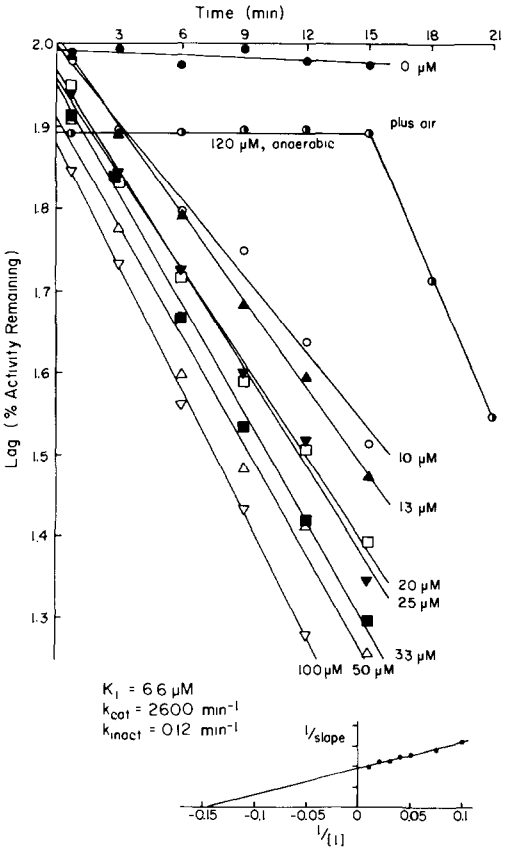
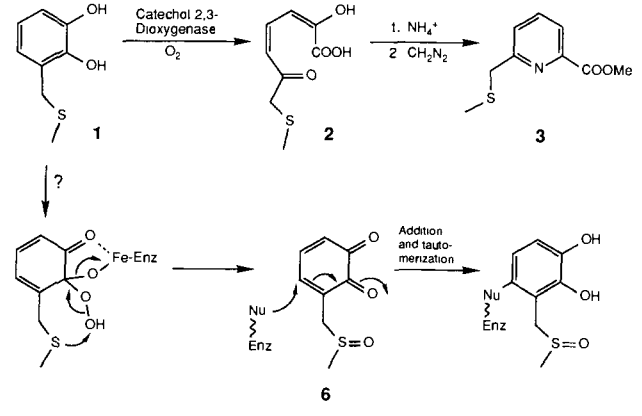


Figure 1. Time course of the inactivation of metapyrocatechase by 3-[(methylthio)methyl]catechol (**1**). In each inactivation experiment, metapyrocatechase (0.5 μg) and catalase (16 mg) were preincubated at 24 °C in potassium phosphate buffer (50 mM, pH 7.5, 100 mL) containing the indicated concentrations (0–100 μM) of **1**. At 3-min intervals, 15-mL aliquots were placed in 5-cm quartz cuvettes, and the enzyme activity was assayed by the changes in absorbance at 375 nm after the addition of catechol to 150 μM.

Scheme I



tivation was observed when enzyme was preincubated with **1** under anaerobic conditions (Figure 1), nor did inactivation occur in the absence of **1**. On the other hand, the presence of catalase did not protect the enzyme from inactivation, nor could inactive enzyme be reactivated by addition of iron salts or reducing agents in various combinations. Several experiments further characterized the inactivation process:

(1) A sample of **1** was exhaustively oxidized by metapyrocatechase, the protein was removed by ultrafiltration, and fresh metapyrocatechase was added to the filtrate. No inactivation was observed, ruling out the normal product **2** as the inactivating agent.

(2) 3-[(Methylthio)[^{3}H]methyl]catechol (**4**)[5] was prepared. Incubation of **4** with metapyrocatechase under aerobic conditions resulted in the incorporation of approximately 1.6 equiv of tritium into the inactivated enzyme.[10] This radiolabel was not removed by gel filtration or anion exchange chromatography, treatment with thiols, or dialysis of the protein against buffer containing sodium dodecyl sulfate, thus indicating that the enzyme is covalently modified in the course of the inactivation process.

(3) 3-Propylcatechol (**5**)[5] was prepared. Compounds **1** and **5** have essentially the same steric requirements, so any variance in the enzymic processing of the two substrates must result from electronic differences. Compound **5** is a good substrate for metapyrocatechase (k_{cat} = 4300 min^{-1}, K_m = 5 μM),[6] and like **1** it is cleaved between carbons 2 and 3,[12] but preincubation of the enzyme with **5** results in *no inactivation*, suggesting that the thioether moiety is essential for the inactivation process.

A plausible mechanism for the inactivation is illustrated in Scheme I. Sulfide oxidation by a peroxidic intermediate (or another oxygenating agent) would lead to the *o*-quinone **6**, a potent electrophile, which might be captured by an enzyme active site nucleophile to yield the inactive, covalently modified enzyme.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM 31801).

Supplementary Material Available: Scheme for the synthesis of **1**, **4**, and **5** and spectrometric data for **1**, **4**, **5**, and **S1–S6** (2 pages). Ordering information is given on any current masthead page.

(10) Different preparations of metapyrocatechase, though homogeneous by SDS gel electrophoresis, vary in specific activity. The maximum activity observed thus far is 320 (μmol/min) mg^{-1} for enzyme containing 3.4 g-atoms of Fe/mol of enzyme.[11] The enzyme is a tetramer of identical subsunits, so the theoretical maximum activity is probably 380 (μmol/min) mg^{-1}. In two separate inactivation experiments, enzyme with specific activities of 14% and 39% of this maximum were labeled with 0.21 and 0.66 equiv of tritium, respectively.

(11) Nakai, C.; Hori, K.; Kagamiyama, H.; Nakazawa, T.; Nozaki, M. *J. Biol. Chem.* **1983**, *258*, 2916–2922.

(12) The product 2-hydroxy-6-oxo-2,4-nonadienoic acid was characterized by conversion to methyl 6-propylpicolinate: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, 3 H, J = 7 Hz, $CH_2CH_2CH_3$), 1.69 (m, 2 H, $CH_2CH_2CH_3$), 2.81 (t, 2 H, J = 8 Hz, $CH_2CH_2CH_3$), 3.93 (s, 3 H, CO_2CH_3), 7.27 (dd, 1 H, J = 8, 1 Hz, Ar H), 7.67 (t, 1 H, J = 8 Hz, Ar H), 7.89 (dd, 1 H, J = 8, 1 Hz, Ar H).

Pentacyclo[4.3.1.0^{1,6}.0^{7,9}.0^{8,10}]decane: A Cyclopropane Edge-Bridged Prismane and Its Rearrangement to a Fulvene

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Short-bridged cyclophanes continue to be of theoretical and experimental interest.[1] Not surprisingly, the strain of these compounds is reflected in their historical sequence of appearance. This is illustrated by the first syntheses of [6]metacyclophane (**1a**; 1972[2]), [6]paracyclophane (**2a**; 1974[3]), [5]metacyclophane (**1b**; 1977[4]), and [5]paracyclophane (**2b**; 1985[5]). An extrapolation

(1) For a recent review, see: Keehn, P. M., Rosenfeld, S. M., Eds. *Cyclophanes*; Academic: New York, 1983.

(2) Fujita, S.; Hirano, S.; Nozaki, H. *Tetrahedron Lett.* **1972**, 403.

(3) Kane, V. V.; Wolf, A.-D.; Jones, M., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 2643.

(4) Van Straten, J. W.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1977**, 4667.

(5) Jenneskens, L. W.; De Kanter, F. J. J.; Kraakman, P. A.; Turkenburg, L. A. M.; Koolhaas, W. E.; De Wolf, W. H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* **1985**, *107*, 3716.

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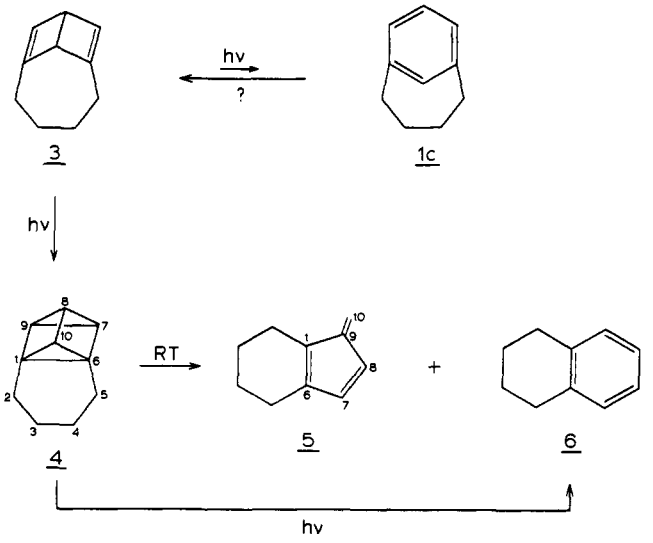
Scheme I



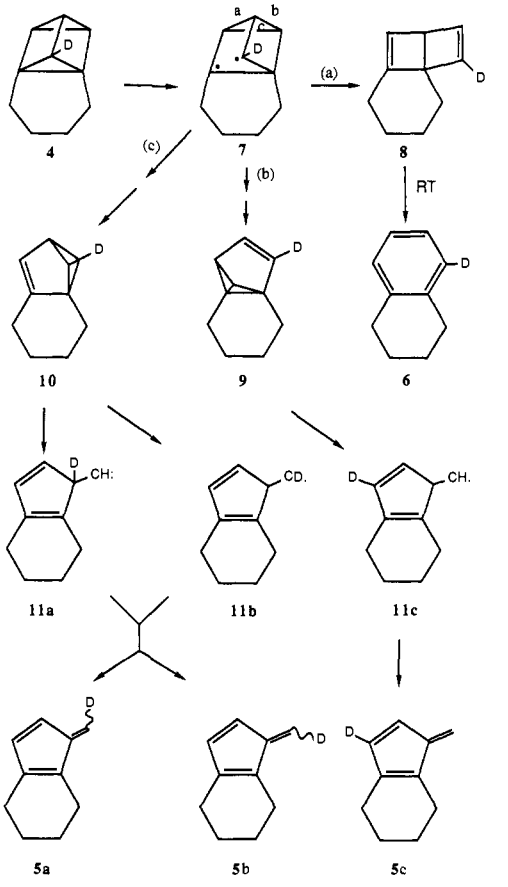
of this line leads to [4]metacyclophane (**1c**) as the next logical candidate. After a previous attempt to prepare **1c** had resulted in the formation of its Dewar isomer **3**,[6] the successful preparation of **2b** by irradiation of the corresponding Dewar isomer[5] inspired us to try the analogous conversion of **3** to **1c**. Again, **1c** was not obtained, but we observed its valence isomer, the title compound **4**, which is unique as a prismane containing the short tetramethylene bridge over a cyclopropane edge; moreover, **4** rearranged to the isomeric fulvene **5** in an unprecedented thermal reaction (Scheme I).

A solution of 4 mg of **3** in THF-d_8 was irradiated in a quartz NMR tube at −50 °C with a low-pressure mercury lamp (254 nm). The ^{1}H NMR spectrum revealed no indications for the presence of **1c**, but within 2 h, **3** was quantitatively converted to **4** which in turn was slowly transformed to tetralin (**6**) on prolonged irradiation. The identification of **4** is based on its characteristic NMR spectra and on the lack of prominent UV absorption.[7]

Our initial disappointment at the rather unsensational conversion of yet another Dewar benzene to its prismane isomer was dispelled by the observation that **4**, on warming to room temperature in THF-d_8 solution (ca. 0.06 M), rearranged cleanly to a mixture of **5** and **6** (about 2:3) within 10 h; no other products were detected by ^{1}H NMR spectroscopy or GCMS analysis. Fulvene **5** was isolated by preparative gas chromatography and identified by its spectral data;[7] it is a yellow liquid which is rather unstable, especially in concentrated solutions.

To our knowledge, the thermal conversion of a prismane to a fulvene is without precedent,[8,9] and its mechanism remains speculative. However, it is evident that the deviating behavior of **4** is a consequence of its unique structural features. A direct, concerted conversion of **4** to **5** is quite unlikely for topological and mechanistic reasons. An acid-catalyzed rearrangement was ruled out by addition of 2 equiv of CF_3COOH to 4 mg of **4** in 0.5 mL of THF-d_8; at −40 °C, no reaction occurred, and above 0 °C, **4** decomposed to a mixture of unidentified products, none of which was **5** or **6**. The course of events depicted in Scheme II is based on the following considerations.

Scheme II



Oth has reported that in the aromatization of hexamethylprismane, hexamethylbenzvalene is an intermediate, and he suggested a radical pathway.[10] In analogy, we propose a homolytic cleavage of one of the cyclopropane bonds of **4** leading to **7**; this cleavage is favored over others as it relieves conformational strain of the six-membered ring. Subsequent cleavage of bond a in **7** could give **8** which is known to aromatize to 6 at room temperature.[11] The formation of **5** from **7** may commence by cleavage of bond b (via **9**) or of bond c (via **10**), analogous to the benzvalene formation mechanism of Oth.[10] The rearrangement of a benzvalene to a fulvene may either be quartz catalyzed[9,12,13] or may proceed via a retro carbene addition; this amounts to a retro 1,2-addition[14,15] (see indicated bonds) in the case of **9** or to a retro 1,4-addition[13-15] in the case of **10**.

Deuterium labeling of **4** at C-10 (Scheme II) showed the former pathway to be the preferred one. By ^{2}H NMR spectroscopy, the ratio of **5a**:**5b**:**5c** was found to be 17:17:62 (3% ^{2}H was at the remaining olefinic position, just detectable above natural abundance). It is not clear at present to what extent **8**–**10** are precursors of **6**.

Finally, it should be pointed out that the matter of accessibility of **1c** remains open. Compound **1c** (MNDO:ΔH_f° = 77.1

(6) Turkenburg, L. A. M.; Van Straten, J. W.; De Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1980**, *102*, 2356.

(7) **4**: ^{1}H NMR (250 MHz, THF-d_8, 200 K) δ 2.33 (d, ^3J(HH) = 5.0 Hz, 2 H, H(7,9)), 2.19 (br s, 1 H, H(10)), 2.15 (td, ^3J(HH) = 5.0, 1.8 Hz, 1 H, H(8)), 1.92 (m, 2 H), 1.71 (m, 2 H), 1.23 (m, 2 H), 0.73 (m, 2 H); ^{13}C NMR (62.89 MHz, THF-d_8, 220 K) δ 42.2 (d, ^1J(CH) = 181 Hz, C(8)), 38.0 (s, C(1,6)), 34.1 (d, ^1J(CH) = 180 Hz, C(10)), 24.8 (t, ^1J(CH) = 127 Hz, C(2,5) or C(3,4), 24.8 (d, ^1J(CH) = 183 Hz, C(7,9)), 22.1 (t, ^1J(CH) = 126 Hz, C(3,4) or C(2,5)); UV (THF) end absorption (log ϵ_{254} = 2.54). **5**: Yellow, unstable liquid, ^{1}H NMR[17] (250 MHz, THF-d_8, 293 K) δ 6.20 (dd, ^3J(HH) = 5.3, ^5J(HH) = 1.3 Hz, 1 H, H(7)), 6.01 (d, ^3J(HH) = 5.3 Hz, 1 H, H(8)), 5.60 (br s, 1 H, H(10)), 5.54 (br s, 1 H, H(10)), 2.32 (m, 4 H), 1.71 (m, 4 H); UV (THF-d_8) λ_{max} 243, 373 nm ($\epsilon_{243}/\epsilon_{373}$ = 35); mass spectrum *m*/*z* (relative intensity) 132 (50, $M^{\cdot+}$), 117 (100), 104 (62), 91 (47); IR (10%, CCl_4) 2925, 2855, 1735, 1455, 1375 cm^{-1}.

(8) Greenberg, A.; Liebman, J. F. *Strained Organic Compounds*; Academic: New York, 1978, and references cited.

(9) Bryce-Smith, D.; Gilbert, A. *Tetrahedron* **1976**, *32*, 1309 and references cited.

(10) Oth, J. F. M. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1185.

(11) (a) Landheer, I. J.; De Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1974**, 2813. (b) Van Straten, J. W.; Turkenburg, L. A. M.; De Wolf, W. H.; Bickelhaupt, F. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 89.

(12) Kaplan, L.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1968**, *90*, 3291.

(13) Christl, M. *Angew. Chem.* **1981**, *93*, 495 and references cited.

(14) (a) Katz, T. J.; Wang, E. J.; Acton, N. *J. Am. Chem. Soc.* **1971**, *93*, 3782. (b) Gandillon, G.; Bianco, B.; Burger, U. *Tetrahedron Lett.* **1981**, *22*, 51.

(15) Burger, U.; Gandillon, G.; Mareda, J. *Helv. Chim. Acta* **1981**, *64*, 844 and references cited.

kcal·mol^{-1})[16] is slightly less stable than **3** ($\Delta H_f°$ = 74.6 kcal·mol^{-1})[16] but certainly much more stable than **4** ($\Delta H_f°$ = 102.7 kcal·mol^{-1}). We consider it likely that **1c** is indeed formed on irradiation of **3** but that the photostationary state is even more unfavorable than in the case of **2b** where 6–7% of **2b** are in photoequilibrium with its Dewar isomer.[5]

(16) Jenneskens, L. W.; De Kanter, F. J. J.; De Wolf, W. H.; Bickelhaupt, F. *J. Comput. Chem.*, in press.
(17) Assignment based on: Hollenstein, R.; Philipsborn, W. v.; Vögeli, R.; Neuenschwander, M. *Helv. Chim. Acta* **1973**, *56*, 847.

Tricyclo[5.3.0.0^{2,8}]deca-3,5,9-triene

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Received November 24, 1986

The inherent capability of cyclobutane σ bonds to interact electronically with neighboring π systems was first demonstrated by us in the case of bicyclo[4.1.1]octa-2,4-diene (β = 1.9 eV).[2] This observation led to a theoretical analysis of the extent to which two mutually perpendicular π systems might effectively interact through the Walsh "relay" orbitals of a four-membered ring.[3] Particular attention was given to the three closed-shell polyolefins **1**–**3**. Whereas the basis orbital energies calculated for **1** and **3**

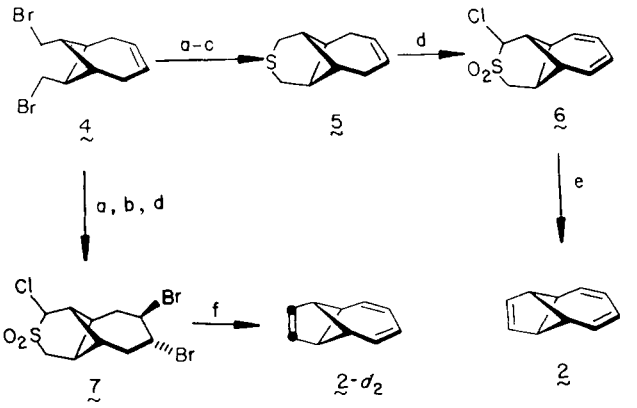
1 **2** **3**

predict that destabilization would be manifested, those present in **2** were deemed to be marginally stabilizing. Tricyclo[3.3.0.0^{2,6}]cota-3,7-diene (**1**) had been earlier synthesized and shown to rearrange rapidly to semibullvalene at 20 °C.[4] More recently, access has been gained to **3**.[5] At 80 °C, this tetraene undergoes formal [1,3]-sigmatropic rearrangement with a half-life of 7 h.

To the extent that through-bond interaction governs the reactivity of these systems, the title compound (**2**) should, on the basis of Gleiter's prediction,[3] prove still more stable than **3**. On the other hand, its strain energy lies intermediate between that of **1** and **3** and the relative importance of this property requires clarification. We report here a synthesis of this $(CH)_{10}$ hydrocarbon and demonstrate its particular sensitivity to structural isomerization by a process very probably involving *biradicaloid* intermediates. This behavior contrasts markedly with the formally *concerted* rearrangement pathway followed by **3**.

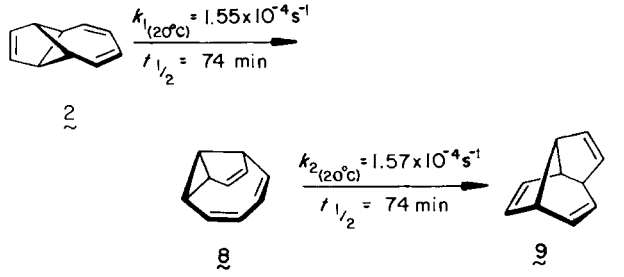
The known dibromide **4**[5] appeared to be an ideal advanced intermediate for the elaboration of **2**. We envisioned that Ramberg–Bäcklund rearrangement of a derived α-chloro sulfone might be performed under conditions sufficiently mild[6] to preserve the structural integrity of the product. The preliminary three-step conversion to **5** proceeded smoothly (84% overall, Scheme I). Due to competing epoxidation, this sulfide was transformed less efficiently (45%) into **6**. When **6** was treated with excess KO-*t*-Bu in THF at 0 °C,[7] desulfonylative ring contraction was seen to be complete within 1 h to give pure **2**, the spectral properties of which[8] are in complete agreement with the structural assignment.

Scheme I

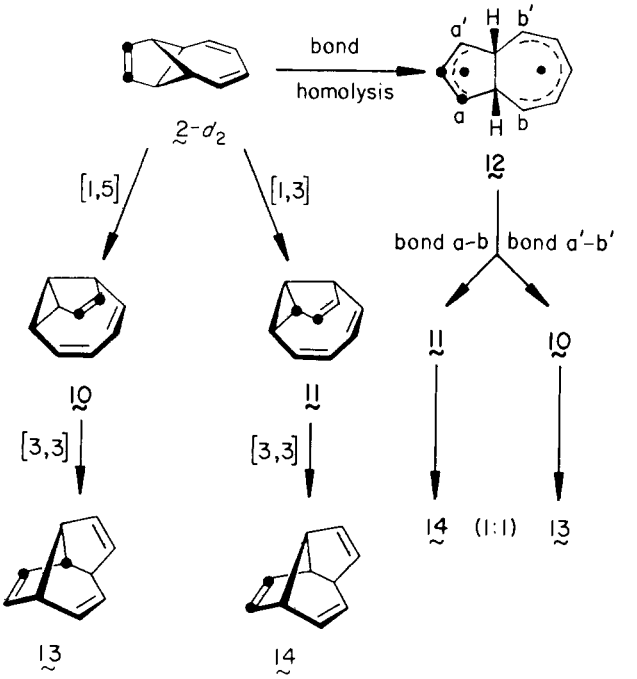


[a] (a) Na_2S, HMPA, 110 °C, 2.75 h; (b) $PyH^+Br_3^-$, CCl_4–HOAc (1:1), room temperature; (c) KO-*t*-Bu, THF, room temperature; (d) NCS, CCl_4, 90 °C, MCPBA; (e) KO-*t*-Bu, THF, 0 °C, 1 h; (f) KO-*t*-Bu (24 equiv), D_2O (12 equiv), THF, −70 to 0 °C during 1 h, 0 °C for 1 h.

Scheme II



Scheme III



(1) Fulbright Scholar, 1982–1983; Evans Fellow, 1985–1986.
(2) Gleiter, R.; Bischof, P.; Volz, W. E.; Paquette, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 8.
(3) Bischof, P.; Gleiter, R.; Haider, R. *J. Am. Chem. Soc.* **1978**, *100*, 1036.
(4) (a) Meinwald, J.; Tsuruta, H. *J. Am. Chem. Soc.* **1969**, *91*, 5877. (b) Meinwald, J.; Schmidt, D. *Ibid.* **1969**, *91*, 5877. (c) Zimmerman, H. E.; Robbins, J. D.; Schantl, J. *Ibid.* **1969**, *91*, 5878.
(5) Paquette, L. A.; Dressel, J.; Chasey, K. L. *J. Am. Chem. Soc.* **1986**, *108*, 512.
(6) Paquette, L. A. *Org. React.* **1977**, *25*, 1.
(7) Bicyclo[2.1.1]hexenes have previously been synthesized by this methodology: Carlson, R. G.; May, K. D. *Tetrahedron Lett.* **1975**, 947.
(8) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, J = 2.3 Hz, 2 H), 6.34–6.24 (m, 2 H), 6.24–6.15 (m, 2 H), 3.56–3.49 (m, 2 H), 1.17 (t, J = 2.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.36, 136.26, 126.69, 78.37, 29.61 ppm.

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