, 61.93, 31.82, 28.28, 25.88, 18.24, 14.15, -5.38 ppm.

(*Z*)-3-Bromo-6-[(*tert*-butyldimethylsilyl)oxy]hepta-1,3-diene (90). Diisobutylaluminum hydride (17.2 mL of a 1.5 M solution in toluene, 25.8 mmol) was added slowly to a solution of bromo ester **89** (8.28 g, 23.6 mmol) in hexane (1.2 L) at -78 °C. After 2 h at -78 °C and 1 h at room temperature, NH_4Cl (4.2 g, 75 mmol), water (0.93 mL, 52 mmol), and methanol (0.93 mL) were added. After 1 h, Celite and $MgSO_4$ were added, and the mixture was filtered and concentrated. The crude aldehyde was immediately dissolved in THF (50 mL) was added via cannula to a previously prepared solution of methylenetriphenylphosphorane at -78 °C. [The phosphorane had been generated by slow addition of *n*-butyllithium (24.0 mL of a 1.0 M solution in hexanes, 24 mmol) to a suspension of methyltriphenylphosphonium bromide (8.4 g, 23.6 mmol) in THF (250 mL) at 0 °C.] After being stirred for 1 h at -78 °C and 30 min at room temperature, the reaction mixture was filtered through a plug of silica gel and the filtrate was concentrated. Flash chromatography of the residue (1.5% EtOAc/hexane) gave 3.42 g (47% from **89**) or bromo diene **90** as a clear oil, R_f 0.5 (5% EtOAc/hexane): IR (neat) 2955 (s), 2858 (s), 1256 (w), 1106 (s), 836 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, J = 10.4, 16.1 Hz, 1 H), 6.01 (t, J = 7.1 Hz, 1 H), 5.53 (d, J = 16.3 Hz, 1 H), 5.16 (d, J = 10.4 Hz, 1 H), 3.64 (t, J = 6.3 Hz, 2 H), 2.58 (q, J = 7.5 Hz, 2 H), 1.69 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H); MS m/e (rel int) 307 (27), 305 (28, M^+), 246 (55), 247 (56), 225 (29), 221 (56), 219 (54), 175 (26), 173 (26), 92 (100); HRMS calcd for $C_{13}H_{25}BrOSi$ 305.0936, found 305.0934. Anal. Calcd for $C_{13}H_{25}BrOSi$: C, 51.14; H, 8.25. Found: C, 51.22; H, 8.16.

(*Z*)-5-Bromo-4,6-heptadien-1-ol (91). A solution of tetra-*n*-butylammonium fluoride (0.65 mL of a 1 M solution in THF, 0.65 mmol) was added to a solution of the bromo diene **90** (180 mg, 0.65 mmol) in THF (2 mL) at room temperature. After 30 min, the reaction mixture was diluted with ether/petroleum ether (1:1, 50 mL) and washed with brine (2 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (30% EtOAc/hexane) gave 86.2 mg (77%) of **91**, R_f 0.21 (30% EtOAc/hexane): IR (neat) 3336 (br, s), 1632 (s), 1054 (s), 907 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, J = 16.0, 10.5 Hz, 1 H), 6.00 (t, J = 7.5 Hz, 1 H), 5.53 (d, J = 16.0 Hz, 1 H), 5.18 (d, J = 10.5 Hz, 1 H), 3.67 (t, J = 6.5 Hz, 2 H), 2.42 (q, J = 7.5 Hz, 2 H), 1.68-1.76 (m, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.83, 133.84, 126.52, 117.43, 62.28, 31.42, 28.07 ppm.

(*Z*)-7-Azido-3-bromohepta-1,3-diene (39). A solution of TsCl (200 mg, 1.04 mmol) and 4-(dimethylamino)pyridine (2 mg, 0.05 mmol) in pyridine (2 mL) was added to a solution of the alcohol **91** at 0 °C. After 2 h, saturated NH_4Cl (10 mL) was added, and the mixture was extracted with ether/petroleum ether (1:1, 2 × 25 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated to provide the crude tosylate **92**. This was dissolved in DMSO (5 mL), and sodium azide (113 mg, 1.74 mmol) and a catalytic amount of sodium iodide (3 mg) were added. After 12 h at room temperature, the mixture was diluted with ether/petroleum ether (1:1, 25 mL) and washed with brine (20 mL). The organic phase was dried

(53) Denney, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998.

($MgSO_4$) and concentrated. Chromatography (3% EtOAc/hexane) gave 32 mg (43% from **91**) of **39** as a colorless liquid, R_f 0.44 (10% EtOAc/hexane): IR (neat) 2096 (vs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, J = 16.0, 10.5 Hz, 1 H), 5.98 (t, J = 7.0 Hz, 1 H), 5.58 (d, J = 16.0 Hz, 1 H), 5.20 (d, J = 10.5 Hz, 1 H), 3.32 (t, J = 7.0 Hz, 2 H), 2.41 (q, J = 7.0 Hz, 2 H), 1.75 (qn, J = 7.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.53, 132.72, 127.03, 117.88, 50.84, 28.72, 27.60 ppm.

(*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-3-(methylthio)hepta-1,3-diene (93). Bromo diene **90** (0.61 g, 2.0 mmol) in THF (20 mL) was cooled to −78 °C, and *tert*-butyllithium (2.05 mL of a 2.0 M solution in pentane, 4.1 mmol) was slowly added. After 2 h, dimethyl disulfide (0.27 mL, 3.0 mmol) was quickly added, and the reaction mixture was allowed to warm to room temperature, poured into saturated NH_4Cl, and extracted with ether/petroleum ether (1:1, three times). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (2% EtOAc/hexane) gave 0.49 g (90%) of diene **93** as a clear oil, R_f 0.44 (5% EtOAc/hexane): IR (neat) 1255 (w), 1105 (s), 836 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, J = 10.4, 16.9 Hz, 1 H), 5.99 (t, J = 7.3 Hz, 1 H), 5.60 (d, J = 16.9 Hz, 1 H), 5.12 (d, J = 10.3 Hz, 1 H), 3.64 (t, J = 6.5 Hz, 2 H), 2.48 (q, J = 7.6 Hz, 2 H), 2.14 (s, 3 H), 1.63 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H); MS m/e (rel int) 271 (M^+, 1), 257 (2), 216 (13), 215 (83), 201 (3), 171 (20), 167 (32), 141 (12), 139 (18), 125 (62); HRMS calcd for $C_{14}H_{29}OSiSH^+$ 273.1708, found 273.1707.

(*Z*)-3-(Methylthio)-4,6-heptadien-1-ol (94). To a solution of silyl ether **93** (0.31 g, 1.12 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (3.3 mL of a 1 M solution in THF, 3.3 mmol) at room temperature. After 18 h, the mixture was poured into saturated NH_4Cl and extracted three times with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (20% EtOAc/hexane) gave 0.15 g (82%) of alcohol **94** as a clear oil, R_f 0.4 (30% EtOAc/hexane): IR (neat) 3344 (br), 1057 (s), 911 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, J = 10.4, 16.9 Hz, 1 H), 5.98 (t, J = 7.5 Hz, 1 H), 5.61 (d, J = 16.9 Hz, 1 H), 5.16 (d, J = 10.3 Hz, 1 H), 3.65 (t, J = 6.3 Hz, 2 H), 2.53 (q, J = 7.4 Hz, 2 H), 2.16 (s, 3 H), 1.70 (m, 2 H); MS m/e (rel int) 158 (45, M^+), 143 (11), 139 (11), 127 (100), 125 (40), 113 (51), 102 (23), 97 (28); HRMS calcd for $C_8H_{14}OS$ 158.0765, found 158.0758.

(*Z*)-7-[(*p*-Tolylsulfonyl)oxy]-3-(methylthio)hepta-1,3-diene (95). *p*-TsCl (0.29 g, 1.5 mmol) was added to an ice-cold solution of alcohol **94** (0.16 g, 1.0 mmol), pyridine (0.16 mL, 2.0 mmol), and (dimethylamino)pyridine (12 mg, 0.1 mmol) in chloroform (1 mL). The reaction was warmed to room temperature, stirred for 6 h, and then diluted with ether/petroleum ether (1:1, 5 mL). The solution was washed successively with 10% HCl, 5% aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (7% EtOAc/hexane) gave 0.29 g (91%) of tosylate **95** as a clear oil, R_f 0.35 (10% EtOAc/hexane): IR (neat) 1358 (s), 1176 (w), 920 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 6.23 (dd, J = 10.4, 16.9 Hz, 1 H), 5.82 (t, J = 7.4 Hz, 1 H), 5.59 (d, J = 16.9 Hz, 1 H), 5.15 (d, J = 10.3 Hz, 1 H), 4.04 (t, J = 6.5 Hz, 2 H), 2.46 (q, J = 7.3 Hz, 2 H), 2.44 (s, 3 H), 2.10 (s, 3 H), 1.76 (m, 2 H); MS m/e (rel int) 312 (3, M^+), 200 (9), 172 (5), 155 (18), 149 (14), 125 (62), 91 (100); HRMS calcd for $C_{15}H_{20}O_3S_2$ 312.0854, found 312.0851.

(*Z*)-7-Azido-3-(methylthio)hepta-1,3-diene (22). Sodium azide (0.17 g, 9.0 mmol) was added to a solution of tosylate **95** (0.27 g, 0.87 mmol) and a few crystals of NaI in DMSO (2 mL). The reaction was stirred for 4 h and then diluted with ether/petroleum ether (1:1, 10 mL). This solution was washed twice with water and twice with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (2% EtOAc/hexane) gave 0.13 g (78%) of azide **22** as a clear oil, R_f 0.5 (5% EtOAc/hexane): IR (neat) 2097 (s), 1281 (s), 1256 (s), 912 (s), cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, J = 10.4, 16.9 Hz, 1 H), 5.93 (t, J = 7.4 Hz, 1 H), 5.62 (d, J = 16.9 Hz, 1 H), 5.17 (d, J = 10.4 Hz, 1 H), 3.30 (t, J = 6.9 Hz, 2 H), 2.53 (q, J = 7.4 Hz, 2 H), 2.15 (s, 3 H), 1.72 (m, 2 H); MS m/e (rel int) 154 (6), 140 (13), 122 (7), 111 (13), 108 (9), 97 (11), 94 (8), 80 (40), 71 (100); HRMS calcd for $C_8H_{12}N_3S$ 182.0739, found 182.0752.

(*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-3-(phenylseleno)-1,3-heptadiene (96). *tert*-Butyllithium (13 mL of a 2.0 M solution in pentane, 26 mmol) was slowly added to a solution of bromo diene **90** (3.85 g, 12.6 mmol) in THF (125 mL) at −78 °C. After 2 h, phenylselenenyl chloride (2.5 g, 13 mmol) in THF (15 mL) was quickly added, and the reaction mixture was allowed to warm to room temperature, poured into saturated NH_4Cl, and extracted three times with ether/petroleum ether (1:1). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (2% EtOAc/hexane) to give 3.8 g (80%) of the title compound as a clear oil, R_f 0.60 (5% EtOAc/hexane): IR (neat) 1477 (s), 1104 (w), 1071 (s), 836 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 5 H), 6.34 (dd, J = 10.3, 16.6 Hz, 1 H), 6.23 (t, J = 7.3 Hz, 1 H), 5.53 (d, J = 16.6 Hz, 1 H), 5.02 (d, J = 10.9 Hz, 1 H), 3.56 (t, J = 6.5 Hz, 2 H), 2.47 (q, J = 7.6 Hz, 2 H), 1.59 (m, 2 H), 0.84 (s, 9 H), 0.01 (s, 6 H); MS m/e (rel int) 382 (M^+, 8), 367 (2), 325 (48), 323 (24), 225 (57), 215 (39), 213 (19), 173 (11), 169 (48), 73 (100); HRMS calcd for $C_{19}H_{30}OSiSe$ 382.1231, found 382.1231. Anal. Calcd for $C_{19}H_{30}OSiSe$: C, 59.28; H, 7.93. Found: C, 59.13; H, 7.98. *Note*: Upon standing, the *Z* isomer of **96** isomerized to a mixture of geometric isomers, as reflected in the following compounds.

(*E*)- and (*Z*)-3-(Phenylseleno)-4,6-heptadien-1-ol (97). Tetrabutylammonium fluoride (36 mL of a 1 M solution in THF, 36 mmol) was added to a solution of the silyl ether **96** (3.8 g, 10 mmol) in THF (40 mL) at room temperature. After 18 h, the reaction mixture was poured into NH_4Cl and extracted three times with EtOAc. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (20% EtOAc/hexane) to give 2.24 g (82%) of alcohol **97** as a clear oil, R_f 0.30 (25% EtOAc/hexane). The alcohol was obtained as an inseparable 75:25 mixture of *Z* and *E* isomers: IR (neat) 3330 (br), 1477 (s), 1023 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 6.68 (dd, J = 10.5, 16.6 Hz, 0.25 H)*, 6.39 (dd, J = 10.3, 16.6 Hz, 0.75 H), 6.25 (t, J = 7.4 Hz, 1 H), 5.65 (d, J = 16.6 Hz, 0.25 H)*, 5.59 (d, J = 16.6 Hz, 0.75 H), 5.24 (d, J = 10.6 Hz, 0.25 H)*, 5.24 (d, J = 10.3 Hz, 0.75 H), 3.61 (t, J = 6.4 Hz, 2 H), 2.54 (q, J = 7.4 Hz, 1.5 H), 2.42 (q, J = 7.4 Hz, 0.5 H)*, 1.67 (m, 2 H), 1.59 (br s, 1 H), (* indicates the signals arising from the minor *E* isomer); MS m/e (rel int) 268 (M^+, 13), 158 (19), 157 (12), 156 (10), 155 (9), 143 (8), 142 (6), 141 (9), 77 (100); HRMS calcd for $C_{13}H_{16}OSe$ 268.0366, found 268.0366. Anal. Calcd for $C_{13}H_{16}OSe$: C, 58.43; H, 6.04. Found: C, 58.50; H, 5.84.

(*E*)- and (*Z*)-3-(Phenylseleno)-7-[(*p*-tolylsulfonyl)oxy]-hepta-1,3-diene (98). TsCl (2.42 g, 12.7 mmol) was added portionwise to an ice-cold solution of the alcohol **97** (2.24 g, 8.4 mmol), pyridine (1.4 mL, 16.8 mmol), and (dimethylamino)-pyridine (98 mg, 0.8 mmol) in $CHCl_3$ (8 mL). The reaction was warmed to room temperature and stirred for 8 h, then diluted with petroleum ether/ether (1:1, 25 mL). The solution was washed with 10% HCl, 5% $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated. Chromatography (10% EtOAc/hexane) gave 3.5 g (99%) of the tosylate **98** as a clear oil, R_f 0.30 (10% EtOAc/hexane). The tosylate was obtained as an inseparable 75:25 mixture of *Z* and *E* isomers: IR (neat) 1359 (s), 1189 (s), 1177 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (m, 2 H), 7.23 (m, 7 H), 6.55 (dd, J = 10.5, 16.6 Hz, 0.25 H)*, 6.35 (dd, J = 10.6, 16.8 Hz, 0.75 H), 6.11 (t, J = 7.3 Hz, 0.75 H), 6.03 (t, J = 7.6 Hz, 0.25 H), 5.63 (d, J = 15 Hz, 0.25 H)*, 5.58 (d, J = 16.0 Hz, 0.75 H), 5.23 (d, J = 10.5 Hz, 0.25 H)*, 5.08 (d, J = 10.9 Hz, 0.75 H), 4.00 (t, J = 6.4 Hz, 2 H), 2.47 (q, J = 7.6 Hz, 1.5 H), 2.43 (s, 3 H), 2.35 (q, J = 7.4 Hz, 0.5 H)*, 7.16 (m, 2 H), (* indicates the signals arising from the minor *E* isomer); MS m/e (rel int) 422 (M^+, 5), 314 (3), 250 (6), 200 (2), 173 (11), 169 (11), 155 (18), 91 (100); HRMS calcd for $C_{20}H_{22}O_3SeS$ 422.0455, found 422.0460.

(*E*)- and (*Z*)-7-Azido-3-(phenylseleno)hepta-1,3-diene (42). Sodium azide (1.63 g, 25 mmol) was added to a solution of tosylate **98** (3.5 g, 8.3 mmol) and a few crystals of NaI in DMSO (8 mL). The reaction was stirred for 18 h and then diluted with petroleum ether/ether (1:1, 30 mL). This solution was washed twice with water and twice with brine, dried ($MgSO_4$), and concentrated. The residue was filtered through a plug of silica gel (eluting with 5% EtOAc/hexane). Concentration of the eluent gave 1.89 g (78%) of azide **42** as a clear oil, R_f 0.5 (5% EtOAc/hexane). The azide was obtained as an inseparable 70:30 mixture of *Z* and *E* isomers: IR (neat) 2096 (s), 1577 (s), 1476 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5 H), 6.65 (dd, J = 10.6, 16.3 Hz, 0.3 H)*, 6.38 (dd, J = 10.1, 16.6 Hz, 0.7 H), 6.21 (t, J = 7.3 Hz, 0.7 H), 6.15

(t, J = 7.6 Hz, 0.3 H)*, 5.66 (d, J = 15.8 Hz, 0.3 H)*, 5.61 (d, J = 17.2 Hz, 0.7 H), 5.27 (d, J = 10.6 Hz, 0.3 H)*, 5.11 (d, J = 10.3 Hz, 0.7 H), 3.24 (t, J = 6.9 Hz, 2 H), 2.54 (q, J = 7.5 Hz, 1.4 H), 2.40 (q, J = 7.4 Hz, 0.6 H)*, 1.68 (m, 2 H), (*indicates the signals arising from the minor E isomer); MS (CI, NH_3) m/e (rel int) 264 (6), 185 (16), 184 (58), 170 (9), 157 (28), 146 (99), 80 (100); HRMS calcd for $C_{13}H_{15}N_3Se{\cdot}NH_3$ 311.0775, found 311.0782.

(*E*)-7-[(*tert*-Butyldimethylsilyl)oxy]-3-(1-ethoxyethoxy)-1,3-heptadiene (100). A solution of *sec*-butyllithium (34.1 mL of a 1.18 M solution in cyclohexane, 40 mmol) was added dropwise to a stirred solution of 3-(1-ethoxyethoxy)-3-(trimethylsilyl)propene[41] (7.4 g 36.6 mmol) in THF (25 mL) at −78 °C. After 30 min, titanium(IV) isopropoxide (10.9 mL, 36.6 mmol) was added. After 45 min, a solution of aldehyde **78**[47] (7.4 g, 36.6 mmol) in THF (5 mL) was added, and the reaction mixture was stirred at −78 °C for an additional hour, at 0 °C for 3 h, and finally at room temperature for 14 h. Brine (200 mL) was added, and the mixture was extracted with ether/petroleum ether (1:1, 2 × 200 mL). The combined organic extracts were filtered through a small plug of silica gel and then concentrated to give 13.55 g of the title compound (118%). The crude material was taken on to the next step without further purification. A 300-mg sample of **100** was purified on silica gel (5% EtOAc/hexane) and exhibited the following properties: R_f 0.26 (5% EtOAc/hexane); IR (neat) 1592 (m), 1473 (m), 1463 (m), 1382 (m), 1254 (s), 1099 (s), 1084 (s), 1052 (s), 837 (s), 775 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (ddd, J = 17, 11, 0.5 Hz, 1 H), 6.59 (t, J = 7.5 Hz, 1 H), 5.08–5.14 (m, 2 H), 3.44–3.54 (m, 1 H), 3.68–3.78 (m, 1 H), 3.61 (t, J = 6.5 Hz, 2 H), 2.18 (q, J = 7.5 Hz, 2 H), 1.59 (qn, J = 7.5 Hz, 2 H), 1.41 (d, J = 5 Hz, 3 H), 1.19 (t, J = 7 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3 128.4, 114.12, 110.01, 99.3, 62.2, 62.5, 33.5, 26.0, 22.6, 20.5, 18.3, 15.3, −5.3 ppm; HRMS calcd for $C_{17}H_{34}O_3Si$ 314.2277, found 314.2271.

(*E*)-5-(1-Ethoxyethoxy)-4,6-heptadien-1-ol. A solution of tetrabutylammonium fluoride (1 M solution in THF, 40 mL, 40 mmol) was added to a stirred solution of **100** (13.25 g of crude material from above) in THF (80 mL) at 0 °C. After warming to room temperature and stirring for 1 h, the reaction mixture was diluted with petroleum ether/ether (1:1, 400 mL), washed with brine (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (35% EtOAc/hexane) gave 5.32 g (66% from **78**) of the title compound as a clear colorless liquid, R_f 0.24 (35% EtOAc/hexane): IR (neat) 3480 (br), 1446 (w), 1381 (w) 1240 (w), 1137 (s), 1081 (s), 1050 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (dd, J = 17.0, 11.0 Hz, 1 H), 5.60 (dd, J = 17.0, 2.0 Hz, 1 H), 5.12 (m, 2 H), 4.95 (t, J = 8.0 Hz, 1 H, 3.70–3.78 (m, 1 H), 3.64 (q, J = 6.0 Hz, 2 H), 3.45–3.55 (m, 1 H), 2.22 (q, J = 7.0 Hz, 2 H), 2.18 (br s, 1 H), 1.65 (qn, J = 7.0 Hz, 2 H), 1.42 (d, J = 5.0 Hz, 3 H), 1.19 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 128.0, 114.4, 109.7, 99.1, 61.9, 61.3, 33.1, 22.5, 20.3, 15.1 ppm; MS m/e (rel int) 200 (M^+), 154 (1), 110 (3), 95 (3), 83 (9), 73 (70), 55 (20), 45 (100); HRMS (CI, NH_3) calcd for $C_{11}H_{20}H_3NH_4$ (MNH_4^+) 218.1756, found 218.1760. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.88; H, 10.07.

(*E*)-7-Azido-3-(1-ethoxyethoxy)hepta-1,3-diene (32). A solution of TsCl (5.48 g, 28.7 mmol) in pyridine (25 mL) was added dropwise to a stirred solution of (*E*)-5-(1-ethoxyethoxy)-4,6-heptadien-1-ol (2.74 g, 13.68 mmol) and 4-(dimethylamino)-pyridine (0.084 g, 5 mol %) in pyridine (125 mL) at 0 °C for 14 h; the reaction mixture was diluted with petroleum ether/ether (1:1, 300 mL), washed sequentially with water (2 × 50 mL) and saturated NH_4Cl (3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. The pyridine residue was removed by evaporation with benzene several times on a rotary evaporator. Chromatography (20% EtOAc/hexane) gave 3.72 g (76.7%) of the tosylate as a clear colorless oil, which was used immediately as follows. Sodium azide (3.41 g, 52.5 mmol) and NaI (0.08 g 0.53 mmol) were added to a solution of the purified tosylate in DMSO (50 mL) at room temperature. After 12 h, the reaction mixture was diluted with petroleum ether (300 mL), washed with water (2 × 100 mL) and brine (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (7% EtOAc/hexane) gave 2.17 g (92%) of **32** as a clear colorless oil, R_f 0.25 (10% EtOAc/hexane): IR (neat) 2097 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, J = 17.0, 11.0 Hz, 1 H), 5.62 (dd, J = 17.0, 2.0 Hz, 1 H), 5.1–5.2 (m, 2 H), 4.9 (t, J = 7.5 Hz, 1 H), 3.45–3.77 (m, 2 H), 3.30 (t, J = 6.8 Hz, 2 H), 2.20 (q, J = 7.5 Hz, 2 H), 1.70 (qn, J = 7.0 Hz, 2 H), 1.40 (d, J = 5.3 Hz, 3 H), 1.2 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 127.9, 115.0, 108.2, 99.1, 61.3, 50.7, 29.5, 23.4, 20.3, 15.3, ppm; MS m/e (rel int) 197 (M^+ − 28, 0.4), 167 (3), 125 (18), 96 (48), 73 (43), 45 (100). Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64, H, 8.5, N, 18.65. Found: C, 58.08; H, 8.69; N, 18.72.

(*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3-(1-ethoxyethoxy)-1,3-octadiene (101). A solution of *sec*-butyllithium (25.4 mL of a 1.3 M solution in cyclohexane, 33 mmol) was added dropwise to a stirred solution of 3-(1-ethoxyethoxy)-3-(trimethylsilyl)propene[41] (6.08 g, 30 mmol) in THF (15 mL) at −78 °C. After 30 min, titanium(IV) isopropoxide (8.93 mL, 30 mmol) was added dropwise, and the reaction mixture was stirred for 45 min. A solution of aldehyde **99** in THF (5 mL) was added, and the resulting mixture was allowed to stir at −78 °C for 1 h, at 0 °C for 3 h, and for 14 h at room temperature. Brine (200 mL) was added, and the mixture was extracted with ether/petroleum ether (1:1, 3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a small plug of silica gel, and concentrated. The crude material was chromatographed (3% EtOAc/hexane) to give 8.52 g (87%) of **101** as a pale yellow oil, R_f 0.25 (5% EtOAc/hexane): IR (neat) 1101 (s), 836 (s), 77 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, J = 17.0, 11.0 Hz, 1 H), 5.59 (dd, J = 17.0, 2.0 Hz, 1 H), 5.08–5.14 (m, 2 H), 4.95 (br t, J = 8.0 Hz, 1 H), 3.68–3.78 (m, 1 H), 3.60 (t, J = 6.0 Hz, 2 H), 3.44–3.54 (m, 1 H), 2.13 (q, J = 7.5 Hz, 2 H), 1.33–1.58 (m, 7 H), 1.19 (t, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.06, 128.33, 114.13, 110.61, 99.26, 63.00, 61.50, 32.33, 26.75, 26.06, 25.98, 20.49, 18.36, 15.27, −5.27 ppm; GCMS m/e (rel int) 239 (M − OEE, 0.1), 197 (9), 131 (14), 95 (24), 85 (32), 75 (100), 55 (55). Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.8; H, 11.05; Si, 8.52. Found: C, 65.64; H, 11.19; Si, 8.61.

(*E*)-6-(1-Ethoxyethoxy)-5,7-octadien-1-ol. Tetrabutylammonium fluoride (26 mL of a 1 M solution in THF, 26 mmol) was added to **101** (8.0 g, 24.4 mmol) in THF (25 mL) at 0 °C. After warming to room temperature for 1 h, the mixture was diluted with petroleum ether/ether (1:1, 400 mL), washed with brine (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (35% EtOAc/hexane) afforded 4.05 g (78%) of the title compound as a clear colorless oil, R_f 0.2 (35% EtOAc/hexane): IR (neat) 3394 (br), 1592 (w), 1381 (w), 1081 (s), 1051 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (dd, J = 17.0, 11.0 Hz, 1 H), 5.58 (dd, J = 17.0, 2.0 Hz, 1 H), 5.11 (m, 2 H), 4.95 (t, J = 8.0 Hz, 1 H), 3.66–3.76 (m, 1 H), 3.62 (q, J = 6.0 Hz), 2 H), 3.43–3.53 (m, 1 H), 2.15 (q, J = 8.0 Hz, 2 H), 1.42–1.61 (m, 4 H), 1.40 (d, J = 5.0 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 128.2, 114.3, 110.3, 99.2, 62.7, 61.4, 32.2, 26.6, 26.0, 20.4, 15.2 ppm; MS (CI-NH_3) 233 (MNH_4^+ + 1, 13), 232 (MNH_4^+, 100), 215 (9), 186 (81), 160 (92), 125 (23); HRMS calcd for $C_{12}H_{22}O_3NH_4$ (MNH_4^+) 232.1912, found 232.1914.

(*E*)-3-(1-Ethoxyethoxy)-8-[(*p*-tolylsulfonyl)oxy]-1,3-octadiene. A solution of TsCl (200 mg, 1.05 mmol) in pyridine (2 mL) was added dropwise to a stirred solution of (*E*)-6-(1-ethoxyethoxy)-5,7-octadien-1-ol (75.7 mg, 0.35 mmol) and a catalytic amount (5 mol %) of 4-(dimethylamino)pyridine in pyridine (2 mL) at 0 °C. After 1.25 h, the mixture was diluted with petroleum ether/ether (1:1, 200 mL), washed with water (2 × 50 mL) and saturated NH_4Cl (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (20% EtOAc/hexane) gave 117 mg (90%) of the title compound as a clear colorless oil, R_f 0.2 (20% EtOAc/hexane): IR (neat) 1380 (w), 1360 (s), 1177 (s), 1189 (s), 815 (m), 687 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 6.40 (ddd, J = 17.0, 11.0, 0.5 Hz, 1 H), 5.58 (dd, J = 17.0, 2.0 Hz, 1 H), 5.10 (m, 2 H), 4.85 (t, J = 8.0 Hz, 1 H), 4.02 (t, J = 6.0 Hz, 2 H), 3.43–3.36 (m, 2 H), 2.45 (s, 3 H), 2.08 (q, J = 8.0 Hz, 2 H), 1.62–1.71 (m, 2 H), 1.23–1.47 (m, 5 H), 1.18 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 144.6, 129.8, 128.1, 127.8, 114.7, 109.3, 99.1, 70.3, 61.4, 28.3, 26.2, 25.6, 21.6, 20.4, 15.3.

(*E*)-8-Azido-3-(1-ethoxyethoxy)-1,3-octadiene (33). Sodium azide (93 mg, 1.4 mmol) and a cataytic amount of NaI (10 mg, 0.07 mmol) were added to a stirred solution of (*E*)-3-(1-ethoxyethoxy)-8-[(*p*-tolylsulfonyl)oxy]-1,3-octadiene (105 mg, 0.286 mmol) in DMSO (2 mL) at room temperature. After 4 h, the reaction mixture was diluted with petroleum ether (100 mL), water

(2 × 50 mL), and brine (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (7% EtOAc/hexane) gave 41 mg (60%) of **33** as a colorless oil, R_f 0.25 (10% EtOAc/hexane): IR (neat) 2097 (s), 1139 (m), 1081 (s), 1050 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.48 (dd, J = 17.0, 11.0 Hz, 1 H), 5.62 (dd, J = 17.0, 2.0 Hz, 1 H), 5.11–5.16 (m, 2 H), 4.92 (t, J = 7.0 Hz, 1 H), 3.69–3.75 (m, 1 H), 3.46–3.54 (m, 1 H), 3.28 (t, J = 7.0 Hz, 2 H), 2.17 (q, J = 7.5 Hz, 2 H), 1.46–1.67 (m, 7 H), 1.20 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.38, 128.13, 114.62, 109.94, 99.16, 61.33, 51.30, 28.28, 27.49, 25.74, 20.35, 15.22 ppm; MS m/e (rel int) 240 (M^+, 3), 194 (3), 156 (7), 138 (4), 84 (15), 73 (100), 55 (8), 45 (47); HRMS calcd for $C_{12}H_{21}N_3OH^+$ 240.1712, found 240.1703.

(*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4,6-heptadien-1-ol (104). A solution of *sec*-butyllithium (1.4 M in cyclohexane, 7.7 mL, 10.79 mmol) was added dropwise to a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-1,4-pentadiene[42] (1.78 g, 8.99 mmol) in THF (10 mL) at −78 °C to form the pentadienyl anion **102**. After 30 min, oxirane (3.2 mL of a 3.4 M soluton in THF, 10.8 mmol) was added via a syringe. After 45 min, the mixture was diluted with petroleum ether/ether (1:1, 200 mL), washed with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. Crude ^1H NMR indicated a mixture of α- and γ-alkylated products (α:γ = 20:80). The crude material was chromatographed (20% EtOAc/hexane) to give 1.43 g (66%) of pure γ-adduct **104** as a colorless oil, R_f 0.25 (20% EtOAc/hexane): IR (neat) 3338 (br), 1645 (w), 1606 (m), 1473 (m), 1463 (m), 1364 (s), 1290 (m), 1050 (s), 840 (s), 827 (s), 807 (s), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.15 (dd, J = 17, 11 Hz, 1 H), 5.29 (ddd, J = 17, 1.5, 0.5 Hz, 1 H), 4.97 (ddd, J = 10, 1.5, 0.5 Hz, 1 H), 4.80 (t, J = 7.5 Hz, 1 H), 3.63 (q, J = 6 Hz, 2 H), 2.20 (q, J = 7 Hz, 2 H), 1.63 (qn, J = 7 Hz, 2 H), 1.00 (s, 9 H), 0.12 (s, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 135.5, 114.7, 112.5, 62.4, 32.3, 26.0, 22.2, 18.5, −3.6 ppm; MS m/e (rel int) 242 (M^+, 0.3) 185 (6.6), 157 (2), 141 (2), 131 (6), 105 (3), 93 (7), 85 (3), 79 (3), 75 (100), 67 (13), 57 (15), 45 (18); HRMS calcd for $C_{13}H_{26}O_2Si$ 242.1702, found 242.1712. Anal. Cacld for $C_{13}H_{26}O_2Si$: C, 64.42; H, 10.82. Found: C, 64.53; H, 10.96.

The α-alkylated product exhibited the following spectral properties: ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dd, J = 17.0, 10.7 Hz, 2 H), 5.23 (ddd, J = 17.0, 10.7, 1.3 Hz, 4 H), 3.78 m, 2 H), 2.49 (t, J = 5.6 Hz, 1 H), 1.87 (t, J = 5.9 Hz, 2 H), 0.91 (s, 9 H), 0.09 (s, 6 H).

(*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-7-[(*p*-tolylsulfonyl)oxy]-1,3-heptadiene. A solution of TsCl (640 mg, 3.3 mmol) in pyridine (3 mL) was added dropwise to a stirred solution of **104** (270 mg, 1.12 mmol) containing a catalytic amount of 4-(dimethylamino)pyridine (6.8 mg, 0.056 mmol) in pyridine (3 mL) at 0 °C. After 1.5 h, the mixture was diluted with petroleum ether/ether (1:1, 200 mL), washed with water (2 × 50 mL) and saturated NH_4Cl (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. The pyridine residue was removed by evaporation with benzene several times on a rotary evaporator. Chromatography (10% EtOAc/hexane) gave 374 mg (85%) of the title compound as a clear colorless oil, R_f 0.59 (10% EtOAc/hexane): IR (neat) 1707 (w), 1360 (s), 1256 (s), 1175 (s), 968 (s), 938 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, J = 8.0 Hz, 2 H), 7.33 (dd, J = 8.0, 1.0 Hz, 2 H), 6.08 (dd, J = 17.0, 11.0 Hz, 1 H), 5.27 (ddd, J = 17.0, 1.0, 1.0 Hz, 1 H), 4.97 (ddd, J = 11.0, 1.0, 1.0 Hz, 1 H), 4.64 (t, J = 7.5 Hz, 1 H), 4.02 (t, J = 6.5 Hz, 2 H), 2.44 (s, 3 H), 2.12 (q, J = 7.0 Hz, 2 H), 1.70 (m, 2 H), 0.97 (s, 9 H), 0.75 (s, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 144.5, 135.3, 133.3, 129.8, 127.9, 112.9, 112.7, 70.0, 28.8, 25.9, 22.0, 21.6, 18.4, −3.6 ppm; MS (CI, isobutane) m/e (rel int) 397 (M^+, 100), 339 (7), 287 (11), 255 (5), 243 (6), 133 (13), 111 (6), 83 (9); HRMS calcd for $C_{20}H_{32}O_4SSiH^+$ 397.1869, found 397.1867.

(*Z*)-7-Azido-3-[(*tert*-butyldimethylsilyl)oxy]-1,3-heptadiene (26). Sodium azide (174 mg, 2.67 mmol) and a catalytic amount of NaI (20 mg, 0.134 mmol) were added to a solution of the above tosylate in DMSO (5 mL) at room temperature. After 14 h, the mixture was diluted with petroleum ether (100 mL), washed with water (2 × 10 mL) and brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography (3% EtOAc/hexane) gave 220 mg (88%) of azide **26** as a clear colorless oil, R_f 0.25 (5% EtOAc/hexane): IR (neat) 2096 (s), 1605 (w), 1256 (s), 1162, (s), 1050 (s), 840 (s), 780 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.14 (dd, J = 17.0, 11.0 Hz, 1 H), 5.30 (ddd, J =17.0, 1.0, 0.5 Hz, 1 H), 4.98 (ddd, J = 11.0, 1.0, 0.5 Hz, 1 H), 4.75 (t, J = 7.0 Hz, 1 H), 3.27 (t, J = 7.0 Hz, 2 H), 2.17 (q, J = 7.0 Hz, 2 H), 1.65 (qn, J = 7.0 Hz, 2 H), 1.00 (s, 9 H), 0.12 (s, 6 H) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 149.3, 135.3, 113.6, 112.7, 51.1, 28.7, 25.9, 23.2, 18.4, 0.73 ppm; HRMS (CI, NH_3) calcd for $C_{13}H_{25}ON_3SiNH_4^+$ (MNH_4^+) 285.2110, found 285.2114.

(*Z*)-5-(1-Ethoxyethoxy)-4,6-heptadien-1-ol (105). A solution of *sec*-butyllithium (15 mL of a 1.3 M solution in hexane, 19.5 mmol) was added in a dropwise fashion to a stirred solution of 3-(1-ethoxyethoxy)-1,4-pentadiene[42] (2.55 g, 16 mmol) in THF (25 mL) at −78 °C to generate the pentadienyl anion **103**. After 0.5 h, oxirane (14 mL of a 3.4 M solution in THF, 48 mmol) was added, and the mixture was allowed to stir at −78 °C for 1 h, diluted with petrolum ether/ether (1:1, 200 mL), washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. Crude ^1H NMR indicated a mixture of α- and γ-alkylated products in the ratio of 1:1.18. The crude material was chromatographed (25% EtOAc/hexane) to give 2.05 g (63%) of an inseparable mixture of **105** and the corresponding α-alkylated regioisomer as a colorless oil, which was taken on to the next step. For **105**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (dd, J = 17.0, 11.0 Hz, 1 H), 5.36 (d, J = 17.0 Hz, 1 H), 5.24 (d, J = 11.0 Hz, 1 H), 5.01–5.09 (m, 2 H), 3.51–3.66, 3.73–3.83 (m, 4 H), 2.32 (m, 2 H), 2.17 (br s, 1 H), 1.62 (m, 2 H), 1.41 (d, J = 5 Hz, 3 H), 1.16 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.68, 133.53, 119.36, 113.26, 100.69, 61.66, 59.06, 31.91, 21.06, 20.99, 15.29 ppm. For the α-adduct, 3-(1-ethoxyethoxy)-3-vinyl-4-penten-1-ol: ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (dd, J = 17.0, 11.0 Hz, 1 H), 5.99 (dd, J = 17.0 11.0 Hz, 1 H), 5.22–5.28 (m, 4 H), 4.79 (q, J = 5 Hz, 1 H), 3.77 (m, 2 H), 3.45 (q, J = 7 Hz, 2 H), 2.87 (br s, 1 H), 1.82–1.90, 1.98–2.07 (m, 2 H), 1.31 (d, J = 5 Hz, 3 H), 1.16 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.50, 139.90, 115.84, 115.43, 95.59, 81.81, 63.91, 59.39, 40.45, 20.99, 15.28.

(*Z*)-7-Azido-3-(1-ethoxyethoxy)-1,3-heptadiene (29). A solution of TsCl (2.36 g, 12.3 mmol) in pyridine (20 mL) was added dropwise at 0 °C to a 1.18:1 mixture of **105** and its regioisomer (830 mg, 4.08 mmol) in pyridine (30 mL). After 2.5 h, the reaction mixture was diluted with petroleum ether (300 mL), washed with water (2 × 50 mL) and saturated NH_4Cl (3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. The pyridine residue was removed by evaporation with benzene several times on a rotary evaporator. The crude material was chromatographed (20% EtOAc/hexane) to give 200 mg (14%) of pure γ-tosylate and 370 mg (26%) of γ- and α-tosylates (1:2.6). To the unstable γ-tosylate (200 mg, 0.564 mmol) in DMSO (3 mL) at room temperature was added NaN_3 (200 mg, 2.8 mmol) and a catalytic amount of NaI (20 mg, 0.14 mmol). After 1.25 h, the mixture was diluted with petroleum ether (100 mL) and washed with water (2 × 20 mL) and brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (7% EtOAc/hexane) gave 110 mg (86%) of **29** as a colorless oil, R_f 0.53, (10% EtOAc/hexane): IR (neat) 2096 (s), 1604 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.14 (dd, J = 17.0, 11.0 Hz, 1 H), 5.39 (br d, J = 17.0 Hz, 1 H), 4.99–5.08 (m, 3 H), 3.75–3.85 (m, 1 H), 3.50–3.60 (m, 1 H), 3.30 (t, J = 7.0 Hz, 2 H), 2.21–2.41 (m, 2 H), 1.70 (q, J = 7.0 Hz, 2 H), 1.42 (d, J = 5.0 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.98, 133.62, 118.43, 113.56, 100.86, 63.82, 51.05, 28.63, 23.13, 21.05, 15.37 ppm. Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.53; H, 8.56; N, 18.46.

(*Z*)-7-Azido-3-(diisopropylcarbamoyl)-1,3-heptadiene (34). *sec*-Butyllithium (3.9 mL of a 1.0 M solution in cyclohexane, 3.9 mmol) was added slowly to a solution of 1-(trimethylsilyl)-1-(diisopropylcarbamoyl)prop-2-ene[54] (1.0 g, 4 mmol) in THF (8 mL) at −78 °C. After 15 min, 9-methoxy-9-borabicyclo[3.3.1]-nonane (0.62, 4.1 mmol) was added to the yellow solution. After 15 min, boron trifluoride etherate (0.58 g, 4.1 mmol) was added to the now colorless solution, followed immediately by addition

(54) Although this compound is known,[54a] we prepared it by an alternative procedure. 1-(Trimethylsilyl)prop-2-en-1-ol[54b] was acylated with *N,N*-diisopropylcarbamoyl chloride in refluxing toluene containing *N,N*-diisopropylethylamine (67% yield after 14 h). (a) Hoppe, D.; Hanko, R.; Bronneke, A.; Lichtenberg, F.; von Hulsen, E. *Chem. Ber.* **1985**, *118*, 2822. (b) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M. Szczepanski, S. W. *Org. Synth.* **1987**, *66*, 14.

of the aldehyde **71**[18b] (490 mg, 4.3 mmol). After the mixture was allowed to warm slowly to room temperature over 2 h, concentrated H_2SO_4 (20 drops) was added, and the cloudy solution was stirred for an additional 4 h. The mixture was poured into water (50 mL), neutralized with saturated $NaHCO_3$, and extracted with ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (alumina, 5% EtOAc/hexane) gave 0.688 g (63%) of **34**, R_f = 0.12 (5% EtOAc/hexane on silica TLC plates): IR (neat) 2095 (s), 1716 (s), 1611 (s), 1435 (s), 1369 (s), 1346 (s), 1275 (s), 1214 (s), 1186 (s), 1154 (s), 1045 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.25 (dd, J = 17.2, 10.9 Hz, 1 H), 5.29 (t, J = 7.5 Hz, 1 H), 5.15 (d, J = 17.2 Hz, 1 H), 5.04 (d, J = 10.9 Hz, 1 H), 4.06 (m, 1 H), 3.95 (m, 1 H), 3.28 (t, J = 6.8 Hz, 2 H), 2.14 (app q, J = 7.5 Hz, 2 H), 1.69 (pentet, J = 7.0 Hz, 2 H) 1.32 (d, J = 6.8 Hz, 6 H), 1.25 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (90 MHz, $CDCl_3$), δ 152.4, 147.0, 132.3, 120.8, 112.7, 50.9, 46.7, 46.0, 28.0, 23.1, 21.5, 20.4; MS (CI/NH_3) m/e (rel int) 282 (MH^+ + 1, 6), 281 (MH^+, 29), 253 (5), 129 (10), 128 (100), 84 (5); HRMS calcd for $C_{14}H_{24}N_4O_2H$ (MH^+) 281.1978, found 281.1979. Anal. Calcd for $C_{14}H_{24}N_4O_2$: C, 59.97; H, 8.63; N, 19.98. Found: C, 59.74; H, 8.46; N, 19.99.

(*E*)-7-Azido-3-(diisopropylcarbamoyl)-1,3-heptadiene (36). The allylborane was generated using the same procedure as above from 1-(trimethylsilyl)-1-(diisopropylcarbamoyl)prop-2-ene (206.7 mg, 0.804 mmol) in THF (5 mL) with *sec*-butyllithium (0.80 mL of a 1.0 M solution in cyclohexane, 0.804 mmol), 9-methoxy-9-borabicyclo[3.3.1]nonane (0.128 g, 0.84 mmol) and boron trifluoride etherate (0.119 g, 0.84 mmol). The aldehyde **71**[18b] (100 mg, 0.88 mmol) was added at −78 °C, the solution was warmed to room temperature over 2.5 h, and 3 N NaOH (2 mL) was added. After 5 h, the mixture was poured into saturated NH_4Cl (25 mL) and extracted with ether (3 × 25 mL). The combined organic layers were washed with saturated NH_4Cl (2 × 25 mL) and brine (1 × 25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (alumina, 5% EtOAc/hexane) gave 117.3 mg (52%) of **36** as a clear oil, R_f 0.11 (silica, 7% EtOAc/hexane): IR (neat) 2096 (s), 1712 (s), 1599 (m), 1435 (s), 1314 (s), 1219 (s), 1154 (s), 1045 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (dd, J = 17.0, 11.0 Hz, 1 H), 5.12–5.28 (m, 3 H), 3.95 (br s, 2 H), 3.31 (t, J = 6.6 Hz, 2 H), 2.28 (app q, J = 7.3 Hz, 2 H), 1.70 (pentet, J = 7.0 Hz, 2 H), 1.24 (br s, 12 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 145.6, 127.4, 120.9, 114.2, 51.2, 46.3 (br), 28.3, 26.6, 25.8, 21.2 (br), 20.5 (br) ppm; MS (CI/methane) m/e (rel int) 282 (MH^+ + 1, 3), 281), 281 (MH^+, 12), 255 (6), 253 (10), 174 (4), 154 (4), 141 (4), 129 (11), 128 (100), 102 (13), 86 (40), 79 (7); HRMS calcd for $C_{14}H_{24}N_4O_2H$ 281.1978, found 281.1988.

(*Z*)-8-Azido-3-(diisopropylcarbamoyl)-1,3-octadiene (37). The allylborane was generated using the same procedure as above from 1-(trimethylsilyl)-1-(diisopropylcarbamoyl)prop-2-ene (808.7 mg, 3.15 mmol) in THF (6.0 mL) with *sec*-butyllithium (3.15 mL of a 1.05 M solution in cyclohexane, 3.30 mmol), 9-methoxy-9-borabicyclo[3.3.1]nonane (501 mg, 3.30 mmol), and boron trifluoride etherate (468 mg, 3.30 mmol). The aldehyde **72**[39] (440 mg, 3.46 mmol) was added at −78 °C, the solution was warmed to room temperature over 2 h, and concentrated H_2SO_4 (20 drops) was added. After 3 h, the mixture was poured into water (50 mL), neutralized with saturated $NaHCO_3$, and then extracted with ether (3 × 75 mL). The combined organic extracts were washed with water (50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (alumina, 5% EtOAc/hexane) gave 0.466 g (50%) of **37** as a clear oil, R_f 0.13 (10% EtOAc/hexane): IR (neat) 2094 (s), 1716 (s), 1610 (m), 1495 (s), 1369 (s), 1276 (s), 1214 (s), 1153 (s), 1045 (s), 898 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.24 (dd, J = 17.2, 10.9 Hz, 1 H), 5.29 (t, J = 7.5 Hz, 1 H), 5.12 (d, J = 17.2 H, 1 H), 5.01 (d, J = 10.9 Hz, 1 H), 1.05 (m, 1 H), 3.93 (m, 1 H), 3.24 (t, J = 6.6 Hz, 2 H), 2.08 (app q, J = 7.4 Hz, 2 H), 1.59 (m, 2 H), 1.48 (m, 2 H), 1.31 (d, J = 6.8 Hz, 6 H), 1.24 (d, J = 6.8 Hz, 6 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.4, 146.6, 132.4, 121.6, 112.3, 51.2, 47.6, 46.3, 28.5, 25.9, 25.4, 21.5, 20.5 ppm; MS (CI, NH_3) m/e (rel int) 296 (M + 2, 2), 295 (M + 1, 8) 269 (6), 267 (12), 252 (2), 140 (13), 128 (100), 102 (13), 86 (35); HRMS calcd for $C_{15}H_{25}N_4O_2H$ 295.2134, found 295.2144.

(*E*)-8-Azido-3-(diisopropylcarbamoyl)-1,3-octadiene (38). The allylborane was generated using the same procedure as above from 1-(trimethylsilyl)-1-(diisopropylcarbamoyl)prop-2-ene (268.6 mg, 1.04 mmol) in THF (2 mL) with *sec*-butyllithium (1.04 mL of a 1.05 M solution in cyclohexane, 1.09 mmol), 9-methoxy-9-borabicyclo[3.3.1]nonane (165 mg, 1.09 mmol), and boron trifluoride etherate (155 mg, 1.09 mmol). The aldehyde **72**[39] (140 mg, 1.14 mmol) was added at −78 °C, the solution was warmed to room temperature over 2 h, and 3 N NaOH (2 mL) was added. After 3 h, the mixture was poured into saturated NH_4Cl (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed brine (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (alumina, 5% EtOAc/hexane) gave 0.229 g (75%) of **38** as a clear oil, R_f 0.15 (SiO_2, 10% EtOAc/hexane): IR (neat), 2095 (s), 1713 (s), 1599 (m), 1434 (s), 1369 (s), 1314 (s), 1217 (s), 1153 (s), 1045 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 6.53 (dd, J = 17.1, 11.0 Hz, 1 H), 5.23 (m, 2 H), 5.13 (d, J = 11.0 Hz, 1 H), 3.94 (br s, 2 H), 3.26 (t, J = 6.6 Hz, 2 H), 2.23 (app q, J = 7.6 Hz, 2 H), 1.62 (m, 2 H), 1.52 (m, 2 H), 1.24 (br s, 12 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 145.6, 127.4, 120.9, 141.2, 51.2, 46.3 (br), 28.3, 26.6, 25.8, 21.2 (br), 20.5 (br) ppm; MS (CI, NH_3) m/e (rel int) 296 (M + 2, 1.3), 295 (M + 1, 50), 279 (1.4), 267 (8), 168 (5), 140 (13), 128 (100), 122 (9), 102 (12), 86 (36); HRMS calcd for $C_{15}H_{25}N_4O_2H$ 295.2134, found 295.2130.

4-Chloro-1,1-dibromobutane (106). The title compound was synthesized by a modification of the method of Normant.[55] To a three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and a thermometer was charged with a solution of diisopropylamine (26.4 mL, 0.875 mmol) in ether (120 mL). A solution of *n*-butyllithium (78 mL of a 2.5 M solution in cyclohexane, 0.195 mmol) was added dropwise to the stirred solution at −20 °C over a period of 24 min. The resulting solution was allowed to warm to 0 °C and stirred at that temperature for 1 h. THF (100 mL) was added and the solution was cooled to −100 °C. Dibromomethane (13.2 mL, 0.150 mmol) was carefully added, and the temperature was maintained at −95 °C. After 12 min, 3-chloro-1-bromopropane (15 mL, 0.150 mmol) was added dropwise to the reaction mixture followed by the addition of HMPA (26.1 mL, 0.15 mmol). The temperature was kept at around −90 °C and not higher than −85 °C. After 3 h, the mixture was slowly allowed to warm to −50 °C. Aqueous HCl (10%, 100 mL) was slowly added to destroy the HMPA, and then saturated $NaHCO_3$ (300 mL) was carefully added to neutralize the acid. The mixture was diluted with ether/petroleum ether (1:1, 400 mL), and the organic phase was separated. The aqueous layer was again extracted with ether/petroleum ether (1:1, 200 mL). The combined organic extracts were washed with water (2 × 200 mL) and saturated NH_4Cl (3 × 300 mL), dried ($MgSO_4$), filtered, and concentrated. Bulb-to-bulb distillation (40–50 °C (0.7 mmHg)) removed the unreacted starting material (3-chloro-1-bromopropane). Filtration through a plug of alumina with ether gave 23 g (61%, 92% based on recovered starting material) of **106** as a brownish oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (t, J = 6.0 Hz, 1 H), 3.60 (t, J = 6.0 Hz, 2 H), 2.53–2.60 (m, 2 H), 2.00–2.11 (m, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.50, 43.31, 42.41, 30.72 ppm.

(1*E*,3*Z*)-7-Chloro-1-phenyl-3-phenoxy-1,3-heptadiene (107). The general procedure of Takai[44] was used. Titanium tetrachloride (1.96 mL, 17.8 mmol) was added to THF (5 mL) dropwise at 0 °C followed by the addition of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 5.4 mL, 35.6 mmol) at room temperature. After 12 min, zinc powder (2.9 g, 44.6 mmol) was added, and the mixture was stirred at room temperature for 30 min. A solution of dibromide **106** (2.47 g, 8.92 mmol) and phenyl cinnamate (1.0 g, 44.6 mmol) was added in one portion, and the reaction mixture was allowed to stir at room temperature for 12 h. After cooling the mixture to 0 °C, saturated K_2CO_3 (5 mL) was added dropwise. After 30 min, ether (100 mL) was added, and the mixture was filtered through a small plug of basic alumina (grade III) washing with ether/NEt_3 (200:1, 200 mL). The filtrate was dried ($MgSO_4$) and concentrated, and the resultant residue was chromatographed (SiO_2, 2% EtOAc/hexane) to give 0.88 g (66%) of **107** as a colorless oil, R_f 0.33 (silica, 5% EtOAc/hexane): IR (neat) 1595 (s), 1491 (s), 1219 (s), 960 (s), 752 (s), 693 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.37 (m, 8 H), 6.97–7.05 (m,

(55) Normant, J. F.; Villieras, J.; Bacquet, C. *Bull. Soc. Chim. Fr.* **1975**, 1797.

2 H), 6.70 (d, J = 16.0 Hz, 1 H), 6.61 (d, J = 16.0 Hz, 1 H), 5.49 (t, J = 7.5 Hz, 1 H), 3.52 (t, J = 7.0 Hz, 2 H), 2.28 (q, J = 7.5 Hz, 2 H), 1.82–1.92 (m, 2 h) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.58, 150.11, 136.61, 129.57, 129.22, 128.59, 127.70, 126.56, 123.41, 121.48, 120.71, 114.96, 44.31, 32.02, 23.49 ppm; MS m/e (rel int) 301 (M + 3, 1), 300 (M + 2, 9), 299 (M + 1, 5), 298 (M^+, 29), 221 (24), 205 (18), 169 (31), 154 (11), 141 (100), 129 (60), 115 (60), 91 (40), 77 (60); HRMS calcd for $C_{19}H_{19}O^{35}Cl$ 298.1124, found 298.1119.

(1*E*,3*Z*)-7-Azido-1-phenyl-3-phenoxy-1,3-heptadiene (68). To a stirred solution of chloride **107** (460 mg, 1.5 mmol) in THF (5 mL) at room temperature was added tetra-*n*-butylammonium azide (2 g, 7 mmol) in one portion. Potassium iodide (20 mg, 0.14 mmol) was added, and the reaction mixture was stirred for 24 h. The mixture was extracted twice with petroleum ether (400 mL total), and the combined organics were washed with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexane) gave 285 mg (97%) of **68** as a clear colorless oil, R_f 0.7 (30% EtOAc/hexane): IR (neat) 2095 (s), 1664 (s) 1595 (s), 1491 (s), 1219 (s) cm^{-1}; ^{1}H NMR (THF-d_8, 300 MHz) δ 6.88–7.36 (m, 10 H), 6.78 (d, J = 16 Hz, 1 H), 6.56 (d, J = 16 Hz, 1 H), 5.54 (t, J = 7.5 Hz, 1 H), 3.23 (t, J = 7.0 Hz, 2 H), 2.16 (q, J = 7.5 Hz, 2 H), 1.63 (qn, J = 7.0 Hz, 2 H) ppm; ^{13}C NMR (THF-d_8, 75 MHz) δ 157.58, 149.39, 129.39, 126.69, 125.76, 121.15, 117.44, 114.74, 50.80, 28.19, 22.67, 17.68 ppm; MS (CI, NH_3) m/e (rel int) 308 (M + 2, 3), 307 (M + 1, 15), 306 (M^+, 51), 278 (100), 249 (16), 202 (9),186 (49), 146 (14), 106 (9); HRMS calcd for $C_{19}H_{19}N_3OH^+$ 306.1606, found 306.1614.

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Registry No. **4a**, 128845-46-5; (*E*)-**4b**, 99125-90-3; (*Z*)-**4b**, 99125-89-0; **4c**, 128845-83-0; (±)-***cis*-5b**, 128845-90-9; (±)-***trans*-5b**, 128845-79-4; (±)-**6b**, 102422-91-3; (±)-*exo*-**6c**, 128945-96-0; (±)-*endo*-**6c**, 128945-97-1; (±)-**7a**, 128845-84-1; (±)-**7b**, 99125-85-6; (±)-**7c**, 128945-98-2; (±)-**8b**, 41646-17-7; (±)-**9b**, 99125-83-4; **12**, 108782-20-3; (±)-**13**, 128845-06-7; (±)-**14**, 128845-07-8; **15**, 108782-19-0; **16**, 128845-08-9; **17**, 123289-36-1; (±)-**18**, 128845-09-0; **19**, 108782-26-9; **20**, 123289-43-0; **21**, 128845-10-3; **22**, 128845-11-4; (±)-**23**, 128845-12-5; **24**, 128845-13-6; **24** bromide, 128845-44-3; (±)-**25**, 128845-14-7; **26**, 128845-15-8; **26** tosylate, 128869-07-8; (±)-**27**, 128845-16-9; (±)-**28**, 128869-09-0; (±)-**29**, 128845-17-0; (±)-**29** tosylate, 128845-04-5; (±)-**30** (isomer 1), 128845-18-1; (±)-**30** (isomer 2), 128845-86-3; (±)-**31** (isomer 1), 128845-19-2; (±)-**31** (isomer 2), 128845-85-2; (±)-**32**, 128845-20-5; (±)-**32** tosylate, 128844-99-5; (±)-**33**, 128845-21-6; (±)-**33** tosylate, 128845-01-2; **34**, 128845-22-7; **35**, 128845-23-8; **36**, 128845-24-9; **37**, 128845-25-0; **38**, 128869-10-3; **39**, 128845-26-1; (±)-**40**, 128845-27-2; **41**, 128845-28-3; **42**, 128845-29-4; (±)-**43**, 128845-30-7; (±)-**44** (isomer 1), 128845-31-8; (±)-**44** (isomer 2), 128845-87-4; (±)-**45** (isomer 1), 128845-32-9; (±)-**45** (isomer 2), 128845-88-5; (±)-**46** (isomer 1), 128845-33-0; (±)-**46** (isomer 2), 128845-89-6; (±)-**51**, 128845-34-1; (±)-**52**, 128845-35-2; (±)-**53**, 128845-36-3; (±)-**54**, 128845-37-4; (±)-**55**, 128845-38-5; (±)-**56**, 128845-39-6; **57**, 128845-40-9; **58**, 128845-41-0; **68**, 128845-47-6; (±)-**69**, 128845-48-7; (±)-**70**, 128845-49-8; **71**, 99545-47-8; **72**, 114642-97-6; **73**, 123307-77-7; **74**, 128845-50-1; **76**, 73111-16-7; **76** azide, 128845-42-1; **77**, 89922-82-7; **78**, 87184-81-4; (±)-**79**, 128845-51-2; (±)-**80**, 128845-52-3; (±)-**81**, 128845-53-4; (±)-**82**, 128845-54-5; (±)-**83**, 128845-55-6; (±)-**84**, 128845-56-7; (±)-**85**, 128845-57-8; (±)-**86**, 128845-58-9; (±)-**87**, 128845-59-0; (±)-**88**, 128845-60-3; (*E*)-**89**, 128845-03-4; (*Z*)-**89**, 128845-61-4; **90**, 128845-62-5; **91**, 128845-63-6; **92**, 128845-64-7; **93**, 128845-65-8; **94**, 128845-66-9; **95**, 128845-67-0; **96**, 128845-68-1; **97**, 128845-69-2; **98**, 128845-70-5; **99**, 87184-80-3; (±)-**100**, 128845-71-6; (±)-**100** alcohol, 128844-98-4; (±)-**101**, 128845-72-7; (±)-**101** alcohol, 128845-00-1; **102** (Li = H), 115827-67-3; (±)-**103** (Li = H), 128845-73-8; **104**, 128845-74-9; **105**, 128845-75-0; **106**, 118506-60-8; **107**, 128845-76-1; A, 128845-45-4; A (X = OH), 55048-74-3; (±)-B (isomer 1), 99482-70-9; (±)-B (isomer 2), 99125-91-4; (*E*)-C, 99125-92-5; (*Z*)-C, 99482-71-0; (*E*)-D, 128845-77-2; (*Z*)-D, 128845-78-3; (*E*)-D (X = OH), 99125-87-8; (*Z*)-D (X = OH), 99125-88-9; E, 128845-80-7; E (X = OH), 128845-81-8; E (X = OSO_2CH_3), 128845-82-9; TMSCH(OEE)-CH=CH_2, 128844-97-3; (±)-$HO(CH_2)_2C(OEE)(CH{=}CH_2)_2$, 128845-02-3; (±)-$TsO(CH_2)_2C(OEE)(CH{=}CH_2)_2$, 128869-08-9; (±)-TMSCH(OCb)CH=CH_2, 128845-05-6; CH_2Br_2, 74-95-3; Cl-$(CH_2)_3$Br, 109-70-6; (*E*)-PhOCOCH=CHPh, 25695-77-6; *t*-BuSC≡CCH_3, 1595-36-4; $Br(CH_2)_4OH$, 33036-62-3; $CH_3CH{=}CHCO_2Et$, 10544-63-5; (*E*)-$(EtO)_2P(O)CH_2CH{=}CHCO_2Et$, 42516-28-9; TMSC(SPh)=C=CH_2, 123289-30-5; TMSC(SBu-*t*)=C=CH_2, 96692-93-2; (2*S*,3*R*,4*S*)-5-azido-2,3,4-tris(benzyloxy)pentanal, 128845-43-2.

Supplementary Material Available: Characterization data for **4a**,**b**, **5b**, **6b**,**c**, **7a**–**c**, **8b** and **9b** and NMR spectra for compounds described in this paper (41 pages). Ordering information is given on any current masthead page.