eq 1, or via a direct superexchange process.[8,9] Temperature-de-

$$MP_d^*\text{-}M'P_p\text{-}Q \overset{\text{energy migration}}{\rightleftharpoons} MP_d\text{-}M'P_p^*\text{-}Q \xrightarrow{\text{electron transfer}} MP_d\text{-}M'P_p^+\text{-}Q^- \quad (1)$$

pendent measurements and studies with analogues of **3** and **4** containing different metals in the "proximal" position (and hence different energy barriers) may allow us to differentiate between these two limiting mechanistic possibilities. Interestingly, much of the controversy regarding the role of the "spectator" chlorophyll in the bacterial photosynthetic reaction center is being framed in just these terms (explicit intermediate versus superexchange);[3-11] our model systems appear to be the first which bear directly on this issue.

Acknowledgment. This work is dedicated to the memory of the late Professor Iwao Tabushi. We thank the Welch Foundation, the Dreyfus Foundation (New Faculty Grant 1984), and the National Science Foundation (PYI Award, 1986) for financial support. We thank Prof. S. Webber for use of his fluorometer and the staff at the Center for Fast Kinetics Research at the University of Texas at Austin (an NIH supported shared user facility) for helping us to record fluorescence lifetimes. J.L.S. also thanks Profs. R. Friesner and T. Mallouk for helpful discussions and critical comments.

Supplementary Material Available: Characterization data for the free-base dimers **5** and **6**, proton NMR spectra for compounds **1**, **3**, and **5** and reference samples, and emission and absorption spectra for compounds **1-12** (8 pages). Ordering information is given on any current masthead page.

(28) Rapid exoergic intersubunit energy transfer has been observed in loosely linked monometalated dimers: (a) Schwarz, F. P.; Gouterman, M.; Muljiani, Z.; Dolphin, D. *Bioinorg. Chem.* **1972**, *2*, 1-32. (b) Anton, J. A.; Loach, P. A.; Govindjee *Photochem. Photobiol.* **1978**, *28*, 235-242. (c) Mialocq, J. C.; Giannotti, C.; Maillard, P.; Momenteau, M. *Chem. Phys. Lett.* **1984**, *112*, 87-93. (d) Brookfield, R. L.; Ellul, H.; Harriman, A.; Porter, G. *J. Chem. Soc., Faraday Trans. 2* **1986**, *82*, 219-233.

(29) Gouterman, M. In *The Porphyrins*; Dolphin, D., Ed.; Academic: New York, 1978; Vol. III, Chapter 1.

Reinterpretation of the Bicyclomycin-Sodium Methanethiolate Reaction

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Bicyclomycin (**1**) is a clinically useful antibiotic possessing a diverse spectrum of biological activity.[1] In recent years, several chemical hypotheses have been presented to account for the mode of action of this drug.[2-5] Unfortunately, no consensus of mechanism has emerged. In 1979, Iseki and co-workers reported that treatment of **1** with sodium methanethiolate at pH 12.5 led to a 1:1 adduct.[2a] The structure of this compound was assigned as the C(5a)-functionalized sulfide **2** on the basis of the observed ^{1}H NMR and mass spectral data. This finding led to the speculation that sulfhydryl groups present on bacterial inner-membrane proteins irreversibly bind with **1** at the exomethylene group. This result has served as the cornerstone for nearly all current notions concerning the mode of action of bicyclomycin. In this communication, we provide evidence that requires us to reinterpret the proposed structural assignment of the bicyclomycin-sodium methanethiolate adduct **2** and to suggest an alternative mechanism for the chemical activation of bicyclomycin under basic conditions.

Table I. ^{13}C NMR Data for Bicyclomycin Derived Compounds[a]

assignment	**1**	**3**[b]	**4**[c,d]	**2**[e]
C-1	89.46	89.73, 89.81	88.07, 88.21	89.35
C-3	65.50	68.76, 68.81	66.75, 66.95	62.17, 63.36
C-4	36.67	34.21, 34.29	29.86, 30.15[f]	33.18, 34.23
C-5	149.49	48.05	46.52, 46.63	52.10
C-5a	116.95	31.28, 31.37	29.52, 29.73[f]	30.06, 30.65
C-6	82.96	103.40	101.86, 102.01	83.71
C-7	172.52	173.13	169.39, 169.51	172.00[f]
C-9	168.74	175.37	171.84	168.71[f]
C-1′	72.23	80.63	78.85, 78.98	72.62, 72.73
C-2′	78.15	76.88, 76.97	74.77, 74.83	78.03
C-2′-CH_3	24.15	23.41, 23.45	23.56, 23.64	24.20
C-3′	68.42	78.04, 78.09	76.04, 76.14	68.55
other		15.38, 15.66	14.63, 14.72 25.14	15.63, 15.79

[a] The number in each entry is the chemical shift value (δ) observed in ppm relative to Me_4Si. All spectra were obtained at 75.5 MHz. The solvent used was CD_3OD unless otherwise indicated. [b] The NMR spectrum was consistent with the thiolate adducts existing as mixtures of at least two diastereomers present in an approximate 1.4:1 ratio based on comparison of comparable ^{13}C NMR signals. [c] The NMR spectrum was consistent with the thiolate adducts existing as a mixture of at least two diastereomers present in an approximate 1.7:1 ratio. [d] The solvent used was DMSO-d_6. [e] The NMR spectrum was consistent with the thiolate adducts existing as a mixture of two diastereomers present in an approximate 2.1:1 ratio. [f] These peaks may be interchanged.

Treatment of **1** with sodium methanethiolate (1-10 equiv) in aqueous base (pH 12.5) led to the isolation of a semisolid whose ^{1}H NMR spectrum (80 MHz) was virtually identical with the published spectrum of the 1:1 bicyclomycin-methanethiol product[2a] (see Supplementary Material). High resolution mass spectral analysis of the parent ion of this material[6] confirmed the proposed elemental composition ($C_{13}H_{22}N_2O_7S$). Inspection of both the ^{1}H and the ^{13}C NMR spectra indicated that the product mixture consisted of at least two diastereomers. Further analysis of the ^{1}H NMR spectrum (300 MHz) of this adduct revealed several additional features which were in conflict with the originally assigned structure **2**.[7] In particular, the C-3′ diastereotopic protons in the methanethiolate adduct were downfield (~0.26 ppm) from the corresponding protons in bicyclomycin, while the resonance for the C-1′ methine hydrogen was upfield (~0.23 ppm) from the same signal in **1**.[8] The chemical shifts of these protons should not have appreciably changed if the reaction of **1** had occurred exclusively at the exomethylene group in bicyclomycin. Our concerns were amplified upon examination of the ^{13}C NMR spectrum of the methanethiolate adduct (Table I). Comparison of this spectrum with the corresponding spectrum of bicyclomycin[8] showed that large downfield shifts for the C-1′ (8.40 ppm), C-3′ (~9.65 ppm), and C-6 (20.44 ppm) resonances had occurred.[9]

(1) (a) Tanaka, N. *Antibiotics (New York)* **1979**, *5*, 18. (b) Miyoshi, T.; Miyari, N.; Aoki, H.; Kohsaka, M.; Sakai, H.; Imaka, H. *J. Antibiot.* **1972**, *25*, 569. (c) Kamiya, T.; Maeno, S.; Hashimoto, M.; Mine, Y. *Ibid.* **1972**, *25*, 576. (d) Nishida, M.; Mine, Y.; Matsubara, T. *Ibid.* **1972**, *25*, 582. (e) Nishida, M.; Mine, Y.; Matsubara, T.; Goto, S.; Kuwahara, S. *Ibid.* **1972**, *25*, 594.

(2) (a) Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.* **1979**, *32*, 402. (b) Tanaka, N.; Iseki, M.; Miyoshi, T.; Aoki, M.; Imanaka, H. *Ibid.* **1976**, *29*, 155. (c) Someya, A.; Iseki, M.; Tanaka, N. *Ibid.* **1978**, *31*, 712.

(3) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Med. Chem.* **1985**, *28*, 733.

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(5) Pisabarro, A. G.; Canada, F. J.; Vasquez, D.; Arriaga, P.; Rodriguez-Tebar, A. *J. Antibiot.* **1986**, *34*, 914.

(6) Gaskell, S.; Reilly, M. H., unpublished results. Detailed information concerning the mass spectrum of this adduct will be reported elsewhere.

(7) Compound **3**: ^{1}H NMR (CD_3OD, 300 MHz) δ 1.33 (s, C_2-CH_3), 1.75-1.96 (m, C_4HH'), 2.07 (s, SCH_3), 2.22-2.35 (m, C_4HH'), 2.40-2.56 (m, C_5H, $C_{5a}HH'$), 2.80-2.95 (m, $C_{5a}HH'$), 3.83-4.00 (m, C_1·H, C_3·H_2, C_3HH'), 4.03-4.14 (m, C_3HH').

(8) For a comprehensive study of the NMR spectral properties of bicyclomycin, see: Kohn, H.; Abuzar, S.; Korp, J. D.; Zektzer, A.; Martin, G. E. *J. Heterocycl. Chem.*, in press.

(9) Similar chemical shift values were observed[10] for the triose carbon atoms in the bis-spiro products formed upon treatment of **1** with acid.[11]

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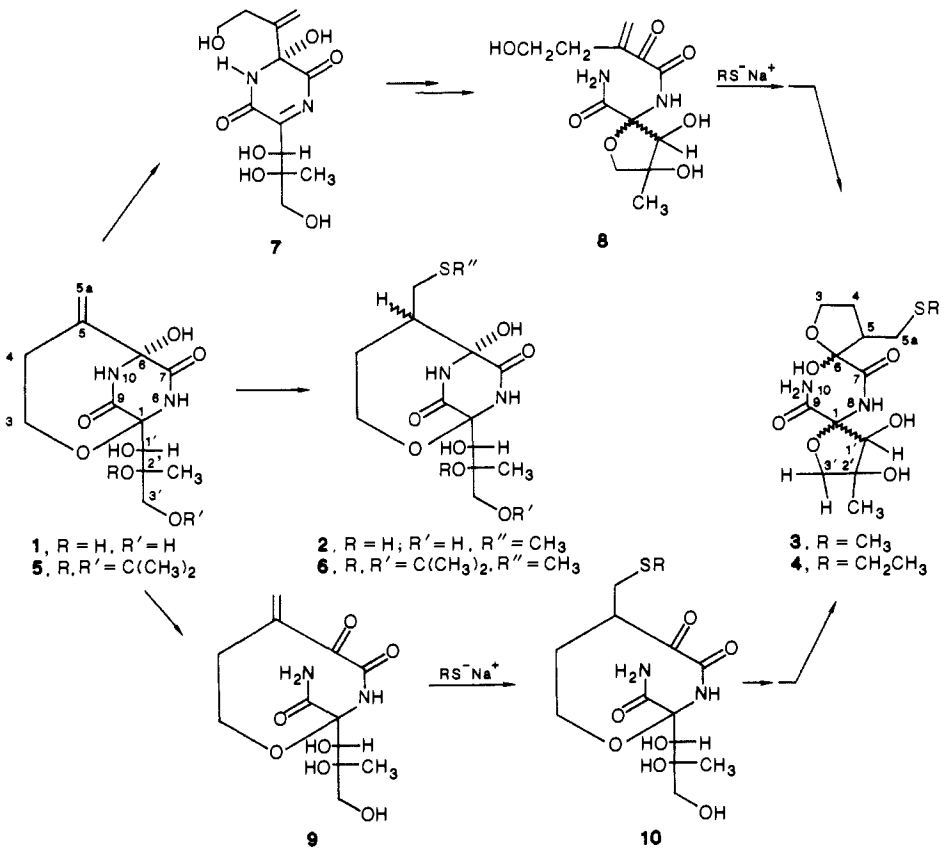
Scheme I



A comparable picture emerged upon inspection of the NMR spectra for the corresponding ethanethiolate adduct.[12]

What then is the structure of the methanethiolate- and ethanethiolate–bicyclomycin products? The results obtained from the ^1H, COSY, proton double quantum coherence,[13] ^{13}C, APT,[14] heteronuclear chemical shift correlation,[15] and long-range heteronuclear multiple quantum chemical shift correlation (HMBC)[16] NMR studies are in agreement with structures **3** and **4**, respectively.[17] Of critical importance in our analysis was the assignment of the peak located at 103.43 ppm in the ^{13}C NMR spectrum of the methanethiolate adduct to the hemiacetal carbon in **3**[19] and the observation of the key long-range connectivity patterns outlined in Figure 1 for **4** obtained in the heteronuclear multiple quantum chemical shift correlation NMR experiment.

Further verification of the proposed assignment of **3** was secured by preparing an authentic sample of **2**. Treatment of bicyclomycin with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid, (DMF, 80 °C, 1 h) furnished the known acetonide **5**,[20] which upon addition of sodium methanethiolate under the conditions prescribed by Williams and co-workers gave the 1:1 adduct **6** as a mixture of diastereomers.[4] Removal of the acetonide linkage with aqueous 50% acetic acid (60 °C, 30 min) afforded **2**.[21] The NMR spectral properties observed for this material, unlike those obtained from the direct reaction of bicyclomycin with sodium methanethiolate, were compatible with the 1:1 structural assignment **2**.

This structure revision permits us to consider the mechanism of the bicyclomycin chemical activation process. Several hypotheses are viable. Two of these are outlined in Scheme I. In both pathways, the reaction is envisioned to proceed through an α,β-unsaturated compound (i.e., **8** and **9**). They differ primarily in the sequence of the cleavage of the C(1)–O(2) aminal bond[11]

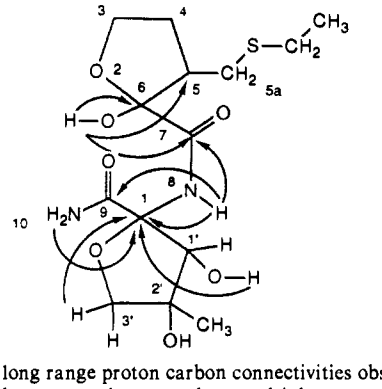


Figure 1. Select long range proton carbon connectivities observed in the proton detected long range heteronuclear multiple quantum chemical shift correlation (HMBC) experiment for **4**. Arrows denote observed connectivities and emanate from the proton and terminate at the carbon which exhibited the response.

(10) Abuzar, S.; Kohn, H., unpublished results.

(11) Maag, H.; Blount, J. F.; Coffen, D. L.; Steppe, T. V.; Wong, F. *J. Am. Chem. Soc.* **1978**, *100*, 6786.

(12) Compound **4**: ^1H NMR (CD_3OD, 300 MHz) δ 1.22 (t, J = 7.3 Hz, SCH_2CH_3), 1.32 (s, C_2-CH_3), 1.76–1.96 (m, C_4HH'), 2.18–2.32 (m, C_4HH'), 2.35–2.60 (m, C_5H, SCH_2CH_3, $C_{5a}HH'$), 2.85–2.98 (m, $C_{5a}CHH'$), 3.82–3.98 (m, C_1-H, C_3-H_2, C_3HH'), 4.03–4.12 (m, C_3HH').

(13) (a) Braunschweiler, L.; Bodenhausen, G.; Ernst, R. R. *Mol. Phys.* **1983**, *48*, 535. (b) Mareci, T. H.; Freeman, R. *J. Magn. Reson.* **1983**, *51*, 531. (c) Martin, G. E.; Sanduja, R.; Alam, M. *J. Org. Chem.* **1985**, *50*, 2383.

(14) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535 and references therein.

(15) Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 401.

(16) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

(17) A rearrangement in the bicyclomycin series involving cleavage of the hemiaminal bond of the piperazinedione ring has been previously reported.[18] Formation of a related product in this study has been ruled out on the basis of the observed NMR data.

(18) Wacker, O.; Kump, W.; Muller, B. W. *Tetrahedron Lett.* **1983**, *24*, 5607.

(19) For reports on the ^{13}C NMR chemical shift values for hemiacetal carbon atoms, see: (a) Wehrli, F. W.; Nishida, T. *Fortschritte der Chem. Org. Naturst.* **1978**, *36*, 1. (b) Sawhney, K. N.; Lemke, T. L. *J. Org. Chem.* **1983**, *48*, 4326.

(20) Kamiya, T.; Maeno, S.; Kitaura, Y. Belgium Patent 847 475.

(21) Compound **2**: ^1H NMR (CD_3OD, 300 MHz) δ 1.32 (s, C_2-CH_3), 2.05 (s, SCH_3), 2.02–2.42 (m, C_4H_2, C_5H, $C_{5a}HH'$), 3.02–3.15 (m, $C_{5a}HH'$), 3.52 (2 dd, J = 12.0 Hz, C_3HH'), 3.66 (d, J = 12.0 Hz, C_3HH'), 3.72–4.02 (m, C_3H_2), 4.03 (s, C_1-H).

and the addition of the thiolate to the activated form of bicyclomycin. Definitive information concerning the precise pathway of this transformation and its relevance to the biological process are still lacking. Investigations are currently in progress aimed at addressing both of these questions.

Acknowledgment. We thank the National Institutes of Health (GM37934) and the Robert A. Welch Foundation (E-607) for their generous support of our work. The National Science Foundation (CHE-8616352) is gratefully acknowledged for providing matching funds for the acquisition of a high field NMR spectrometer. We also express our appreciation to Dr. Gary Martin (College of Pharmacy) and Dr. Russell Geanangel of this Department for their help in the high field NMR studies and Drs. Simon Gaskell and Marc Reilly (Baylor College of Medicine) for their help in the mass spectral studies. Grateful acknowledgement is made to Dr. K. Inokuchi and the Fujisawa Pharmaceutical Co., Ltd., Japan for providing us with a gift of bicyclomycin.

Supplementary Material Available: ^{1}H NMR spectra (80, 300 MHz) for bicyclomycin–sodium methanethiolate adducts **2** and **3** and the proton detected long range heteronuclear multiple quantum chemical shift correlation (HMBC) NMR spectrum and a table of NMR correlations for **4** (6 pages). Ordering information is given on any current masthead page.

The First Cyclooctatetraene to Which Bond Shifting Is More Accessible Than Ring Inversion†

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A vast amount of kinetic and thermodynamic data makes clearly evident the fact that [8] annulenes experience mechanical tub-to-tub ring inversion (RI) more readily than alternation of their double bonds.[1] This has most often,[1,2] though not always,[3] been attributed to the added energy costs associated with a planar-delocalized 4n transition state during the π-bond shifting (BS) process. Only in the case of 1,2,3,4-tetramethylcyclooctatetraene do the values for $\Delta G^{\ddagger}_{BS}$ and $\Delta G^{\ddagger}_{RI}$ become equalized.[4] In this instance, the need to eclipse and buttress a contiguous array of methyl groups external to the annulene core outweighs and levels the customarily distinguishable energy demands imposed intraannularly.[5] We document herein the first example of a cyclooctatetraene which finds bond shifting to be the most kinetically accessible dynamic process available to it. Particular interest is attached to this finding because of its possible bearing on the long-standing mechanistic controversy surrounding the precise reaction profile for BS.

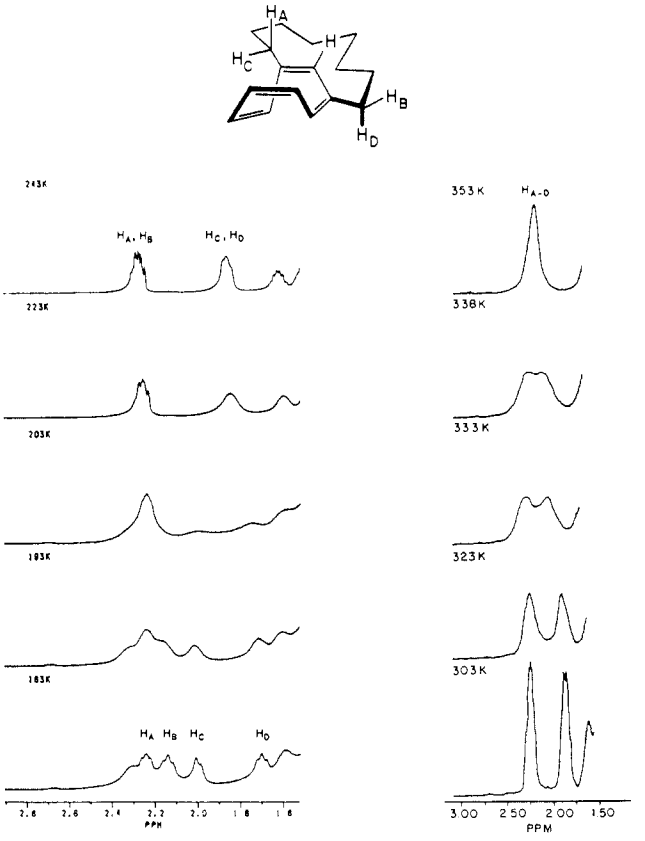
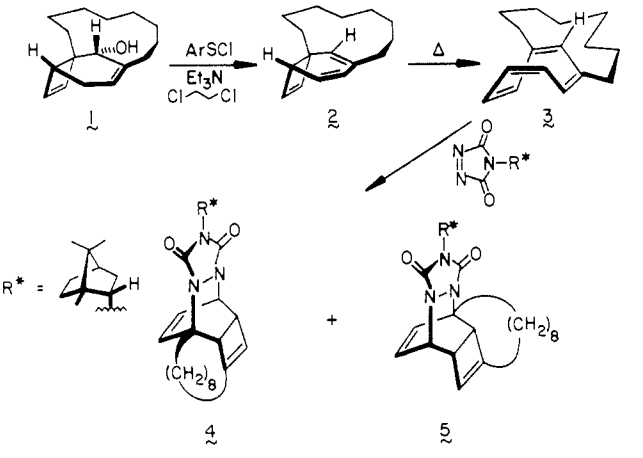


Figure 1. Variable temperature ^{1}H NMR spectra of the allylic protons in **3**: left panel, below room temperature (500 MHz, CD_2Cl_2 solution); right panel, above room temperature (300 MHz, toluene-d_8 solution).

Allylic alcohol **1**[6] is capable of being dehydrated at room temperature with 2,4-dinitrobenzenesulfenyl chloride and triethylamine in 1,2-dichloroethane.[7] The resulting bicyclo[4.2.0]octatriene (**2**)[8] is more stable than its homologues having longer methylene chains because of the necessity that the interior vinylic proton pass through the loop during disrotatory opening of the cyclohexadiene subunit. The $t_{1/2}$ for first-order isomerization of **2** to **3** at 30 °C is approximately 90 min.[9]



† Dedicated to Professor Melvin S. Newman on the occasion of his 80th birthday.

(1) (a) Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 671. (b) Anet, F. A. L.; Bourn, A. J. R.; Lin, Y. S. *Ibid.* **1964**, *86*, 3576. (c) Anet, F. A. L.; Bock, L. A. *Ibid.* **1968**, *90*, 7130. (d) Oth, J. F. M. *Pure Appl. Chem.* **1971**, *25*, 573. (e) Paquette, L. A. *Ibid.* **1982**, *54*, 987. (f) Maier, G.; Sayrac, T.; Kalinowski, H.-O.; Askani, R. *Chem. Ber.* **1982**, *115*, 2214. (g) Paquette, L. A.; Wang, T.-Z.; Cottrell, C. E. *J. Am. Chem. Soc.* **1987**, *109*, 3730 and relevant references cited in these papers.

(2) (a) Allinger, N. L. *J. Org. Chem.* **1962**, *27*, 443. (b) Snyder, L. C. *J. Chem. Phys.* **1962**, *66*, 2299. (c) Finder, C. J.; Chung, D.; Allinger, N. L. *Tetrahedron Lett.* **1972**, 4677. (d) Wipff, G.; Wahlgren, U.; Kochanski, E.; Lehn, J. M. *Chem. Phys. Lett.* **1971**, *11*, 350. (e) Allinger, N. L.; Sprague, J. T.; Finder, C. J. *Tetrahedron* **1973**, *29*, 2519.

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(4) Paquette, L. A.; Gardlik, J. M.; Johnson, L. K.; McCullough, K. J. *J. Am. Chem. Soc.* **1980**, *102*, 5026.

(5) (a) Gardlik, J. M.; Paquette, L. A.; Gleiter, R. *J. Am. Chem. Soc.* **1979**, *101*, 1617. (b) Paquette, L. A.; Gardlik, J. M. *Ibid.* **1980**, *102*, 5033.

(6) Wang, T.-Z.; Paquette, L. A. *Tetrahedron Lett.* **1988**, *29*, 41.

(7) (a) Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051. (b) Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1986**, *51*, 5232.

(8) All new compounds reported have been fully characterized by IR, ^{1}H/^{13}C NMR, and high resolution mass spectrometry and/or combustion analysis.

(9) Ring opening of the lower homologue of **2** having a $(CH_2)_7$ bridge proceeds yet more slowly and is conveniently amenable to kinetic analysis: $\Delta H^{\ddagger}_{25°C}$ = 24.4 kcal/mol, $\Delta S^{\ddagger}_{25°C}$ = 1.7 eu, $\Delta G^{\ddagger}_{25°C}$ = 23.9 kcal/mol, and E_a = 25.0 kcal/mol.

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