that binding (presumably initially reversible) to macromolecules is important, resulting in, for instance, triggering of a receptor or inhibition of an enzyme (as happens when fluorocitrate is added to the aconitase system). Geometrical constraints for ligand/macromolecule interactions are presumably much more stringent than the constraints on the crystal packing of small molecules, so that the weaker C-F··X interactions may become very significant.

Acknowledgment. We thank Dr. M. F. Richardson for helpful discussions. All ball-and-stick diagrams were drawn with the computer program VIEW.[66] This research was supported by Grants CA-10925, CA-22780, CA-06927, and RR-05539 from the National Institues of Health, BC-242 from the American Cancer Society, and an appropriation from the Commonwealth of Pennsylvania.

Registry No. 1, 85114-71-2.

Supplementary Material Available: Tables containing atomic parameters and anisotropic temperature factors, observed and calculated structure factors, fluorocitrate dimensions, literature on C-F··O contacts, and literature on C-F··N contacts (33 pages). Ordering information is given on any current masthead page.

Regioselective Functionalization of Bicyclic Piperazinedione Bridgehead Carbanions

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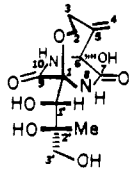
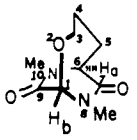
Abstract: Generation of the bridgehead carbanions of bicyclic piperazinediones **2** and **3** with LDA in THF at −78 °C (kinetic conditions) followed by quenching with various electrophiles results in mixtures of the two monosubstitution products **12** and **13** with relatively poor regiochemical control. Addition of HMPA to **2** and **3** followed by LDA treatment and addition of an electrophile significantly favors functionalization of the carbanion adjacent to the bridging methylene (product **12**). HMPA facilitates the interconversion of bridgehead anions **15** and **16** to produce a preponderance of the thermodynamically more stable carbanion **15**. This methodology provides a highly regioselective and efficient synthesis of the unsymmetrically substituted bicyclic piperazinediones.

As part of a program directed toward the total synthesis of the novel antibiotic bicyclomycin[1,2] (**1**) and the synthesis of analogues,



1



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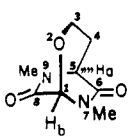


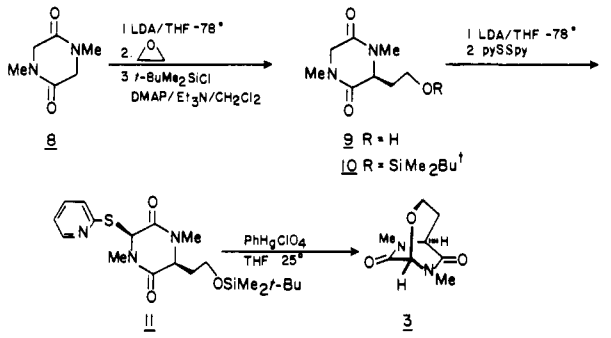
3

we have had the opportunity to study the interesting behavior of the bridgehead carbanions derived from bicyclic piperazinediones **2**[3] and **3**.

Our primary objectives in this area were to develop a rapid and efficient entry to the general bicyclomycin ring system with an inherently high degree of flexibility to allow the preparation of a wide variety of bicyclomycin analogues that would be valuable in elucidating the apparently unique mechanism of action of the natural product.

Several synthetic approaches to the bicyclomycin ring system have appeared,[3,4] yet no total synthesis has been achieved. Recently we reported[5] a short and efficient synthesis of bicyclic piperazinedione **2** and the regio- and stereocontrolled conversion of **2** into *N,N'*-dimethyl-4-desmethylenebicyclomycin via functionalization of the corresponding bridgehead carbanions. We have examined the reactivity of the bridgehead carbanions derived from model compounds **2** and **3** for several reasons. First, we

Scheme I



8 **9** R = H **10** R = $SiMe_2Bu^t$ **11** **3**

(1) (a) T. Miyoshi, N. Miyairi, H. Aoki, M. Kohsaka, H. Sakai, and H. Imanaka, *J. Antibiot.*, **25**, 569 (1972); (b) T. Kamiya, S. Maeno, M. Hashimoto, and Y. Mine, *ibid.*, **25**, 576 (1972); (c) M. Nishida, Y. Mine, T. Matsubara, S. Goto, and S. Kuwahara, *ibid.*, **25**, 582 (1972); (d) M. Nishida, Y. Mine, T. Matsubara, S. Goto, and S. Kuwahara, *ibid.*, **25**, 594 (1972).

(2) (a) S. Miyamura, N. Ogasawara, H. Otsuka, S. Miwayama, H. Tanaka, T. Take, T. Uchiyama, H. Ochiai, K. Abe, K. Koizumi, K. Asao, K. Matsuki, and T. Hosino, *J. Antibiot.*, **25**, 610 (1972); (b) S. Miyamura, N. Ogasawara, H. Otsuka, S. Niwayama, H. Tanaka, T. Take, T. Uchiyama, and H. Ochiai, *ibid.*, **26**, 479 (1973).

(3) R. M. Williams, *Tetrahedron Lett.*, **22**, 2341 (1981).

(4) (a) H. Maag, J. F. Blount, D. L. Coffen, T. V. Steppe, and F. Wong, *J. Am. Chem. Soc.*, **100**, 6786 (1978); (b) H. Maag, 2nd Chemical Congress of the North American Continent, Division of Organic Chemistry, Las Vegas, Nevada, Aug 1980; Abstr. 347; (c) L. V. Dunkerton and R. W. Ahmed, *Tetrahedron Lett.*, **21**, 1803 (1980); (d) S. Nakatsuka, K. Yoshida, and T. Goto, *ibid.*, **22**, 2009 (1981); (e) C. Shin, Y. Sato, and J. Yoshimura, *ibid.*, **22**, 2401 (1981); (f) T. Fukuyama, B. D. Robins, and R. A. Sachleben, ibid., **22**, 4155 (1981); (g) J. H. Hoare and P. Yates, *J. Chem. Soc., Chem. Comm.*, 1126 (1981); (h) S. Nakatsuka, K. Yoshida, and T. Goto, *Tetrahedron Lett.*, **22**, 4973 (1981).

(5) R. M. Williams, O. P. Anderson, R. Armstrong, J. Josey, H. Meyers, and C. Eriksson, *J. Am. Chem. Soc.*, **104**, 6092 (1982); see also; 183rd National ACS Meeting, Division of Organic Chemistry, Las Vegas, Nevada, Mar 1982; Abstr. 17.

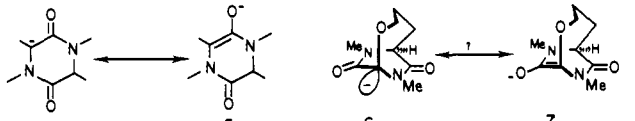
0002-7863/83/1505-3214$01.50/0

Table I

entry	substrate	electrophile	reaction time[b]	12, %	13, %	14, %
1	2	H_3COD[a]	1 min	1	53	7
2	2	H_3CI[a]	1 min, −115 °C	19	43	22
3	**3**	H_3COD[a]	5 min	28	11	11
4	2	PhCOCl[a]	1 min	50	41	
5	2	PhCOCl[a]	1 h	49	27	
6	3	H_3CI[a]	1 h	60	25	
7	2	PhCHO[a]	1 min	45	47	
8	2	PhCHO[a]	1 h	40	26	
9	2	H_3CI	1 h	74	3	5
10	2	PhCOCl	1 h	92	2.6	
11	2	Me_3SiCl	1 h	66.5[c] 53.3		
12	2	MeSSMe	1 h	80.5[c] 72	6	
13	2	MoOPh[d]	1 min	65		
14	2	PhCHO	1 h	82.1	10.5	
15	2	$BrCH_2CH=CH_2$	1 h	67	1	
16	**3**	Me_3SiCl	1 h	65.6		22
17	**3**	H_3CI	1 h	75.1[c] 40.3		16[c] 8.6
18	3	$BrCH_2CH=CH_2$	1 h	83		
19	**3**	PhCOCl	1 h	82[c] 44.3		
20	**3**	MeSSMe	1 h	66[c] 33		33[c] 16

[a] These reactions were carried out with LDA in THF at −78 °C without HMPA. All other entries in the table were done with HMPA (see Experimental Section). [b] Reaction time refers to the time the anion was stirred at −78 °C before addition of the electrophile. [c] Yield is based on recovered starting material. [d] See ref 5 for experimental procedure.

recognized the potential of the bicyclic 1,6-*unsubstituted* piperazinediones such as **2** as versatile intermediates for the preparation of structurally diverse bicyclomycin analogues that are not possible to prepare by degradation[6] of the readily available natural product or from the other synthetic approaches.[4] Second, the bridgehead methine protons of **2** and **3** are each in very similar *steric* environments, and these simple systems seemed ideally suited for examining the fundamental nature of *electronic* (O vs. CH_2) influences on the kinetic and thermodynamic acidity of the bridgehead protons. Additionally, unlike the carbanions derived from monocyclic piperazinediones (**4**) in which overlap of the



4 **5** **6** **7**

carbanion with the amide carbonyl (**5**) is geometrically favorable and considered important for stabilization, the question as to whether the bridgehead carbanions of bicyclic piperazinediones could participate in enolate-type resonance (i.e., **6** ↔ **7**) intrigued us, since such "enolate" structures (**7**) would be in violation of Bredt's rule.

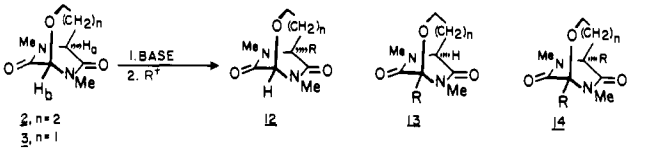
In this paper we report the reaction of carbanions derived from **2** and **3** with a variety of electrophiles and examine factors affecting regiocontrol that are of practical importance and theoretical significance.

Results and Dicussion

Bicyclic piperazinedione **2** was prepared as described elsewhere.[5] The homologue **3** was prepared along similar lines in 33% overall yield from sarcosine anhydride as shown in Scheme I.

Piperazinediones **2** and **3** were treated with base (typically LDA) at low temperature and the anions generated were quenched with various electrophiles 1 min and 1 h after metalations. The two monoderivatized regioisomers (**12** and **13**) along with (in most cases) the difunctionalized compounds (**14**) were separated by prepative layer chromatography. The results are shown in Table I (Scheme II).

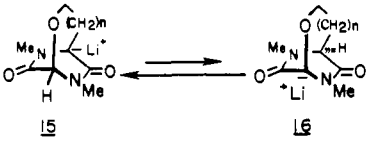
Scheme II



2, n = 2
3, n = 1

12 **13** **14**

We have observed that generation of the carbanions derived from **2** and **3** with LDA in THF at low temperature followed by quenching with an electrophile gives a mixture of **12**, **13**, and **14** with relatively poor regiochemical control. Under these conditions, rapid quenching of the carbanions generated from abstraction of the bridgehead protons H_a and H_b indicate that the *kinetic acidity* of H_a and H_b in both **2** and **3** are similar, H_b being kinetically more acidic than H_a for **2** (Table I, entires 1, 2, 4, 7) and H_a apparently being kinetically more acidic than H_b for **3** (Table I, entry 3). When the anion was allowed to stir for 1 h at −78 °C and then quenched with an electrophile, an increase in the proportion of product **12** over **13** resulted (Table I, entries 5, 6, 8). Although the ratios obtained under these conditions were not useful from a synthetic standpoint, these results indicate that the bridgehead carbanions (**15** and **16**) slowly equilibrate, favoring



15 **16**

the *thermodynamically more stable carbanion* **15**. From these observations, it is possible that the "rapid" (1 min) quench of **3** with H_3COD does not represent an accurate "kinetic" quench since the initially formed carbanion may equilibrate much more rapidly than that derived from **2** and partial equilibration during quenching is not an uncommon phenomenon.[7] Thus, it is possible that H_b is also the kinetically most acidic proton for both **2** and **3**, but we were not able to obtain kinetic control in the case of **3**.

We have measured the $J(^{13}C-H)$ of the bridgehead positions for both **2** and **3** (Table II). The relative magnitude of the C–H

(6) For the preparation of semisynthetic bicyclomycin analogues, see; B. W. Müller, O. Zak, W. Kump, W. Tosch, and O. Wacker, *J. Antibiot.*, **32**, 402 (1979).

(7) A. G. Abatjoglou, E. L. Eliel, and L. F. Kuyper, *J. Am. Chem. Soc.*, **99**, 8262 (1977).

Table II. ^{13}C NMR Data for Compounds 2 and 3 ($CDCl_3$ 90.54 MHz, δ $CDCl_3$)

2				3			
carbon	ppm[a]	multiplicity[b]	J, Hz[c]	carbon	ppm[a]	multiplicity[b]	J, Hz[c]
C-1	84.66	d	167.9	C-1	87.06	d	169.12
C-3	63.82	t		C-3	62.17	t	
C-4	31.41	t		C-4	28.07	t	
C-5	25.16	t		C-5	60.69	d	150.88
C-6	61.12	d	143.9	C-6	164.9	s	
C-7	164.6	s		N_7-CH_3	32.23	q	
N_8-CH_3	31.63	q		C-8	170.8	s	
C-9	169.7	s		N_9-CH_3	31.99	q	
N_{10}-CH_3	31.63	q					

[a] The chemical shifts of each carbon atom were determined from a noise-decoupled ^{13}C NMR spectrum. [b] The multiplicities of each signal were determined by an off-resonance ^{13}C NMR spectrum. [c] The $J(^{13}C-H)$ were obtained from a fully coupled ^{13}C-H NMR spectrum.

Table III. Effect of HMPA on the Regioselectivity of Bridgehead Anion Functionalization

entry	base[b]	time	HMPA, equiv	ratio of products[a] 12	13
1	LDA/THF	1 h	0	1–2	1
2	LDA/THF	1 h	0.1	3	1
3	LDA/THF	1 h	0.9	5	1
4	LDA/THF	1 h	3.0	10	1
5	LDA/THF	1 h	5.0	>25	1
6	LDA/THF	0.5 min	5.0	1.67	1

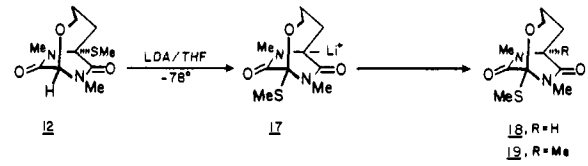
[a] The electrophiles used in this study were CH_3I and CH_3SSCH_3 and the substrate was 2. [b] At −78 °C.

coupling has been correlated[8a,b] to the amount of s character in the C–H bond and has been used as a measure of relative kinetic acidities. As can be seen from Table II, the bridgehead ^{13}C–H coupling constants for the methines adjacent to the bridging oxygen atom are 24 and 18 Hz larger than the $J(^{13}C-H)$ of the methines adjacent to the bridging methylene for both **2** and **3**, respectively. Our experimental results for the kinetic quenching of the carbanion derived from **2** agree with the $J(^{13}C-H)$ correlation and, as discussed above, accurate kinetic quenching for **3** was not obtained. More significantly, the magnitude of these coupling constants (144–169 Hz) indicates[8b] considerable s character in these C–H bonds (~29–33% s). This hybridization effect may be largely responsible for the acidity of these protons in the absence of the geometrically unlikely enolate resonance stabilization.

In the hope of exploiting the apparently greater *thermodynamic acidity* of H_a, we have found that addition of HMPA dramatically increases the proportion of product **12** over that of **13** to where ratios of >20–30:1 can be obtained with a wide variety of electrophiles (Table I and Table III). Table III shows the effects of increasing amounts of HMPA on the relative proportions of regioisomers **12** and **13** produced from electrophilic quenching of the monoanions derived from **2** and **3**. These ratios should accurately reflect the equilibrium concentrations of the monoanions **15** and **16** (1 h quench, Table III, entries 1–5) present during the quenching step, since the product ratio was dependent on the amount of time the carbanion was allowed to stir prior to quenching (Table III; compare entries 5 and 6). Specifically, reaction of **2** with 5 equiv of HMPA in THF with LDA for 30 s followed by methyl iodide quench produced a 1.67:1 ratio of **12** and **13**, respectively. Identical conditions with the exception of allowing the anion to stir 1 h prior to methyl iodide quench produced a 25:1 ratio of **12**:**13**! These results clearly indicate that HMPA facilitates the formation of the more stable species **15**.

Since both H_a and H_b are in very similar steric environments, the difference in the stability of the bridgehead carbanions can be directly attributed to the *electronic effect* of a methylene group (for H_a) vs. an ether-type oxygen atom (for H_b), the piperazinedione moiety being identical for both H_a and H_b. Calculations of Lehn[9] indicate a 10–15 kcal/mol stabilization effect of an oxygen atom vs. a CH_2 group adjacent to an sp^3 hybridized carbanion, this stabilization being ascribed to the greater electronegativity of the oxygen atom. Such calculations apply to the gas phase and do not include the effect of solvents, however. On the other hand, Hine[10] has shown the *destabilizing* effect of oxygen atoms adjacent to sp^2-hybridized carbanions, this effect being ascribed to electron pair–electron pair repulsions. Although the structures and corresponding hybridization of the bridgehead anions have not been established, it would seem likely that they are predominantly pyramidal due to the geometric constraints[11] imposed by the bicyclic ring structure, this being particularly compelling in the case of **3**. On the basis of our data, it seems clear that in both cases the bridging oxygen atom exerts a net *destabilizing effect* on the adjacent bridgehead anion, presumably through electrostatic repulsion. Separation of the Li^+–carbanion ion pair by HMPA should increase the electron density on the piperazinedione substrate, enhancing the repulsive interactions between the bridging-oxygen lone pairs and the C-1 lone pair (**16**). If this effect is to raise the relative ground-state energy of **16** over that of **15**, one would expect the thermodynamic equilibrium to greatly favor **15**; our data (Table I, entries 9–20; Table III) support this hypothesis.

Scheme III



Additional evidence for the thermodynamic stability of carbanion **15** relative to **16** was obtained from the following, rather unexpected observation. When the thiomethyl derivative **12** (n = 2, R = SCH_3) was treated with LDA and quenched with methanol, compound **12** rearranged[12] to the regioisomer **18** (90% yield, Scheme III). The intermediate anion **17** could also be trapped with methyl iodide to furnish **19**, the regiochemistry of which was unambiguously established by Raney nickel removal of the sulfur to provide **12** (n = 2, R = CH_3). These results, together with the HMPA studies, unambiguously establish the thermodynamic stability of the carbanion adjacent to the bridging

(8) (a) A. Streitweiser, Jr., R. A. Caldwell, and W. R. Young, *J. Am. Chem. Soc.*, **91**, 529 (1969); (b) R. D. Bertrand, D. M. Grant, E. L. Allred, J. C. Hinshaw, and A. Brent Strong, *ibid.*, **94**, 997 (1972).

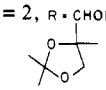
(9) J.-M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, **98**, 7498 (1976).

(10) J. Hine and P. D. Dalsin, *J. Am. Chem. Soc.*, **94**, 6998 (1972).

(11) The olefin strain energies (OS) of the "parent" hydrocarbons bicyclo[4.2.2]dec-1-ene and bicyclo[3.2.2]non-1-ene corresponding to the "enolate" structures of **2** and **3** have been calculated to be 7.9 and 20.6 kcal/mol, respectively (W. F. Maier and P. von R. Schleyer, *J. Am. Chem. Soc.*, **103**, 1891 (1981)). From these values, a bridgehead olefinic structure corresponding to the enolate of **2** should be isolable and that for **3** should be unstable; the extra rigidity of the piperazinedione amides, however, should make the actual strain energies of **2** and **3** considerably higher than that calculated for the parent hydrocarbons.

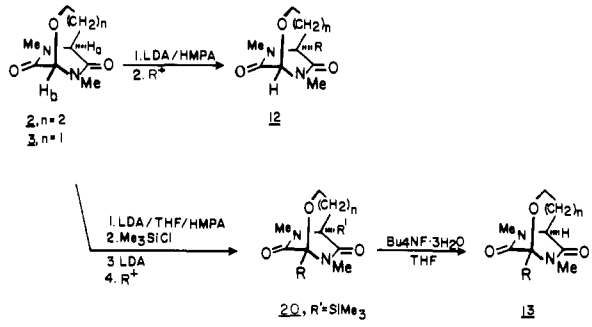
(12) The mechanism of this interesting trans sulfenylation is not clear at the present time and is under investigation in these laboratories.

Table IV. Regioselective Syntheses of 13

entry	substrate	electrophile	product	yield, %
1	**12**, $n = 1$, R = $SiMe_3$	CH_3I	**13**, $n = 1$, R = CH_3	59 (93[a])
2	2	CH_3I	**13**, $n = 2$, R = CH_3	56[b]
3	2		**13**, $n = 2$, R = 	80[b]
4	**12**, $n = 1$, R = $SiMe_3$	$BrCH_2CH{=}CH_2$	**13**, $n = 1$, R = $CH_2CH{=}CH_2$	46 (52[a])

[a] Yield is based on recovered starting material. [b] The product **13** was directly obtained from 2 by a three-step, one-pot procedure.

Scheme IV



methylene over that of the carbanion adjacent to the bridging oxygen atom.

Since the addition of HMPA to the carbanions permits the regioselective synthesis of isomers **12**, we also desired to establish a regiocontrolled route to the isomers **13**. The most convenient involved preparation of trimethylsilyl derivatives **12** by the method described above. Formation of the bridgehead carbanions followed by quenching with an electrophile furnished the fully substituted derivatives **20**. The silyl group can thus be removed cleanly with tetra-*n*-butylammonium fluoride to afford the regiochemically pure isomers **13** (Table IV). Thus the simple unsubstituted bicyclic piperazinediones **2** and **3** can be regioselectively converted into either monoderivatized product **12** or **13** by efficient one-pot procedures. These monosubstitution products each, in turn, can be converted into the unsymmetrical disubstituted derivatives (eg., **20**) via functionalization of the remaining bridgehead position.

As summarized in Scheme IV, the methodology described herein offers a flexible and versatile means for preparing a large number of structurally diverse bicyclomycin analogues that should be useful in establishing the realm of biomechanistic and pharmacological potentialities of a structurally unique class of antibiotics represented by **1**. Other synthetic, mechanistic, and biological studies along these lines are in progress and shall be reported in due course.

Experimental Section

^1H NMR spectra were obtained on a Varian EM-360 (60 MHz), JEOL FX-100 (100 MHz), or Nicolet (360 MHz) spectrometers in $CDCl_3$ unless otherwise stated and are reported in δ values. Melting points were recorded on a Mel-Temp instrument in open capillaries and are uncorrected. Infrared spectra were recorded on a Beckman 4240 spectrophotometer and are reported as γ_{max} in cm^{-1}. Mass spectra were determined on a VGMM16F GC–MS instrument.

Thin-layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silica gel glass plates (60F-254) by using 5% phosphomolybdic acid in ethanol-heat and/or UV light as developing agent. Preparative layer chromatography was carried out on a Harrison Res. Chromatotron using 1.0-, 2.0-, or 4.0-mm layer thickness silica gel adsorbents. Flash chromatography was performed by using E. Merck silica gel 60 (230–400 mesh).

All reactions were carried out under a nitrogen atmosphere by using dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. NMR multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant in Hz. The chemical shifts of protons part of an AB quartet ($^1/_2$AB q) was calculated by using a standard weighting formula.

The following abbreviations are used throughout this section: THF = tetrahydrofuran, HMPA = hexamethylphosphoramide, Et_2O = diethyl ether, EtOAc = ethyl acetate, MeOH = methanol, LDA = lithium diisopropylamide, Me_4Si = tetramethylsilane, EtOH = ethanol, and MoOPh = oxodiperoxymolybdenum (hexamethylphosphoric triamide) (pyridine).

Microanalyses were performed by MHW laboratories and are within ±0.3% of the calculated values.

1,4-Dimethyl-3-(2-hydroxyethyl)-2,5-piperazinedione (9). To a stirred solution of sarcosine anhydride (2.577 g, 17.5 mmol, 1.0 equiv) in THF (60 mL) at −78 °C was added LDA (17.5 mmol, 1.0 equiv) in THF (10 mL). After the enolate was stirred 10 min at −78 °C ethylene oxide (excess) was added via cannula. The mixture was stirred for 20 min at −78 °C, allowed to warm to room temperature, and stirred an additional 4 h. The mixture was diluted with CH_2Cl_2, 1 N HCl in MeOH (26.25 mL, 1.5 equiv) was added, and the mixture was evaporated to dryness. The residue was separated on flash column silica gel (eluted with 10% MeOH in CH_2Cl_2) to afford 2.55 g (76%, 79% based on recovered starting material) of the alcohol (**9**); mp 98–99 °C (recrystallized from EtOAc/hexanes).

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.7–2.18 (2 H, m), 2.27 (1 H, m, D_2O exchange), 2.93 (3 H, s), 2.95 (3 H, s), 3.7–4.2 (5 H, m); IR (NaCl, neat) 3400 (br), 1650, 1485, 1400, 1335, 1255, 1060, 1045 cm^{-1}; mass spectrum, *m/e* 186 (M^+, 58.4%), 155 (44.1), 142 (50.7), 141 (32.6), 113 (57.1), 44 (100). Anal. ($C_8H_{14}N_2O_3$) C, H, N.

1,4-Dimethyl-3-[2-((*tert*-butyldimethylsilyl)oxy)ethyl]-2,5-piperazinedione (10). To a stirred solution of alcohol **9** (552 mg, 2.97 mmol, 1.0 equiv) and *tert*-butyldimethylsilyl chloride (492 mg, 3.27 mmol, 1.0 equiv) in dry CH_2Cl_2 (20 mL) at 25 °C was added 4-(dimethylamino)pyridine (36.3 mg, 0.3 mmol, 0.1 equiv). The solution was cooled to 0 °C and Et_3N (0.5 mL, 3.56 mmol, 1.2 equiv) was added. After the addition was complete, the cooling bath was removed and stirring continued for 72 h at room temperature. The mixture was diluted with CH_2Cl_2, poured into 0.1 N HCl, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 878 mg of the pure silyl ether **10** (98%); mp 56–58 °C (recrystallized from hexanes).

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 0.02 (6 H, s), 0.845 (9 H, s), 2.03 (2 H, m), 2.91 (3 H, s), 2.93 (3 H, s), 3.66 (2 H, d, d, *J* = 6.35 Hz, *J* = 5.12 Hz), 3.78 (1 H, $^1/_2$AB q, *J* = 17.1 Hz), 3.99 (1 H, t, *J* = 4.6 Hz), 4.05 (1 H, $^1/_2$AB q, *J* = 17.1 Hz); IR (NaCl, neat) 1660, 1640, 1485, 1408, 1398, 1325, 1255, 1243, 1045, 828, 780 cm^{-1}; mass spectrum, *m/e* 300 (M^+, 3.9%), 285 ($M^+ - CH_3$, 4%), 243 ($M^+ - C_4H_9$, 86.5%). Anal. ($C_{14}H_{28}N_2O_3Si$) C, H, N.

1,4-Dimethyl-3-[2-((*tert*-butyldimethylsilyl)oxy)ethyl]-6-(2-pyridylthio)-2,5-piperazinedione (11). To a stirred solution of **10** (630 mg, 2.07 mmol, 1.0 equiv) in THF (8 mL) at −78 °C was added a solution of LDA (2.48 mmol, 1.2 equiv) in THF (3 mL). The enolate solution was stirred 5 min at −78 °C and transferred via cannula into a solution of 2,2′-dipyridyl disulfide (684 mg, 3.1 mmol, 1.5 equiv) in THF (4 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C, allowed to warm to room temperature, diluted with CH_2Cl_2, poured into H_2O, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 10% acetone in Et_2O) to afford the sulfide **11** (542 mg, 63%); mp 109.5–111.5 °C (recrystallized from Et_2O/hexanes).

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 0.07 (3 H, s), 0.09 (3 H, s), 0.89 (9 H, s), 2.0–2.14 (2 H, m), 2.98 (3 H, s), 3.02 (3 H, s), 3.71–3.86 (2 H, m), 4.07 (1 H, t, *J* = 6.6 Hz), 6.56 (1 H, s), 6.99–7.15 (2 H, m), 7.45–7.62 (1 H, m), 8.45 (1 H, m); IR (NaCl, neat) 1670, 1570, 1445, 1415, 1250, 1100, 830, 755 cm^{-1}; mass spectrum, *m/e* 409 (M^+, 7.2%), 352 (1.8), 2.99 (29.6), 241 (90.6), 141 (100). Anal. ($C_{19}H_{31}N_3O_3SiS$) C, H, N, S.

7,9-Dimethyl-7,9-diaza-2-oxabicyclo[3.2.2]nonane-6,8-dione (3). A solution of phenylmercuric perchlorate was prepared in situ as follows: Phenylmercuric chloride (1.51 g, 4.83 mmol, 2.1 equiv) was dissolved in THF (25 mL), and $AgClO_4$ (1.00 g, 4.83 mmol, 2.1 equiv) was added in one portion. The mixture was vigorously stirred under nitrogen for 15 min and the white precipitate of AgCl was allowed to settle. The

supernatant was transferred via syringe into a stirred solution of piperazinedione **11** (944.4 mg, 2.3 mmol, 1.0 equiv) in THF (50 mL). The mixture was stirred vigorously for 20 min at room temperature, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 50% acetone in Et_2O) to afford 287.5 mg (68%) of pure, crystalline bicyclic **3**; mp 162.5–164 °C (recrystallized from CH_2Cl_2/hexanes).

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.95–2.11 (2 H, m), 2.99 (3 H, s), 3.00 (3 H, s), 3.86 (3 H, m), 4.92 (1 H, s); IR (NaCl, neat) 1680, 1470, 1390, 1290, 1055, 980, 790 cm^{-1}; mass spectrum, *m/e* 184 (M^+, 40%), 156 (13.6), 127 (43.3), 42 (100). Anal. ($C_8H_{12}N_2O_3$) C, H, N.

General Procedure for Bridgehead Carbanion Functionalization. A stirred solution of the bicyclic piperazinedione (**2** or **3**) (~0.05 M in THF, 1.0 equiv) containing HMPA (10 mol % or 3 equiv) was cooled to −78 °C. A 0.1 M solution of LDA (1.3 equiv) in THF (prepared at 0 °C, 5 min) was added dropwise via syringe. The solution was allowed to stir for 1 h at −78 °C and then quenched by addition of the appropriate electrophile (5 equiv) via syringe. After the addition was complete, the mixture was allowed to come to room temperature, diluted with CH_2Cl_2, poured into saturated NaCl solution, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated by preparative thin-layer chromatography on silica gel. Solvent systems for separations are given with the reaction scale and spectral data for each compound.

The carbanions quenched with CH_3OD were analyzed by integration of the ^1H NMR spectrum and mass spectral analysis of the deuterated product (isolated as described above); the average of the ^1H NMR and MS determinations are reported in the table and are within ±5%.

6,8,10-Trimethyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (12, *n* = 2, R = CH_3; Table I, Entry 9) (Oil). From 25.8 mg (0.13 mmol) of **2** was obtained 20.4 mg (0.096 mmol, 74%) of product (chromatographed on PTLC silica gel with 50% acetone in ether); 0.9 mg (0.004 mmol, 3%) of regioisomer **13** and 1.5 mg (0.006 mmol, 5%) of dialkylated **14** were also obtained.

^1H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.65 (3 H, s), 1.64–1.78 (2 H, m), 1.9–2.1 (2 H, m), 2.98 (3 H, s), 3.03 (3 H, s), 3.3–3.8 (2 H, m), 5.14 (1 H, s); IR (NaCl, neat) 1670, 1455, 1425, 1390, 1310, 1240, 1155 cm^{-1}; mass spectrum, *m/e* 212 (M^+, 2.22%), 170 (47.9), 154 (1.9), 56 (100).

1,8,10-Trimethyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (**13**, *n* = 2, R = CH_3; Table I, Entry 9) (Oil). ^1H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.65–2.17 (4 H, m), 1.76 (3 H, s), 2.98 (3 H, s), 3.02 (3 H, s), 3.03–4.07 (3 H, m); IR (NaCl, neat) 1670, 1450, 1420, 1385 cm^{-1}; mass spectrum, *m/e* 212 (M^+, 14.82%), 154 (19.32), 126 (53.92), 56 (100).

1,6,8,10-Tetramethyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (**14**, *n* = 2, R = CH_3; Table I, Entry 9) (Oil). ^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.6–2.03 (4 H, m), 1.63 (3 H, s), 1.75 (3 H, s), 2.96 (3 H, s), 3.01 (3 H, s), 3.3–3.7 (2 H, m); IR (NaCl, neat) 1655, 1450, 1415, 1385, 1250, 1145, 1090, 1070, 1035, 745, 725 cm^{-1}; mass spectrum, *m/e* 226 (M^+, 5.0%), 211 (1.5), 198 (5.7), 168 (33), 140 (52), 56 (100).

8,10-Dimethyl-8,10-diaza-6-(methylthio)-2-oxabicyclo[4.2.2]decane-7,9-dione (12, *n* = 2; Table I, Entry 12). mp 160–161 °C (recrystallized from $CHCl_2$/hexanes). From 27.1 mg (0.13 mmol) of **2** was obtained 24 mg (0.1 mmol, 72%, 80.5% based on recovered **2**) of product (chromatographed on PTLC silica gel with 33% acetone in Et_2O); 2 mg (6%) of regioisomer **13** and 2.9 mg (10.7%) of unreacted **2** were also obtained.

^1H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.63–2.21 (4 H, m), 1.96 (3 H, s), 3.09 (3 H, s), 3.19 (3 H, s), 3.19–3.83 (2 H, m), 5.13 (1 H, s); IR (NaCl, neat) 1670, 1425, 1390, 1305, 1240, 1060, 910, 730 cm^{-1}; mass spectrum, *m/e* 244 (M^+, 4.6%), 197 (100), 169 (21.3), 141 (42.5). Anal. ($C_{10}H_{16}N_2O_3S$) C, H, N, S.

8,10-Dimethyl-8,10-diaza-1-(methylthio)-2-oxabicyclo[4.2.2]decane-7,9-dione (**13**, *n* = 2, R = SCH_3; Table I, Entry 12) (Oil). ^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.6–2.2 (4 H, m), 2.05 (3 H, s), 3.02 (3 H, s), 3.24 (3 H, s), 3.4–4.12 (3 H, m); IR (NaCl, neat) 1675, 1460, 1395, 1380, 1250, 1110, 1095, 1075, 1060, 1035, 735 cm^{-1}; mass spectrum, *m/e* 244 (M^+, 4.9%), 198 (45.2), 186 (2.7), 172 (52.4), 58 (66.8), 43 (100).

8,10-Dimethyl-8,10-diaza-6-(hydroxybenzyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (12, *n* = 2, R = CHOHPh; Table I, Entry 14). mp 156–157 °C (recrystallized from Et_2O/hexanes/CH_2Cl_2) (major diastereoisomer). From 29.2 mg (0.14 mmol) of **2**, 36.8 mg (0.12 mmol, 82.1%) of product was obtained. This was a 2:1 mixture of diastereoisomers, which were separated on PTLC silica gel (eluted with 20% acetone in Et_2O); 4.7 mg (10.5%) of regioisomers **13** was also obtained.

Major diastereoisomer (**12**): ^1H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.73–2.67 (4 H, m), 2.97 (3 H, s), 3.05 (3 H, s), 3.13 (1 H, d, *J* = 5.6 Hz, D_2O exchange), 3.4–3.73 (3 H, m), 5.05 (1 H, s), 5.96 (1 H, d, *J* = 5.6 Hz), 7.3 (5 H, m); IR (NaCl, neat) 3320, 1675, 1660, 1460, 1410, 1330, 1270, 1250, 1115, 1100, 1075, 1060, 745 cm^{-1}; mass spectrum, *m/e* 198 (100%), 169 (30.8), 141 (18.3), 105 (29.3). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

Minor diastereoisomer (**12**): ^1H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.53–2.79 (4 H, m), 2.92 (3 H, s), 3.02 (3 H, s), 4.91 (1 H, d, *J* = 11.47 Hz), 5.16 (1 H, s), 5.73 (1 H, d, *J* = 11.47 Hz, D_2O exchange), 7.31 (5 H, s); IR (NaCl, neat) 3420, 1690, 1670, 1415, 1280, 1075, 1060, 750 cm^{-1}; mass spectrum, *m/e* 198 (100%), 169 (31.4), 141 (18.8), 105 (20.5).

8,10-Dimethyl-8,10-diaza-1-(hydroxybenzyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (**13**, *n* = 2, R = CHOHPh; Table I, Entry 14). mp 200–201 °C (recrystallized from Et_2O/hexanes/CH_2Cl_2). ^1H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.8–2.2 (4 H, m), 2.94 (3 H, s), 3.04 (3 H, s), 3.34 (1 H, broad s, D_2O exchange), 3.05–4.13 (3 H, m), 6.11 (1 H, broad s), 7.3 (5 H, m); IR (NaCl, neat) 3440 (broad), 1690, 1470, 1415, 1080, 1065, 750, 720 cm^{-1}; mass spectrum, *m/e* 304 (M^+, 10.6%), 286 (1.9), 198 (17.1), 141 (17), 105 (100). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

^1H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.78–2.17 (4 H, m), 2.93 (3 H, s), 2.98 (3 H, s), 3.3–4.07 (3 H, m), 5.18 (1 H, d, *J* = 10.26 Hz), 5.92 (1 H, d, *J* = 10.25 Hz, D_2O exchange), 7.3 (5 H, m); IR (NaCl, neat) 3425 (broad), 1680, 1455, 1395, 1260, 1100, 1055, 735, 700 cm^{-1}; mass spectrum, *m/e* 304 (M^+, 3.4%), 286 (2.7), 198 (17), 105 (54), 43 (100).

Note: Both of these diastereoisomers are formed in roughly equal amounts in both the presence or absence of HMPA. A stereochemical assignment has not been made.

8,10-Dimethyl-8,10-diaza-6-allyl-2-oxabicyclo[4.2.2]decane-7,9-dione (12, *n* = 2, R = $CH_2CH{=}CH_2$; Table I, Entry 15) (Oil). From 23.4 mg (0.11 mmol) of **2**, 8.2 mg (0.034 mmol, 31%, 67% based on recovered **2**) of product was obtained (chromatographed on PTLC silica gel with 25% acetone in ether); 0.3 mg (1%) of regioisomer **13** and 13.2 mg (57%) of starting **2** were also obtained.

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.6–2.04 (4 H, m), 2.4–2.5 (1 H, dd), 2.96 (3 H, s), 3.04 (3 H, s), 3.0–3.74 (3 H, m), 5.13 (1 H, s), 5.05–5.62 (3 H, m); IR (NaCl, neat) 1665, 1440, 1425, 1390, 1310, 1240, 1055 cm^{-1}; mass spectrum, *m/e* 238 (M^+, 48.79%), 196 (44.8), 181 (43.3), 82 (100).

8,10-Dimethyl-8,10-diaza-1-allyl-2-oxabicyclo[4.2.2]decane-7,9-dione (**13**, *n* = 2, R = $CH_2CH{=}CH_2$; Table I, Entry 15) (Oil). ^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.63 −1.74, (2 H, m), 2.0–2.2 (2 H, m), 2.57 (1 H, dd), 2.98 (3 H, s), 3.01 (3 H, s), 3.04–4.1 (4 H, m), 5.05–5.57 (3 H, m); IR (NaCl, neat) 1670, 1440, 1390, 1045, 730 cm^{-1}; mass spectrum, *m/e* 238 (M^+, 100%), 180 (19.5), 152 (45.9), 82 (48.6), 42 (68.5).

8,10-Dimethyl-8,10-diaza-6-benzoyl-2-oxabicyclo[4.2.2]decane-7,9-dione (12, *n* = 2, R = COPh; Table I, Entry 10). mp 181–182 °C (recrystallized from Et_2O/CH_2Cl_2). From 22.6 mg (0.11 mmol) of **2**, 31.5 mg (0.1 mmol, 92%, 96.5% based on recovered **2**) of product was obtained (chromatographed on PTLC silica gel with 25% acetone in ether); 0.9 mg (2.6%) of regioisomer **13** and 1.2 mg (5%) of **2** were also obtained.

^1H NMR (100 MHz) $CDCl_3$ δ (Me_4Si) 1.8–2.6 (4 H, m), 2.67 (3 H, s), 3.09 (3 H, s), 3.2–3.9 (2 H, m), 5.35 (1 H, s), 7.26–7.57 (3 H, m), 7.85–7.89 (2 H, m); IR (NaCl, neat) 1700, 1665, 1460, 1410, 1325, 1265, 1245, 1080 cm^{-1}; mass spectrum, *m/e* 302 (M^+, 2.09%), 180 (20.1), 122 (18.5), 105 (100). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N.

8,10-Dimethyl-8,10-diaza-1-benzoyl-2-oxabicyclo[4.2.2]decane-7,9-dione (**13**, *n* = 2, R = COPh; Table I, Entry 10). mp 170–171 °C (recrystallized from Et_2O/CH_2Cl_2). ^1H NMR ($CDCl_3$) δ (Me_4Si) 1.85–2.32 (4 H, m), 2.74 (3 H, s), 3.03 (3 H, s), 3.67–3.74 (3 H, m), 7.26–7.96 (5 H, m); IR (NaCl, neat) 1715, 1680, 1450, 1390, 1250, 1110, 1060, 960 cm^{-1}; mass spectrum, *m/e* 302 (M^+, 0.4%), 197 (10.6), 105 (100). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N.

8,10-Dimethyl-8,10-diaza-6-(trimethylsilyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (12, *n* = 2, R = $SiMe_3$; Table I, Entry 11). mp 163–164 °C (recrystallized from CH_2Cl_2/hexanes). From 30 mg (0.15 mmol) of **2**, 21.4 mg (53.3%, 66.5% based on recovered **2**) of product was obtained (chromatographed on PTLC silica gel with 33% acetone in Et_2O); 6.4 mg (21.3%) of unreacted **2** was also obtained.

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 0.29 (9 H, s), 1.23–1.73 (4 H, m), 2.95 (3 H, s), 2.96 (3 H, s), 3.0–3.8 (2 H, m), 5.08 (1 H, s); IR (NaCl, neat) 1665, 1455, 1390, 1305, 1250, 1055, 840, 750 cm^{-1}; mass spectrum, *m/e* 271 (M^+, 2.4%), 255 (2.0), 198 (49.2), 170 (23.4), 112 (42.5), 73 (46.8), 42 (100). Anal. ($C_{12}H_{22}N_2O_3Si$) C, H, N.

7,9-Dimethyl-7,9-diaza-5-(trimethylsilyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (12, *n* = 1, R = $SiMe_3$; Table I, Entry 16). mp 118–118.5 °C (recrystallized from hexanes). From 40 mg (0.21 mmol) of **3**, 35.3 mg (0.14 mmol, 65.6%, 71% based on recovered **3**) of product was obtained

(chromatographed on PTLC silica gel with 50% acetone in ether); 4.2 mg of **3** (10.5%) and 15.4 mg (22%) of the difunctionalized **14** were also obtained.

^{1}H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 0.28 (9 H, s), 1.78–2.18 (2 H, m), 2.97 (3 H, s), 3.05 (3 H, s), 3.86 (2 H, m), 4.91 (1 H, s); IR (NaCl, neat) 1675, 1380, 1290, 1270, 1250, 1230, 1005, 940, 860, 840, 805 cm^{-1}; mass spectrum, *m/e* 256 (M^+, 4.9%), 241 (30.8), 226 (28.8), 211 (21.6), 183 (4.1), 73 (100). Anal. ($C_{11}H_{20}N_2O_3Si$) C, H, N.

7,9-Dimethyl-7,9-diaza-1,5-bis(trimethylsilyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (**14**, n = 1, R = $SiMe_3$; Table I, Entry 16). mp 199–200 °C (recrystallized from hexanes). ^{1}H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 0.26 (9 H, s), 0.29 (9 H, s), 1.8–2.0 (2 H, m), 2.99 (3 H, s), 3.04 (3 H, s), 3.7–3.9 (2 H, m); IR (NaCl, neat) 1655, 1405, 1350, 1240, 1090, 835 cm^{-1}; mass spectrum, *m/e* 331 (M^+ + 2, 2.5%), 329 (M^+, 2.6), 313 (8.8), 256 (5.2), 73 (100). Anal. ($C_{14}H_{28}N_2O_3Si_2$) C, H, N.

7,9-Dimethyl-7,9-diaza-5-allyl-2-oxabicyclo[3.2.2]nonane-6,8-dione (12, n = 1, R = $CH_2CH{=}CH_2$; Table I, entry 18). From 26.7 mg (0.14 mmol) of **3**, 10.9 mg (0.05 mmol, 33.5%, 83% based on recovered **3**) of product was obtained (chromatographed on PTLC silica gel with 25% acetone in Et_2O); 15.9 mg (59.5%) of **3** was also recovered.

^{1}H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.85–2.13 (2 H, m), 2.49 (2 H, m), 3.04 (3 H, s), 3.08 (3 H, s), 3.83 (2 H, m), 4.99 (1 H, s), 5.11–5.88 (3 H, m); IR (NaCl, neat) 1680, 1430, 1385, 1240, 1040, 985 cm^{-1}; mass spectrum, *m/e* 224 (M^+, 51%), 183 (23.3), 167 (73.3), 42 (100).

7,9-Dimethyl-7,9-diaza-5-(methylthio)-2-oxabicyclo[3.2.2]nonane-6,8-dione (12, n = 1, R = SCH_3; Table I, Entry 20). mp 115–116 °C (recrystallized from Et_2O). From 23.7 mg (0.12 mmol) of **3**, 9.6 mg (0.04 mmol, 33%, 66% based on recovered **3**) of product was obtained (chromatographed on PTLC silica gel with 25% acetone in ether); 5.6 mg (16%) of disulfenylated product **14** and 12.1 mg (51%) of **3** were also obtained.

^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 1.9–2.3 (2 H, m), 2.08 (3 H, s), 3.07 (3 H, s), 3.22 (3 H, s), 3.83 (2 H, m), 4.97 (1 H, s); IR (NaCl, neat) 1680, 1380, 1295, 1265, 1250, 1230, 1085, 1000, 970, 810, 800 cm^{-1}; mass spectrum, *m/e* 230 (M^+, 24.6%), 215 (17.1), 183 (44.0), 173 (36.7), 68 (100). Anal. ($C_9H_{14}N_2O_3S$) C, H, N, S.

7,9-Dimethyl-7,9-diaza-1,5-bis(methylthio)-2-oxabicyclo[3.2.2]nonane-6,8-dione (**14**, n = 1, R = SCH_3; Table I, Entry 20) (Oil). ^{1}H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.66–2.02 (2 H, m), 2.10 (3 H, s), 2.27 (3 H, s), 3.30 (6 H, s), 3.88–3.96 (2 H, m); IR (NaCl, neat) 1680, 1400, 1335, 1310, 1070, 1050, 985 cm^{-1}; mass spectrum, *m/e* 229 (M^+ – SCH_3, 33%), 182 (7.1), 171 (47.6), 88 (100).

7,9-Dimethyl-7,9-diaza-5-benzoyl-2-oxabicyclo[3.2.2]nonane-6,8-dione (12, n = 1, R = COPh; Table I, Entry 19). mp 180–181 °C (recrystallized from EtOAc, hexanes). From 24.7 mg (0.13 mmol) of **3**, 17.1 mg (0.06 mmol, 44.3%, 82% based on recovered **3**) of product was obtained (chromatographed on PTLC silica gel with 25% acetone in Et_2O).

^{1}H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.75–2.50 (2 H, m), 2.72 (3 H, s), 3.13 (3 H, s), 3.73–4.08 (2 H, m), 5.15 (1 H, s), 7.26–8.08 (5 H, m); IR (NaCl, neat) 1675, 1440, 1380, 1290, 1260, 1235, 1060, 1035, 980 cm^{-1}; mass spectrum, *m/e* 288 (M^+, 5.7%), 231 (1.6), 183 (3.6), 105 (100). Anal. ($C_{15}H_{16}N_2O_4$) C, H, N.

5,7,9-Trimethyl-7,9-diaza-2-oxabicyclo[3.2.2]nonane-6,8-dione (12, n = 1, R = CH_3; Table I, Entry 17) (Oil). From 27.3 mg (0.15 mmol) of **3**, 11.8 mg (0.06 mmol, 40.3%, 75.1% based on recovered **3**) of product was obtained (chromatographed on PTLC silica gel with 25% acetone in ether); 2.7 mg (8.6%) of dialkylated **14** and 12.7 mg (46.5%) of **3** were also obtained.

^{1}H NMR (100 MHz) ($CDCl_3$) δ (Me_4Si) 1.57 (3 H, s), 1.81–1.99 (2 H, m), 2.99 (3 H, s), 3.07 (3 H, s), 3.86 (2 H, m), 5.01 (1 H, s); IR (NaCl, neat) 1670, 1390, 1240, 1180, 1045 cm^{-1}; mass spectrum, *m/e* 198 (M^+, 24.9%), 184 (5.2), 141 (41.6), 56 (100).

1,5,7,9-Tetramethyl-7,9-diaza-2-oxabicyclo[3.2.2]nonane-6,8-dione (**14**, n = 1, R = CH_3; Table I, Entry 17) (Oil). ^{1}H (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.56 (3 H, s), 1.65 (3 H, s), 1.75–1.89 (2 H, m), 2.99 (3 H, s), 3.00 (3 H, s), 3.72–3.85 (2 H, m); IR (NaCl, neat) 1670, 1380, 1360, 1250, 1145 cm^{-1}; mass spectrum, *m/e* 212 (M^+, 6.7%), 198 (8.7), 184 (31.3), 56 (100).

1,7,9-Trimethyl-7,9-diaza-2-oxabicyclo[3.2.2]nonane-6,8-dione (13, n = 1, R = CH_3; Table I, Entry 6) (Oil). Obtained from alkylation of **3** in the absence of HMPA in 25% yield. ^{1}H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.65 (3 H, s), 1.96–2.08 (2 H, m), 2.98 (3 H, s), 3.04 (3 H, s), 3.8–3.98 (3 H, m); IR (NaCl, neat) 1680, 1390, 1240, 1150, 1135, 1045 cm^{-1}; mass spectrum, *m/e* 198 (M^+, 34.4%), 184 (8.0), 154 (5.7), 141 (41.8), 56 (100).

Rearrangement of 12 (n = 2, R = SCH_3) to 18. To a stirred solution of the thiomethyl ether **12** (13 mg, 0.053 mmol, 1 equiv) in THF (1 mL) at –78 °C was added a solution of LDA (0.08 mmol, 1.5 equiv) in THF (1 mL). The mixture was stirred for 1 h at –78 °C, was quenched with MeOH (0.5 mL), and was allowed to warm to room temperature. Evaporation of the solvent and purification on PTLC silica gel (eluted with 20% acetone in Et_2O) afforded 11.6 mg (90%) of the pure regioisomer **18** (**13**, n = 2, R = SCH_3), which was identical in every respect with that obtained from the procedure described above.

Trapping of the Rearranged Anion 17 from 12 (n = 2, R = SCH_3) with Methyl Iodide. To a stirred solution of **12** (n = 2, R = SCH_3) (58 mg, 0.24 mmol, 1.0 equiv) in THF (3 mL) at –78 °C was added a solution of LDA (0.35 mmol, 1.5 equiv) in THF (1 mL). The mixture was stirred 1 h at –78 °C, and methyl iodide (22 μL, 0.35 mmol, 1.5 equiv) was added. After stirring 15 min at –78 °C, the solution was allowed to come to room temperature, diluted with CH_2Cl_2, poured into brine, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 10% acetone in Et_2O) to afford 53.6 mg (88%) of **19**; mp 150–152 °C (recrystallized from hexanes/CH_2Cl_2).

^{1}H NMR ($CDCl_3$) δ ($CHCl_3$) 1.65 (3 H, s), 1.63–2.15 (4 H, m), 2.04 (3 H, s), 3.02 (3 H, s), 3.25 (3 H, s), 3.2–3.87 (2 H, m). A stirred solution of **19** (13 mg, 0.05 mmol) in THF (1 mL) was treated with a 2-mL suspension of w-5 Raney nickel in 2-propanol under a hydrogen atmosphere for 30 min at room temperature. The mixture was filtered, evaporated, and separated on PTLC silica gel (eluted with 10% acetone in Et_2O) to afford 6.8 mg (64%) of product **12** (n = 2, R = CH_3), which was identical in every respect with that obtained from the procedure described above.

Regioselective Synthesis of 13 (n = 1, R = CH_3; Table IV, Entry 1). To a stirred solution of **12** (n = 1, R = $SiMe_3$) (12 mg, 0.05 mmol, 1.0 equiv) in THF (2 mL) at –78 °C was added a solution of LDA (0.14 mmol, 3.0 equiv) in THF (1 mL). The mixture stirred for 1 h at –78 °C and was quenched with methyl iodide (15 μL, 0.23 mmol, 5.0 equiv). The solution was allowed to warm to room temperature, diluted with CH_2Cl_2, poured into brine, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 20% hexanes in Et_2O) to afford 7.4 mg (59%, 99% based on recovered **12**) of **20** (R′ = $SiMe_3$, R = CH_3) (oil).

^{1}H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 0.31 (9 H, s), 1.63 (3 H, s), 1.7–2.0 (2 H, m), 2.95 (3 H, s), 3.09 (3 H, s), 3.85 (2 H, m). A stirred solution of **20** (6.5 mg, 0.024 mmol, 1.0 equiv) in THF (1.5 mL) was treated with tetra-*n*-butylammonium fluoride-3H_2O (50 mg, 6.6 equiv) at room temperature for 40 min. Evaporation of the solvent and purification on PTLC silica gel (eluted with 25% acetone in Et_2O) afforded 4.4 mg (94%) of **13** (n = 1, R = CH_3), which was identical in every respect with that obtained above from the alkylation of **3** in the absence of HMPA.

One-Pot Synthesis of 13 (n = 2, R = CH_3) from 2 (Table IV, Entry 2). To a stirred solution of **2** (35 mg, 0.176 mmol, 1.0 equiv) plus HMPA (0.15 mL, 0.88 mmol, 5.0 equiv) in THF (2 mL) at –78 °C was added a solution of LDA (0.19 mmol, 1.1 equiv) in THF (1 mL). The mixture was stirred for 1 h at –78 °C, and chlorotrimethylsilane (34 μL, 0.265 mmol, 1.5 equiv) was added. The mixture was allowed to come to room temperature for 30 min and was recooled to –78 °C. A solution of LDA (0.265 mmol, 1.5 equiv) in THF (1 mL) was added and the solution was stirred for 25 min at –78 °C. Methyl iodide (55 μL, 0.88 mmol, 5.0 equiv) was added and the mixture was allowed to come to room temperature. After the solution was stirred for 40 min at room temperature, tetra-*n*-butylammonium fluoride trihydrate (334 mg, 1.06 mmol, 6.0 equiv) was added in one portion. After stirring 20 min at room temperature, the mixture was diluted with CH_2Cl_2, poured into brine, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with Et_2O and then 10% acetone in Et_2O) to afford 21.1 mg (56.3%) of **13** (n = 2, R = CH_3), which was identical in every respect with that obtained as a minor product described above; 11.8 mg (29.5%) of dialkylated **14** (n = 2, R = CH_3) was also obtained.

One-Pot Synthesis of Aldol 13 (n = 2, R = $CHOHC(Me)CH_2OC(Me)_2O$ (Table IV, Entry 3). To a stirred solution of **2** (35.4 mg, 0.18 mmol, 1.0 equiv) in THF (2 mL) plus HMPA (0.16 mL, 0.9 mmol, 5 equiv) at –78 °C was added a solution of LDA (0.19 mmol, 1.1 equiv) in THF (1 mL). The mixture was stirred for 1 h at –78 °C, chlorotrimethylsilane (34 μL, 0.27 mmol, 1.5 equiv) was added, and the solution was allowed to warm to room temperature. After 15 min, the mixture was cooled to –78 °C and a solution of LDA (0.27 mmol, 1.5 equiv) in THF (1 mL) was added. After the mixture was stirred for 20 min at –78 °C, 2-methyl-2,3-*O*-isopropylidenylpropionaldehyde[13] (128 mg, 0.9 mmol,

(13) Prepared from the corresponding alcohol by oxidation with Me_2SO, oxalyl chloride, and Et_3N (Swern conditions); see ref 5 and P. Calinaud and J. Gelas, *Bull. Soc. Chim. Fr.*, 1228 (1975); H. Maag, J. F. Blount, D. L. Coffen, T. V. Steppe, and F. Wong, *J. Am. Chem. Soc.*, **100**, 6786 (1978).

5 equiv) was added dropwise, and the cooling bath was removed. After the solution was stirred for 40 min at room temperature, a solution of tetra-*n*-butylammonium fluoride trihydrate (338 mg, 1.07 mmol, 6.0 equiv) in THF (2 mL) was added. The mixture was stirred for 30 min, diluted with CH_2Cl_2, poured into brine, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel column (eluted with Et_2O, then 10% acetone in Et_2O) to afford 39 mg (64%, 82% based on recovered **2**) of the aldols **13**. The major diastereoisomer (56% yield) was separated from two minor, inseparable isomers on PTLC silica gel (33% acetone in Et_2O). Major diastereoisomer mp 195-196 °C (recrystallized from hexane/CH_2Cl_2).

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.16 (3 H, s), 1.33 (3 H, s), 1.38 (3 H, s), 1.48-2.25 (4 H, m), 2.94 (3 H, s), 3.04 (3 H, s), 3.12-4.16 (5 H, m), 4.11 (1 H, d, J = 10 Hz), 6.45 (1 H, d, J = 10 Hz, D_2O exchange); IR (NaCl, neat) 3380 (broad), 1670, 1210, 750 cm^{-1}; mass spectrum, m/e 327 ($M^+ - CH_3$, 8.0%), 227 (65.4), 198 (8.3), 115 (100). Anal. ($C_{16}H_{26}N_2O_6$) C, H, N.

Regioselective Synthesis of 13 (n = 1, R = $CH_2CH{=}CH_2$; Table IV, Entry 4). The same procedure as described above for **13** (n = 1, R = CH_3), starting from **12** (n = 1, R = $SiMe_3$) and allyl bromide, was used. From 13 mg (0.05 mmol) of **12**, 3.5 mg (24%, 74% based on recovered **12**) of **20** (R′ = $SiMe_3$, R = $CH_2CH{=}CH_2$) was obtained (chromtographed on PTLC silica gel eluted with 20% hexanes in Et_2O) (oil). ^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 0.16 (9 H, s), 1.83-2.13 (2 H, m), 2.27 (2 H, m), 2.51 (3 H, s), 3.81 (3 H, s), 3.88-4.22 (2 H, m), 4.9-6.4 (3 H, m). From 3 mg (0.01 mmol) of **20**, 1 mg (46%, 70% based on recovered **19**) of **13** (n = 1, R = $CH_2CH{=}CH_2$) was obtained (chromatographed on PTLC silica gel eluted with 20% acetone in Et_2O) (oil).

^1H NMR (100 MHz) ($CDCl_3$) δ ($CHCl_3$) 1.74-2.27 (4 H, m), 2.45 (3 H, s), 3.17 (3 H, s), 3.56 (1 H, m), 3.88 (2 H, m), 4.95-6.09 (3 H, m); IR (NaCl, neat) 1650, 1480, 1330, 1270, 1110, 1095, 910 cm^{-1}; mass spectrum, m/e 224 (M^+, 3.4%), 195 (2), 188 (2.3), 157 (41.4), 110 (100).

Acknowledgment. Acknowledgement is made to the National Institutes of Health Grant 1 R01 AIGM 18957-01, the donors of the Petroleum Research Fund administered by the American Chemical Society (No. 12786-G1), Research Corp., and the Colorado State University Biomedical Research Support Grant 537276 for support of this work. NMR measurements at 360 and 90.54 MHz were obtained at the Colorado State University Regional NMR Center, funded by the National Science foundation Grant CHE 78-18581.

Registry No. 2, 78877-97-1; **3**, 85168-14-5; **8**, 5076-82-4; **9**, 85168-15-6; **10**, 85168-16-7; **11**, 85168-17-8; **12** (n = 1, R = $SiMe_3$), 85168-18-9; **12** (n = 1, R = $CH_2CH{=}CH_2$), 85168-19-0; **12** (n = 1, R = SCH_3), 85168-20-3; **12** (n = 1, R = COPh), 85168-21-4; **12** (n = 1, R = CH_3), 85168-22-5; **12** (n = 2, R = CH_3), 78878-06-5; **12** (n = 2, R = SCH_3), 85168-23-6; **12** (n = 2, R = CHOHPh) (isomer 1), 85168-24-7; **12** (n = 2, R = CHOHPh) (isomer 2), 85201-87-2; **12** (n = 2, R = $CH_2CH{=}CH_2$), 85168-25-8; **12** (n = 2, R = COPh), 85168-26-9; **12** (n = 2, R = $SiMe_3$), 85168-27-0; **13** (n = 1 R = $CH_2CH{=}CH_2$), 85185-14-4; **13** (n = 1, R = CH_3), 85185-15-5; **13** (n = 2, R = CH_3), 78878-02-1; **13** (n 2, R = CHOHPh) (isomer 1), 85168-28-1; **13** (n = 2, R = CHOHPh) (isomer 2), 85201-88-3; **13** (n = 2, R = $CH_2CH{=}CH_2$), 85168-29-2; **13** (n = 2, R = COPh), 85168-30-5; **13** (n = 2, R = $CHOHC(Me)CH_2OC(Me)_2O$), 85168-31-6; **14** (n = 1, R = $SiMe_3$), 85185-16-6; **14** (n = 1, R = SCH_3), 85185-17-7; **14** (n = 1, R = CH_3), 85185-18-8; **14** (n = 2, R = CH_3), 85168-32-7; **18**, 85168-33-8; **19**, 85168-34-9; **20** (n = 1, R = CH_3; R′ = $SiMe_3$), 85185-19-9; pySSpy, 2127-03-9; ethylene oxide, 75-21-8; 2-methyl-2,3-*O*-isopropylidenepropionaldehyde, 68691-67-8; allyl bromide, 106-95-6.

Acid-Catalyzed Hydrolysis of 1,1-Bis(methylthio)ethene. Buffer- and Thiol-Dependent Changes in the Rate-Determining Step

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Abstract: Acid-catalyzed hydrolysis of 1,1-bis(methylthio)ethene has been studied kinetically in 10% aqueous acetonitrile at 30 °C. The rate increased with buffer concentration, showing saturation at higher concentrations. Addition of 2-mercaptoethanol had little influence on the rate at the limiting zero buffer concentration, but it greatly accelerated the reaction in buffer solutions and followed a saturation curve. It was concluded that the rate-determining step is largely the protonation of the double bond at zero buffer concentration (k_2/k_{-1} = 3.13) but it changes to the attack of water on the intermediate carbenium ion as the buffer concentration increases. The ^1H NMR spectral analysis of the reaction products in 80% CH_3CN-D_2O showed that the H-D isotope exchange at the 2-position of the substrate occurred extensively in a formate buffer but only moderately in a DCl solution during the hydrolysis.

Acid-catalyzed hydrolyses of vinyl ethers,[1-3] vinyl sulfides,[4-6] and ketene acetals[7-12] occur through hydration of the carbon-carbon double bond; a hemiacetal, or a hydrogen ortho ester, thus formed rapidly decomposes to the ultimate reaction products (eq 1). It is known that ketene dithioacetals undergo hydrolysis similarly to give thiolesters.[13-15]

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