Novel Ring Contractions via [2,3] Wittig Type Rearrangements: Synthesis of 2-Desoxy-2-methylenebicyclomycin

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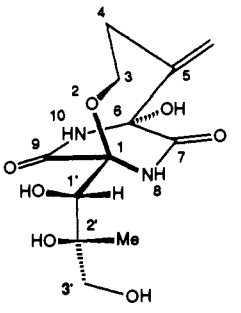
Abstract: Bridgehead carbanion generation of bicyclo[5.2.2] and bicyclo[7.2.2] allyl ether bridged piperazinediones result in novel ring contractions via unusual [2,3] Wittig type and [3,3] Claisen rearrangements. The application of the [2,3] Wittig rearrangements to the construction of 2-desoxy-2-methylenebicyclomycin (**3**) is described.

Introduction

Bicyclomycin (**1**) is a commercially significant antimicrobial natural product[1] that has been the subject of numerous synthetic,[2] mechanistic,[3] and biological[4] studies. Maag and associates[5] demonstrated over 10 years ago that bicyclomycin undergoes a thermodynamically driven bis-spiro ring-forming dehydration to the tricyclic substances **2**. The significance of the putative (leucyl- and isoleucyl-derived) amino acid oxidation states at the α-positions (both carrying oxygenation) has been the subject of several provocative studies[3,6] and remains an unresolved issue requiring further experimental clarification.



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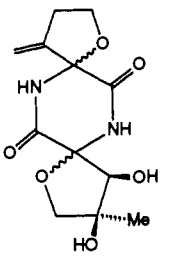

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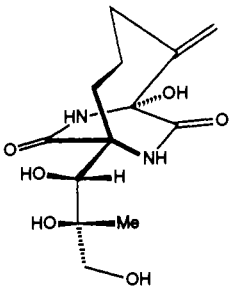

3

We[6] and others[7] have invoked the significance of the bridgehead hydroxyl (at C-6) as a leaving group obligate for the creation of a latent Michael acceptor following hypothetical enzyme-catalyzed cleavage of the 9,10-amide linkage. On the other hand, Kohn and Abuzar[3d-h] have placed emphasis on the capacity of the bridging-ether oxygen atom (at C-1) to allow for spiro ring formation during the base-catalyzed reaction of **1** with thiols and other nucleophiles. These authors[3e,f,h] have also disclosed an interesting intramolecular Claisen condensation of **1** under conditions of thiol capture. In the latter capacity, the bridging-ether oxygen atom is a "spectator" atom playing no immediately apparent role in the process of "drug activation"[3e,f,h] for eventual covalent modification of the target macromolecule.

(1) For a review, see: Williams, R. M.; Durham, C. A. *Chem. Rev.* **1988**, *88*, 511.

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(3) (a) Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.* **1979**, *32*, 402. (b) Williams, R. M.; Tomizawa, K.; Armstrong, R. W.; Dung, J-S. *J. Am. Chem. Soc.* **1985**, *107*, 6419. (c) Williams, R. M.; Tomizawa, K.; Armstrong, R. W.; Dung, J-S. *J. Am. Chem. Soc.* **1987**, *109*, 4028. (d) Kohn, H.; Abuzar, S. *J. Am. Chem. Soc.* **1988**, *110*, 3661. (e) Abuzar, S.; Kohn, H. *J. Am. Chem. Soc.* **1988**, *110*, 4089. (f) Abuzar, S.; Kohn, H. *J. Org. Chem.* **1989**, *54*, 4000. (g) Kohn, H.; Abuzar, S. *J. Org. Chem.* **1988**, *53*, 2769. (h) Abuzar, S.; Kohn, H. *J. Am. Chem. Soc.* **1990**, *112*, 3114.

(4) (a) Tanaka, N.; Iseki, M.; Miyoshi, T.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1976**, *29*, 155. (b) Tokuma, Y.; Koda, S.; Miyoshi, T.; Morimoto, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 18. (c) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 480. (d) Iseki, M.; Miyoshi, T.; Konomi, T.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 488. (e) Ochi, K.; Tsurumi, Y.; Shigematsu, N.; Iwami, M.; Umehara, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 1106. (f) Someya, A.; Tanaka, K.; Tonaka, N. *Antimicrob. Agents Chemother.* **1979**, *16*, 87. (g) Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.* **1978**, *31*, 712. (h) Muller, B. W.; Zak, O.; Kump, W.; Tosch, W.; Wacker, O. *J. Antibiot.* **1979**, *32*, 689.

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

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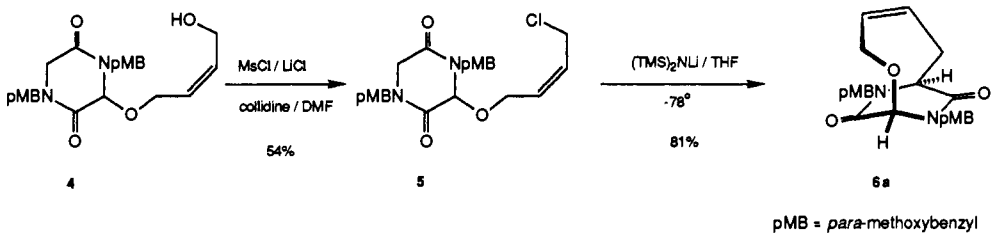
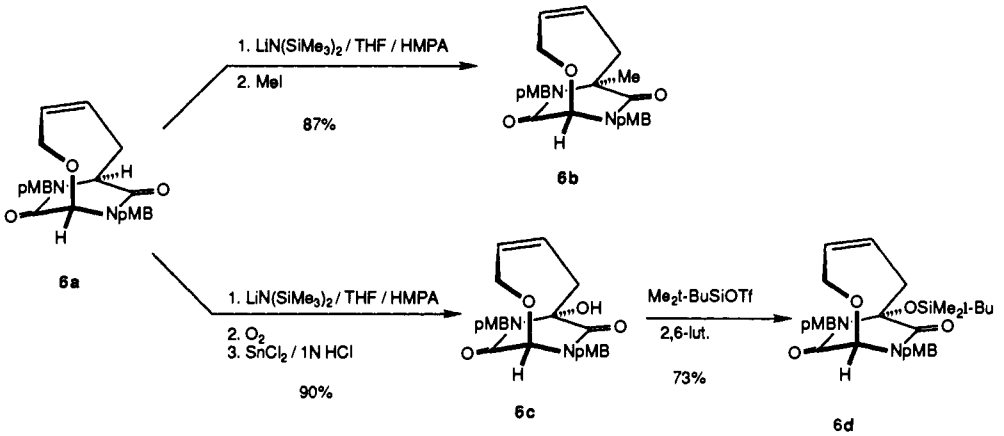
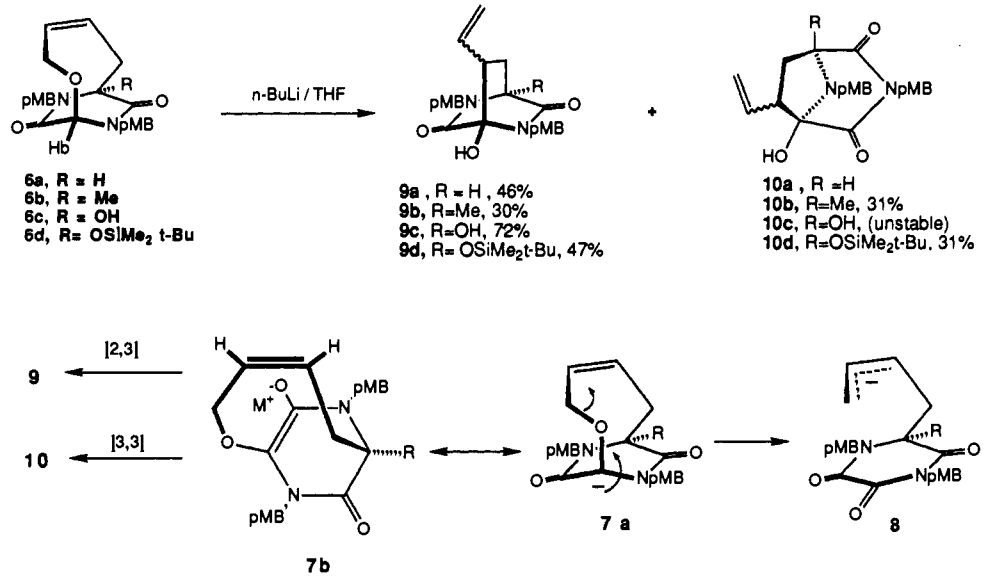
Scheme I



Scheme II



Scheme III



In an effort to directly address the functional significance of the bridging-ether oxygen atom as an obligatory moiety for antimicrobial activity, we desired the total synthesis of the 2-desoxy-2-methylene analogue of **1** (structure **3**). Since a four-carbon bridge connects the two putative amino acid building blocks, the synthesis of **3** required the development of a new C–C bond-forming strategy that would embrace the functional complexities inherent in this substance. After examining several unsuccessful straightforward approaches, a novel [2,3] Wittig rearrangement reaction was discovered that concomitantly installs the correct oxidation state at C-6 and the requisite branching of the *exo*-methylene moiety. To the best of our knowledge, this is the only [2,3] Wittig type process yet observed to occur at the α-position of an α-amino acid derivative.

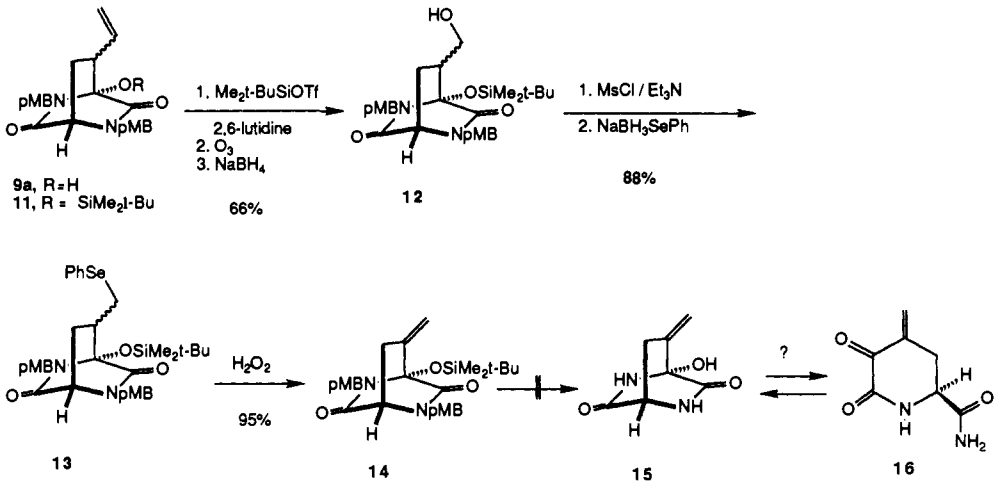
Results

The initial discovery of this process was made on the simple bicyclo[5.2.2] substance **6a** that was recently communicated from these laboratories[21] (Scheme I). Bridgehead carbanion functionalization of **6a** displayed the expected[21] regioselectivity as demonstrated in Scheme II. The bridgehead methine adjacent to the bridging $-CH_2-$ moiety could be selectively removed under thermodynamic control and the resulting carbanion functionalized; methyl iodide alkylation produced **6b** in 87% yield, and oxidation with O_2 followed by $SnCl_2$ reduction of the incipient peroxide[8] produced carbinol **6c** in 90% yield.

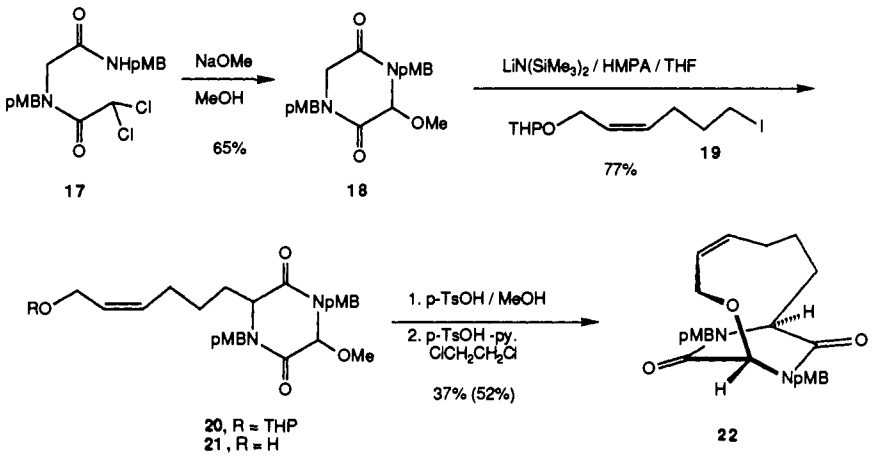
When we attempted to generate the bridgehead carbanion adjacent to the bridging allylic ether oxygen atom and functionalize as above, we obtained none of the expected bicyclo[5.2.2] derivatives and instead obtained the bicyclo[2.2.2] and bicyclo[3.2.1] substances **9** and **10** (Scheme III). The fact that the bicyclo[3.2.1] system is produced (**10b** and **10d** specifically) would suggest two plausible mechanistic explanations. One possibility, depicted in Scheme III, involves the fragmentation of the incipient carbanion **7a** to the allylic anion **8**; subsequent readdition in an

(8) Williams, R. M.; Dung, J-S. *Tetrahedron Lett.* **1985**, *26*, 37.

Scheme IV



Scheme V



entropically favored least motion pathway to both carbonyls of the 1,2-oxalimide system would then produce the observed ring-contracted bicyclo[3.2.1] (**10**) and bicyclo[2.2.2] (**9**) products. Alternatively, the (albeit, strained) enolate resonance form of the carbanion (**7b**) could undergo *both* [2,3] Wittig and [3,3] Claisen rearrangements producing **9** and **10**, respectively. While no detailed mechanistic evidence is available, we tend to favor the latter mechanism on the basis of indirect evidence. First, we could not detect products resulting from the proton quenching of **8**. Secondly, these rearrangements proved to be entirely stereoselective, furnishing single diastereoisomers of **9** and **10**. Were allyl anion **8** an intermediate, one would expect diastereomeric mixtures due to the unencumbered steric environment and rotational mobility of the allyl anion moiety. Additional supporting information will be discussed below.

When **6a** was treated with 1.1 equiv of butyllithium at −78 °C and allowed to stir for 50 min, only the [2,3] Wittig type product **9a** was isolated (46%). The modest yield of **9a** implies that **10a** was likely produced as well, but does not survive isolation and workup. The relative stereochemistries of **9** and **10** have not been secured.

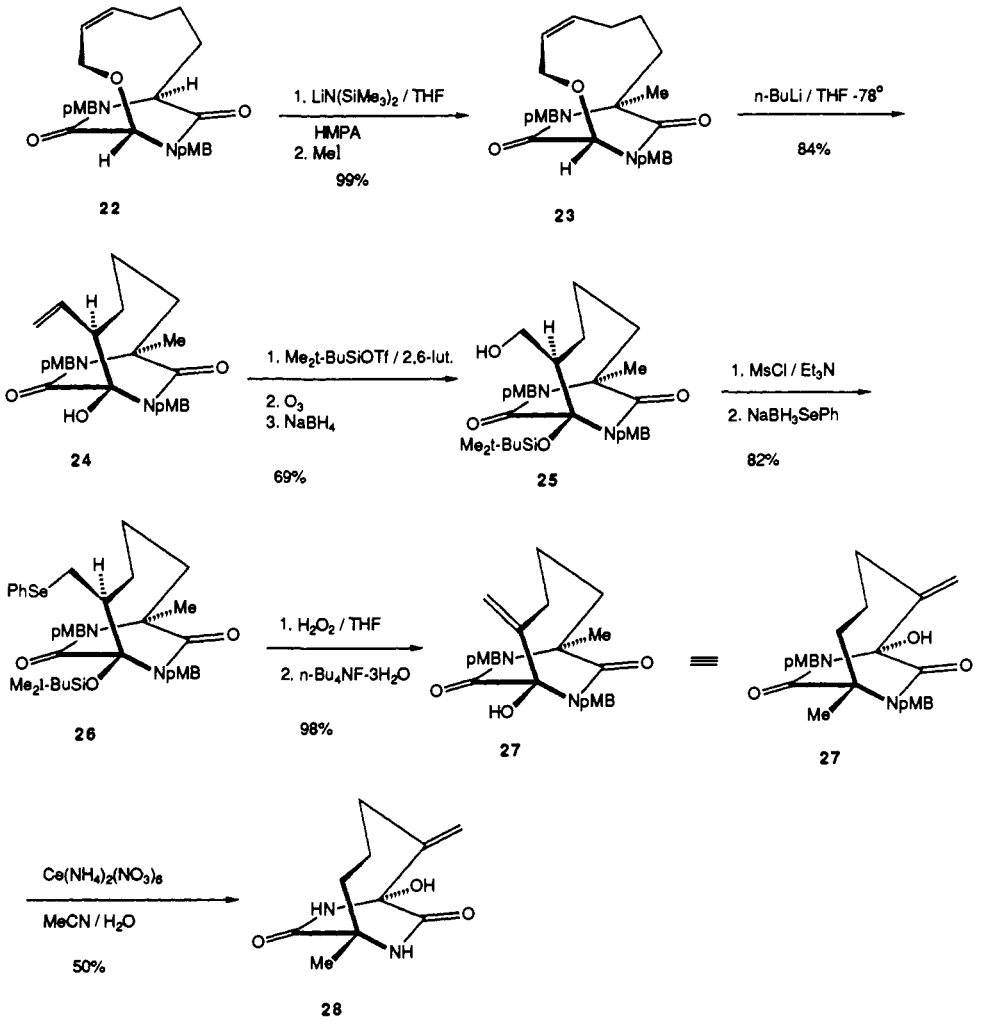
Substance **9a** has been subsequently transformed into *exo*-methylene carbinol **14** as shown in Scheme IV. Silylation of **9a** furnished **11**, which was ozonolyzed and reduced in 66% overall yield to provide **12**. Conversion to selenide **13** proceeded in high yield; subsequent oxidative elimination furnished the *exo*-methylene derivative **14** in 95% yield. This substance proved to be devoid of antimicrobial activity.[6] All attempts to remove the *N*-(*p*-methoxybenzyl) groups[1] from **14** under the standard cerric ammonium nitrate conditions[9] resulted in complete decomposition with no isolable traces of **15** being observed. It is possible that if **15** were formed, the inherent ring strain should favor ring-opening tautomerization to the α,β-unsaturated pyruvamide **16**, which is expected[1] to be highly reactive to nucleophile capture and perhaps polymerization. Despite the failure to obtain **15**, the serendipitous discovery of the [2,3] Wittig process, modeled herein, demonstrated the functional group feasibility of reaching **3**.

For the preparation of the target system **3**, the requisite bicyclo[7.2.2] allylic ether substrate **22** was prepared as shown in Scheme V. Regioselective[1] enolate functionalization of **18** with (*Z*)-1-(tetrahydropyranyloxy)-6-iodo-2-hexene (**19**) furnished the desired alkylated piperazinedione **20** as an inseparable syn/anti mixture in 77% yield. This mixture was carried on directly to **22**. Removal of the THP ether with *p*-toluenesulfonic acid in methanol furnished **21**. Macrocyclization of this substance proved to be much more difficult than the smaller ring systems and required extensive investigation. The optimum conditions found to date involve refluxing **21** in 1,2-dichloroethane at 0.01 M containing 0.05 equiv of *p*-toluenesulfonic acid and 0.95 equiv of pyridinium *p*-toluenesulfonate for 3 days. We also found that running the reaction on a 1.5-mmol scale reproducibly gives 37% isolated yield of **22** (52% based on recovered **21**), while larger and smaller scale runs *under identical conditions* give depressed yields. No explanation for this sensitivity is apparent.

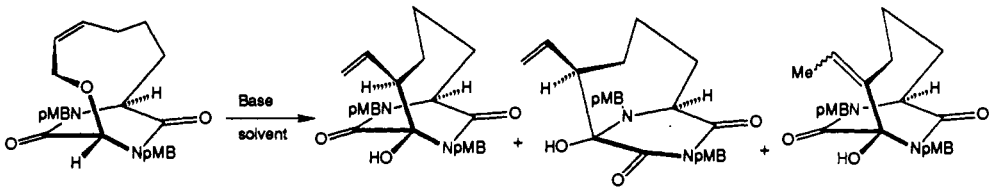
At this juncture, we investigated the fundamental carbanion chemistry of **22**. Treatment of **22** with lithium hexamethyldisilylamide in THF containing HMPA at −78 °C followed by methyl iodide quenching afforded the expected bridgehead methylation product **23** in 99% yield (Scheme VI). Treatment of this substance with *n*-BuLi in THF at −78 °C cleanly afforded the desired [2,3] Wittig rearrangement product **24** in 84% yield as a single diastereoisomer. To demonstrate the functional utility of this process, **24** was further manipulated to the simple analogue

(9) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

Scheme VI



Scheme VII



Base	Solvent	Temperature	Ratio (29 : 30 : 31)	Yield
LDA / n-BuLi	THF	-78°C	1 : 3.67 : 0	56%
NaH	DME	25°C	3.6 : 0 : 1	61 - 87%

28. Silylation of the bridgehead hydroxyl followed by ozonolysis and reduction provided the primary alcohol **25** in 69% overall yield. Dehydration via the phenyl selenide **26** proceeded smoothly to give, after fluoride removal of the silyl group, the protected *exo*-methylene derivative **27** in 80% overall yield from **25**. A single-crystal X-ray analysis of **27** secured the structure (Figure 1). Finally, removal of the *N*-(*p*-methoxybenzyl) groups with cerric ammonium nitrate in aqueous acetonitrile[9] furnished the simple bicyclomycin analogue[10] **28** in 50% yield.

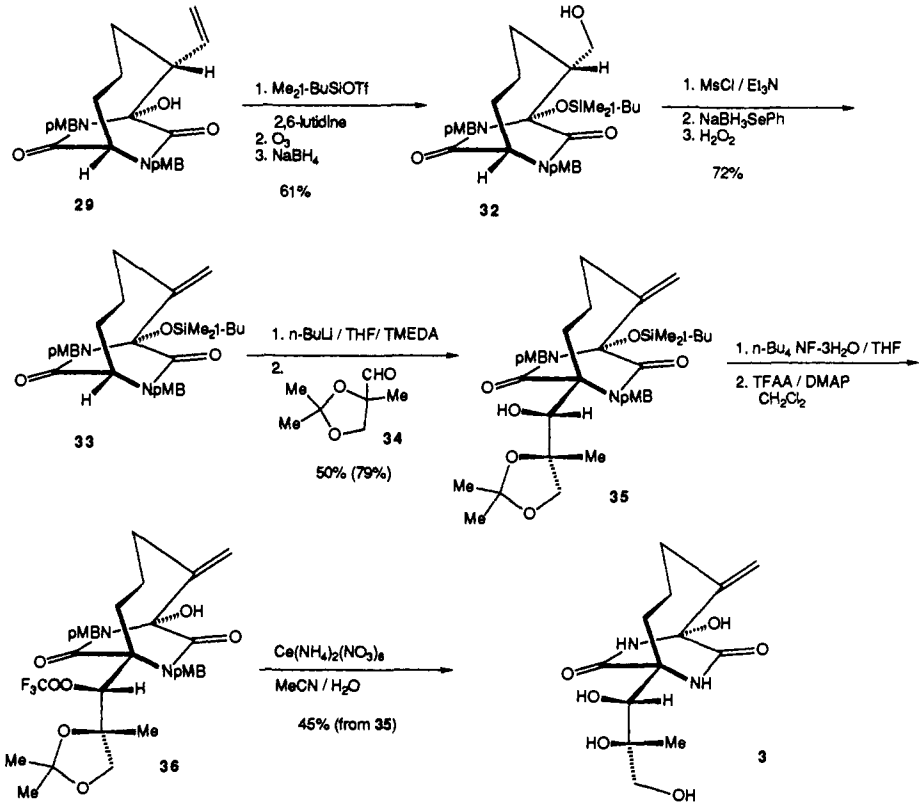
The direct [2,3] Wittig rearrangement of **22** proved to be capricious relative to **23** and required extensive experimentation. An abbreviated summary of these investigations is described below. Treatment of **22** sequentially with LDA, trimethylsilyl chloride,[11] and *n*-BuLi in THF at −78 °C resulted in the [2,3] Wittig product **29** (12%) and [3,3] Claisen product **30** (44%, Scheme VII). We next examined a range of equilibrating basic conditions on the premise that only the carbanion adjacent to the allylic ether will undergo irreversible rearrangement. In the event, sodium hydride in dimethoxyethane at room temperature for 3–10 h cleanly provides the [2,3] Wittig product **29** as the major product in 61–87% yield along with the olefin isomerization product **31** (3.6:1 ratio). In both instances, the reaction was entirely stereoselective,

(10) Substance **28** was devoid of antimicrobial activity.

(11) The trimethylsilyl chloride was used in an attempt to C-silylate the thermodynamically more acidic methine adjacent to the bridging $-CH_2-$. This procedure has proven to be superfluous in terms of producing both **29** and **30** (LDA alone suffices) but reproducibly gives the highest combined yield.

(12) A more complete antimicrobial analysis of **3** is to be published elsewhere.

Scheme VIII



producing single diastereomers of **29** and **31** (see below); the olefin geometry of **31** has not been unambiguously assigned.

With a controlled method to obtain the functionalized bicyclo[4.2.2] ring system available, the preparation of **3** followed the previously established protocol employed to synthesize bicyclomycin[1] (Scheme VIII). Silylation of **29** followed by ozonolysis and reduction furnished **32** in 61% overall yield. Dehydration via the selenide furnished the key *exo*-methylene substrate **33** (72% from **32**). Aldol condensation of **33** with (±)-**34**[1] furnished **35** (50%, or 79% based on recovered **33**) plus 12% (or 18% based on recovered **33**) of a C-1′ diastereomer. This is yet another example of the remarkable double diastereodifferentiating aldolization of aldehyde **34** with the bicyclomycin bridgehead enolate system.[1] All known cases[1] of related aldolizations in this family give, as a major aldol product, the natural relative stereochemistry of the side chain. Since there is no authentic sample available

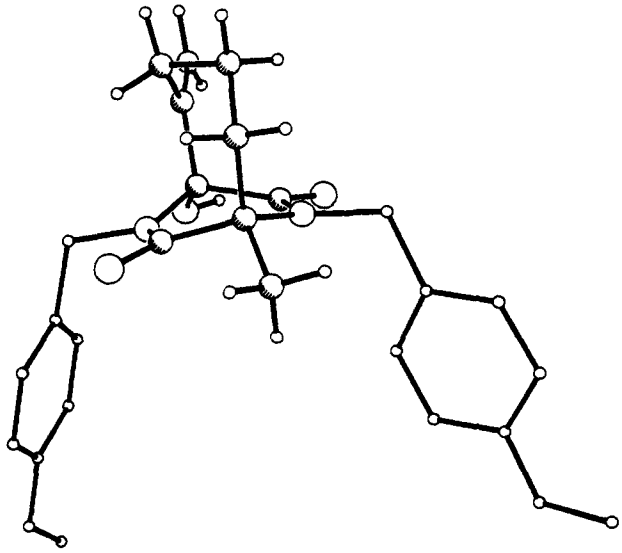
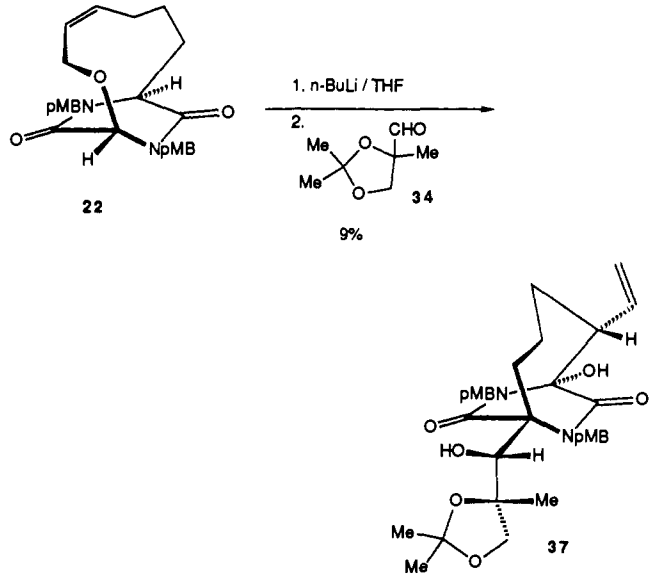


Figure 1. Molecular structure of **27**. Spheres are of fixed, arbitrary radius. The *N*-(*p*-methoxybenzyl) group has been diminished for clarity.

Scheme IX

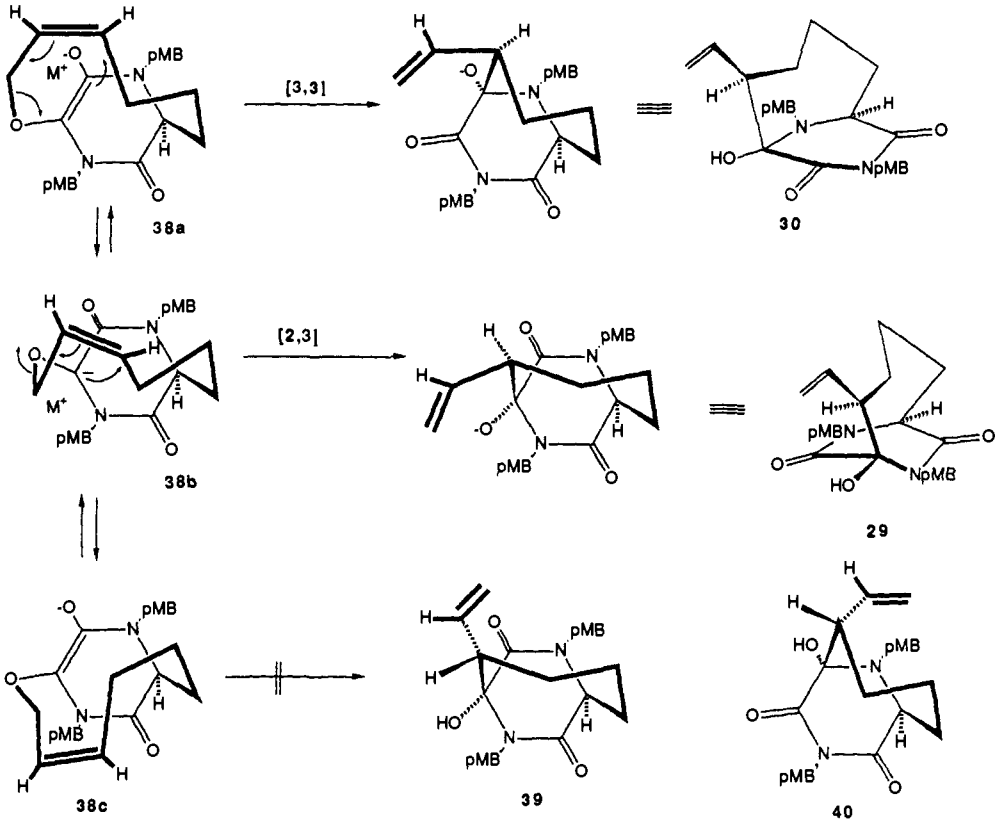


of compound **3**, the relative stereochemical assignments for **35** (and consequently **3**) were based on ^{1}H NMR spectral characteristics of the C-1′–C-3′ side chain (see the Experimental Section), which parallel those of the aldol products of the bicyclomycin systems.[1]

Removal of the silyl group from **35** with *n*-Bu_4NF followed by conversion to the C-1′ trifluoroacetate **36** proceeded in high yield by treatment with TFAA in methylene chloride containing DMAP. Deprotection of the fully protected substrate **36** to **3** proved quite troublesome, but was eventually realized in 45% overall yield from **35** under carefully controlled conditions with cerric ammonium nitrate.

In one diversion, we found that **22** could be rearranged and aldolized in a single step by treatment with excess *n*-BuLi and aldehyde **34**. The derivatized structure **37** was obtained in 9% overall yield, but was not processed further. The stepwise synthesis

Scheme X



of **3** as shown in Scheme VIII proved more efficient in terms of producing useable quantities of **3**.

Discussion

Mechanistically, we envisioned that both products (**29** and **30**) resulting from base-induced rearrangement should only be possible via two closely related conformers of the enolate derived from **22** (**38a** and **38b**, Scheme X). Slight twisting of the *Z* olefin over the two enolate carbons positions the allylic moiety for the [2,3] and [3,3] processes. The alternate conformer (**38c**) places the reacting centers much too distant to achieve the transition state of the Claisen. The entirely stereoselective outcome of both processes supports the pericyclic mechanisms rather than the alternative allyl anion fragmentation discussed above (cf. Scheme III, structure **8**). Single-crystal X-ray analysis of **29** (Figure 2) indirectly supports the mechanistic interpretation detailed in Scheme X. None of the alternate diastereomers **39** or **40** were produced from these reactions; isomer **40** could only reasonably arise via allyl anion fragmentation and readdition since, as mentioned above, the pericyclic conformer **38c** is too extended for the [3,3] Claisen process.

Several studies[13] have addressed the conformational preference of the [2,3] sigmatropic rearrangement process. Houk and Marshall[14] have proposed an early transition-state structure for this process where the cation (Li^+ in the calculations) coordinates nearly antiperiplanar to the developing C–C bond and breaking O–C bond (shown in Scheme XI). Significantly, the electron-withdrawing group (in the present case, the amide carbonyl) in general favors the endo position in these [2,3] sigmatropic rearrangements[13,14] (cf. **38b**). The difference in energy based on steric interactions between the endo (**38b**) and exo (**38c**) conformers is presumed to be negligible due to the relative planarity of the piperazinedione ring. The observed proclivity for [2,3] rearrangement via conformer **38b** is in accord with experimental[13] and theoretical[14] results.

To rationalize the change in mechanism for substrate **22** when utilizing the lithium versus sodium cations, we speculate that the lithium enolate adopts a tightly coordinated O–Li enolate structure favoring the [3,3] anionic oxy-Claisen. The sodium counterion would be expected to be more loosely associated with the enolate

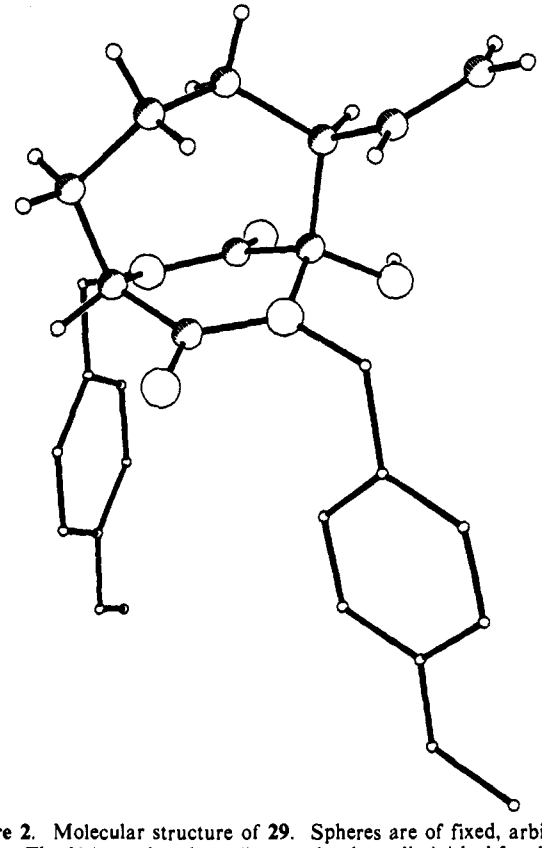
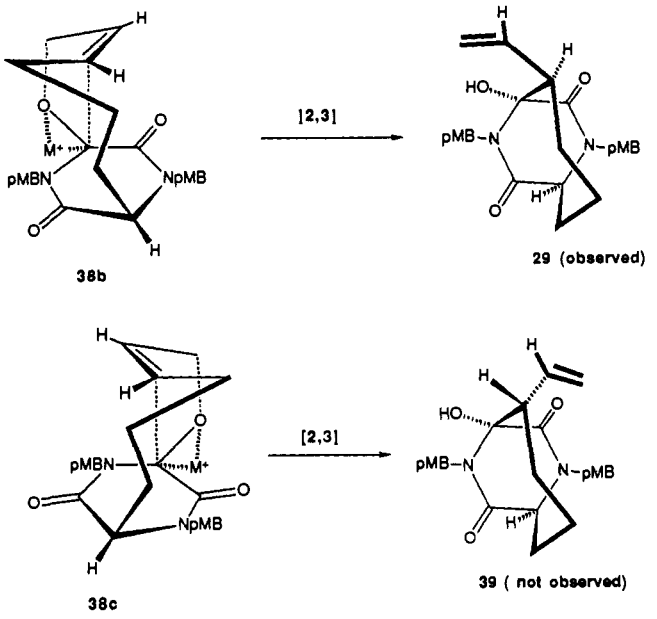


Figure 2. Molecular structure of **29**. Spheres are of fixed, arbitrary radius. The *N*-(*p*-methoxybenzyl) group has been diminished for clarity.

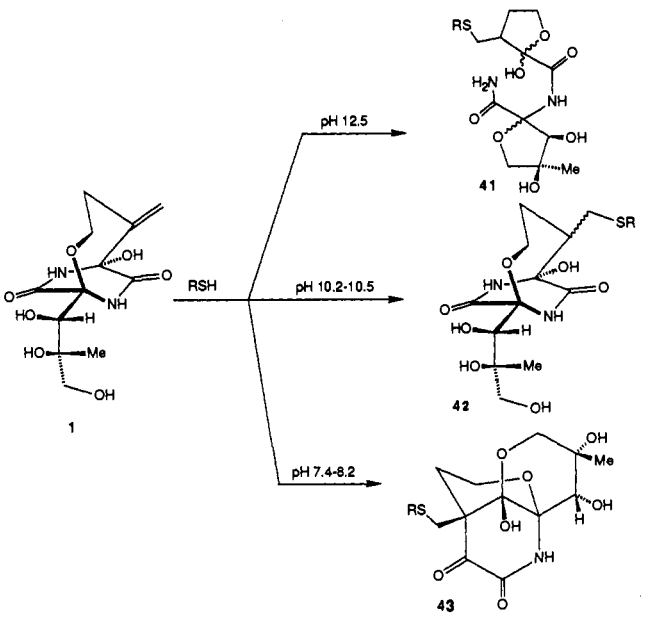
(13) (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563. (b) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(14) Wu, Y-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421.

Scheme XI



Scheme XII



oxygen atom resulting in increased electron density at the enolate α-carbon and thus favoring the [2,3] Wittig process. Less clear, however, is the remarkable [2,3] preference of the methylated substrate **23** (Scheme VI), which does not display the ambident behavior of **22** with Li^+. Models hint that an eclipsing interaction between the bridgehead methyl group and one of the methylene hydrogens occurs from the conformer (see **38a** for comparison) that positions the alkene correctly for the Claisen, whereas this interaction is gauche when the alkene is shifted slightly toward the bridgehead carbon for the [2,3] process (see **38b** for comparison). In any event, **22**, **23**, and similar derivatives provide interesting substrates to learn more about competing [2,3] and [3,3] sigmatropic rearrangements.[15]

An initial screening of **3** against several Gram-negative organisms that bicyclomycin displays activity toward (*Escherichia coli* 25922, *Klebsiella pneumonia* 10031, and *Seratia marcescens*) and Gram-positive microbes (*Micrococcus luteus* 9431, *Staphyllococcus aureus*, and *Bacillus subtilis*) at concentrations up to 5 mg/mL showed no evidence for antimicrobial activity.[12]

Kohn and Abuzar[3h] have detailed the very interesting change in product profile when bicyclomycin is reacted with thiols at different pH. At high pH, the spiro-rearranged product **41** is produced (Scheme XII); at pH 10.2–10.5, the unrearranged Michael adduct **42** is formed, whereas at physiological pH, the unusual Claisen-rearranged thiol adduct **43** is produced. If any of these reaction products have relevancy to the mechanism of action of bicyclomycin, the bridging-ether oxygen atom would not, a priori, play a functional role in the formation of either **42** or **43**; only the spiro product **41** would require the presence of this oxygen atom. Analogue **3** is therefore incapable of forming substances such as **41**. While other biomechanistic roles for the C-1 position of bicyclomycin may be invoked, the complete lack of antimicrobial activity displayed by **3** reinforces our initial[3b,c] doubts about the significance of products such as **42** as well as that of **43**. The significance of spiro reactions culminating in **2** (which is itself devoid of antimicrobial activity), **42**, or other substitution reactions at C-1 should, in light of these studies, warrant more careful consideration.

While one must be very careful not to overinterpret the results of an initial antimicrobial screen as an intrinsic measure of enzyme-inhibitory properties, these results at least point out the functional group significance of the bridging-ether oxygen atom in the bicyclomycin structure. The intricacies of the transport of **1** versus **3** across the outer membrane and peptidoglycan to the inner membrane where the bicyclomycin-binding proteins reside is not known.[16] These results deepen the rather unique mystery[1,6] that envelops the remarkable sensitivity of the bicyclomycin structure[4h] to structural change. Studies are in progress to elucidate the intrinsic reactivity of **3** relative to **1** toward nucleophilic capture, ring opening, proteolysis, and rearrangement that may shed light on this interesting biomechanistic problem.

Experimental Section[18]

All ^1H NMR spectra were obtained on a Bruker WP 270 SY (270 MHz) spectrometer in $CDCl_3$ unless otherwise stated, and are reported in δ values. ^{13}C NMR spectra were obtained on a Bruker WP 270 SY (75.47 MHz) spectrometer in $CDCl_3$ unless otherwise stated. Melting points were recorded on a Mel-Temp instrument in open capillaries and are uncorrected. Infrared spectra were recorded on a Beckman 4240 or a Perkin-Elmer 1600 FT-IR spectrophotometer and are reported as λ_{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 Research 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 (THF) 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 hertz. The chemical shifts of protons that are part of an AB quartet ($^1/_2$ AB q) were calculated by using a standard weighting formula.

The following abbreviations are used throughout this section: THF = tetrahydrofuran, HMPA = hexamethylphosphoramide, LHMDS = lithium hexamethyldisilazide.

Microanalyses were performed by MHW Laboratories, Phoenix, AZ, or Spang Microanalytical Laboratory, Eagle Harbor, MI, and are within ± 0.4% of the calculated values.

***N*-(*p*-Methoxybenzyl)-2-[*N*'-(*p*-methoxybenzyl)-*N*'-(dichloroacetyl)-amino]acetamide (17).** To a stirred solution of *N*,*N*'-bis(*p*-methoxybenzyl)-α-aminoacetamide (3.6 g, 11.5 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added a solution of potassium carbonate (1.75 g, 12.6 mmol, 1.1 equiv) in water (20 mL). The mixture was vigorously stirred at 0

(15) For leading references to related competitive [2,3] and [3,3] sigmatropic processes, see: Ziegler, F. *Chem. Rev.* **1988**, *88*, 1423.

(16) It should be noted in this context that **1** and **3** have virtually indistinguishable solubility properties and polarity as evidenced by their mobility on silica gel.

(17) Details of both crystal structure determinations will be published elsewhere: Thompson, M. A.; Anderson, O. P. Submitted for publication.

(18) All compounds described in this paper are racemic.

°C while a solution of dichloroacetyl chloride (1.8 g, 13.7 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added dropwise over 15 min. The reaction was stirred at 0 °C for 2 h, allowed to warm to room temperature, and stirred an additional 14 h. The organic layer was separated, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined extracts and organic layer were dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was recrystallized from EtOAc–hexane to afford 4.0 g (82%) of **17** as a mixture of conformational isomers: mp 108–109 °C (recrystallized from EtOAc–hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.76 (s, 6 H), 3.94 (s) and 4.04 (s) (2 H), 4.25 (d, J = 5.6 Hz) and 4.34 (d, J = 5.6 Hz) (2 H), 4.59 (s) and 4.77 (s) (2 H), 5.82 (bs) and 6.24 (bs) (1 H), 6.30 (s, 1 H), 6.83–6.90 (m, 4 H), 7.13–7.17 (m, 4 H); IR (KBr) 3310, 1688, 1657, 1608 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 425 (M^+, 4), 391 (10), 355 (50), 313 (14), 207 (41), 121 (100). Anal. Calcd for $C_{20}H_{22}Cl_2N_2O_4$ (425.31): C, 56.48; H, 5.21; N, 6.59. Found: C, 56.73; H, 5.31; N, 6.64.

(*Z*)-1,4-Bis(*p*-methoxybenzyl)-3-(4′-hydroxy-2′-butenoxy)-2,5-piperazinedione (4). To a stirred solution of *cis*-2-butene-1,4-diol (1.98 g, 22.5 mmol, 15 equiv) and potassium *tert*-butoxide (0.35 g, 3.3 mmol, 2.2 equiv) in THF (5 mL) at 0 °C was added dropwise over 10 min a solution of dichloride **17** (0.64 g, 1.5 mmol, 1.0 equiv) in THF (4 mL). The mixture was refluxed for 2 h, cooled to room temperature, and diluted with CH_2Cl_2 (200 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Radial chromatography of the residue (4-mm thickness, eluted with 5% MeOH in CH_2Cl_2) afforded 547 mg (83%) of **4** as a viscous oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.54 (t, J = 6.0 Hz, 1 H), 3.75 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 3.78 (s, 6 H), 4.03–4.32 (m, 6 H), 4.33 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.61 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.78 (s, 1 H), 4.97 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.41–5.60 (m, 1 H), 5.82–6.01 (m, 1 H), 6.84–6.88 (m, 4 H), 7.14–7.20 (m, 4 H); IR (NaCl, neat) 3600–3200, 1675, 1610 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 422 ($M^+ - H_2O$, 1), 352 (14), 231 (20), 121 (100). Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.50): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.20; H, 6.36; N, 6.39.

(*Z*)-1,4-Bis(*p*-methoxybenzyl)-3-(4′-chloro-2′-butenoxy)-2,5-piperazinedione (5). To a stirred solution of alcohol **4** (480 mg, 1.1 mmol, 1.0 equiv), 2,4,6-trimethylpyridine (266 mg, 2.2 mmol, 2.0 equiv), and lithium chloride (93 mg, 2.2 mmol, 2.0 equiv) in *N*,*N*-dimethylformamide (3 mL) at 0 °C was added methanesulfonyl chloride (252 mg, 2.2 mmol, 2.0 equiv). The reaction was stirred at 0 °C for 15 min and at 25 °C for 3 h. The mixture was diluted with EtOAc, washed with dilute hydrochloric acid and water, dried over anhydrous sodium sulfate, filtered, and evaporated. The crude product was recrystallized from EtOAc–hexane to afford 270 mg (54%) of **5**: mp 93–94 °C (recrystallized from EtOAc–hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.76–4.28 (m, 7 H), 3.80 (s, 6 H), 4.34 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 4.67 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 4.73 (s, 1 H), 5.00 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 5.57–5.69 (m, 1 H), 5.74–5.90 (m, 1 H), 6.85–6.88 (m, 4 H), 7.15–7.20 (m, 4 H); IR (KBr) 1655, 1607, 1504 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 459 (M^+, 1), 423 (4), 353 (83), 217 (11), 136 (63), 121 (100). Anal. Calcd for $C_{24}H_{27}ClN_2O_5$ (458.94): C, 62.81; H, 5.93; N, 6.10. Found: C, 62.53; H, 6.14; N, 6.08.

(*Z*)-9,11-Bis(*p*-methoxybenzyl)-9,11-diaza-2-oxabicyclo[5.2.2]undec-4-ene-8,10-dione (6a). To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (458 mg, 2.84 mmol, 1.0 equiv) in THF (15 mL) at 0 °C under a nitrogen atmosphere was added *n*-butyllithium (1.8 mL, 2.84 mmol, 1.1 equiv). The solution was stirred for 15 min and cooled to −78 °C. To this solution was added chloride **5** (1.19 g, 2.59 mmol, 1.0 equiv) in THF (5 mL). The mixture was stirred for 2 h, and the reaction was quenched by addition of 10 mL of a saturated ammonium chloride solution. The mixture was diluted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The crude product was purified by Chromatotron (4-mm thickness, eluted with 33% hexane in EtOAc) to afford 885 mg (81%) of **6a**: mp 162–163 °C (recrystallized from EtOAc–hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.65–2.85 (m, 2 H), 3.53 (dd, J = 13.3, 10.8 Hz, 1 H), 3.63 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.84 (dd, J = 13.3, 7.0 Hz, 1 H), 4.02 ($^1/_2$ AB q, J = 14.3 Hz, 1 H), 4.16 (dd, J = 7.9, 3.5 Hz, 1 H), 4.93 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.05 ($^1/_2$ AB q, J = 14.3 Hz, 1 H), 5.15 (s, 1 H), 5.59 (dt, J = 10.7, 7.6 Hz, 1 H), 5.98 (dt, J = 10.8, 6.6 Hz, 1 H), 6.84–6.93 (m, 4 H), 7.14–7.29 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 28.8, 46.0, 46.8, 55.1, 56.6, 57.2, 81.8, 114.1, 114.3, 126.4, 126.9, 129.9, 130.1, 131.6, 159.4, 159.6, 165.0, 169.6; IR (KBr) 1662, 1609 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 422 (M^+, 34), 136 (100), 121 (83). Anal. Calcd for $C_{24}H_{26}N_2O_5$ (422.48): C, 68.23; H, 6.20; N, 6.63. Found: C, 68.04; H, 6.37; N, 6.57.

(*Z*)-9,11-Bis(*p*-methoxybenzyl)-9,11-diaza-7-methyl-2-oxabicyclo-[5.2.2]undec-4-ene-8,10-dione (6b). To 1,1,1,3,3,3-hexamethyldisilazane (92 mg, 0.57 mmol, 1.2 equiv) dissolved in tetrahydrofuran (15 mL) at 0 °C under a nitrogen atmosphere was added *n*-butyllithium in hexane (0.36 mL, 0.57 mmol, 1.2 equiv). The solution was stirred for 15 min, and then hexamethylphosphoric triamide (168 mg, 0.94 mmol, 2.0 equiv) was added and the solution was cooled to −78 °C. A solution of **6a** (200 mg, 0.47 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) was added, and the resulting solution was stirred for 1 h at −78 °C under a nitrogen atmosphere. Iodomethane (200 mg, 1.41 mmol, 3.0 equiv) was added, the solution was stirred for 1 h at −78 °C, and the reaction was quenched with the addition of 5 mL of a saturated ammonium chloride solution. The mixture was diluted with 200 mL of dichloromethane, washed with two 40-mL portions of water, and dried over anhydrous sodium sulfate. The crude product was chromatographed on a Chromatotron (2-mm thickness, eluted with 67% ethyl acetate in hexane) to afford 179 mg (87%) of **6b** as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.69 (s, 3 H), 2.53 (dd, J = 15.5, 9.1 Hz, 1 H), 2.90–2.99 (m, 1 H), 3.57 (dd, J = 12.9, 11.1 Hz, 1 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 3.79–3.90 (m, 2 H), 4.07 ($^1/_2$ AB q, J = 14.2 Hz, 1 H), 4.90 ($^1/_2$ AB q, J = 15.2 Hz, 1 H), 5.11 ($^1/_2$ AB q, J = 14.2 Hz, 1 H), 5.22 (s, 1 H), 5.59–5.68 (m, 1 H), 5.85–5.97 (m, 1 H), 6.81 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.14 (d, J = 8.6 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H); IR (KBr) 1662, 1604 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 436 (M^+, 44), 421 (5), 121 (100). Anal. Calcd for $C_{25}H_{28}N_2O_5$ (436.51): C, 68.79; H, 6.46; N, 6.42. Found: C, 68.69; H, 6.55; N, 6.55.

(*Z*)-9,11-Bis(*p*-methoxybenzyl)-9,11-diaza-7-hydroxy-2-oxabicyclo-[5.2.2]undec-4-ene-8,10-dione (6c). To 1,1,1,3,3,3-hexamethyldisilazane (497 mg, 3.1 mmol, 1.3 equiv) dissolved in tetrahydrofuran (30 mL) at 0 °C under a nitrogen atmosphere was added *n*-butyllithium in hexane (1.9 mL, 3.1 mmol, 1.3 equiv). The solution was stirred for 15 min, and then hexamethylphosphoric triamide (849 mg, 4.7 mmol, 2.0 equiv) was added and the solution was cooled to −78 °C. A solution of **6a** (1.00 g, 2.37 mmol, 1.0 equiv) in tetrahydrofuran (20 mL) was added, and the resulting solution was stirred for 1 h at −78 °C under a nitrogen atmosphere. Moisture-free oxygen was bubbled into the solution for 1 h, and the reaction was quenched with 10 mL of water. The mixture was extracted with 300 mL of dichloromethane, and the organic phase was washed with two 30-mL portions of a 1.0 M stannous chloride solution in 1.0 M hydrochloric acid (to reduce hydroperoxide) and two 80-mL portions of brine, and dried over anhydrous sodium sulfate. The crude product was purified by Chromatotron (4-mm thickness, eluted with 67% ethyl acetate in hexane) to afford 939 mg (90%) of **6c**: mp 189–190 °C (recrystallized from ethyl acetate); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.75 (dd, J = 15.5, 9.3 Hz, 1 H), 2.91–2.99 (m, 1 H), 3.62 (dd, J = 12.9, 10.9 Hz, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 3.85 (dd, J = 13.3, 7.0 Hz, 1 H), 4.29 ($^1/_2$ AB q, J = 14.1 Hz, 1 H), 4.38 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 4.55 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 4.88 (s, 1 H), 4.99 ($^1/_2$ AB q, J = 14.1 Hz, 1 H), 5.17 (s, 1 H), 5.30–5.43 (m, 1 H), 5.78–5.88 (m, 1 H), 6.79–6.90 (m, 4 H), 7.24–7.42 (m, 4 H); IR (KBr) 3600–3200, 1671, 1645, 1607, 1508 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 438 (M^+, 14), 246 (36), 211 (46), 121 (100). Anal. Calcd for $C_{24}H_{26}N_2O_6$ (438.48); C, 65.74; H, 5.98; N, 6.39. Found: C, 65.93; H, 5.93; N, 6.22.

(*Z*)-9,11-Bis(*p*-methoxybenzyl)-9,11-diaza-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[5.2.2]undec-4-ene-8,10-dione (6d). To alcohol **6c** (40 mg, 0.091 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added 2,6-lutidine (20 mg, 0.18 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl triflate (96 mg, 0.36 mmol, 4.0 equiv). The reaction was stirred for 15 h and diluted with CH_2Cl_2 (50 mL). The organic phase was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by PTLC (eluted with 50% ethyl acetate in hexane) to afford 36 mg (73%) of **6d** as an oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.24 (s, 3 H), 0.40 (s, 3 H), 0.81 (s, 9 H), 2.64 (dd, J = 15.3, 9.4 Hz, 1 H), 3.12 (dd, J = 15.3, 6.7 Hz, 1 H), 3.56–3.65 (m, 1 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 3.87 (dd, J = 13.2, 6.6 Hz, 1 H), 4.03 ($^1/_2$ AB q, J = 14.2 Hz, 1 H), 4.46 (s, 2 H), 5.09 (s, 1 H), 5.15 ($^1/_2$ AB q, J = 14.2 Hz, 1 H), 5.55–5.64 (m, 1 H), 5.77–5.87 (m, 1 H), 6.76–6.87 (m, 4 H), 7.17–7.26 (m, 4 H); IR (NaCl, neat) 1670, 1602, 1501 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 552 (M^+, 44), 136 (49), 121 (100).

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-1-hydroxy-2-ethenylbicyclo-[2.2.2]octane-5,7-dione (9a). To **6a** (100 mg, 0.24 mmol, 1.0 equiv) in tetrahydrofuran (15 mL) at −78 °C under a nitrogen atmosphere was added *n*-butyllithium (0.17 mL, 0.26 mmol, 1.1 equiv). The yellow solution was stirred for 50 min, and then quenched with saturated aqueous ammonium chloride solution (5 mL). The crude mixture was diluted with dichloromethane (80 mL), washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. Chromatography (Chromatotron, 2-mm thickness, eluted with 67% ethyl acetate in hexane) yielded 46 mg (46%) of **9a** as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.55–1.62 (m, 1 H), 1.95–2.04 (m, 1 H), 2.48–2.59 (m, 1 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 3.98 (dd, J = 3.5, 2.0 Hz, 1 H), 4.33 ($^1/_2$

AB q, J = 14.6 Hz, 1 H), 4.40 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.60 (s, 1 H), 4.65 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.67 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.09–5.16 (m, 2 H), 5.43–5.56 (m, 1 H), 6.77–6.88 (m, 4 H), 7.10–7.23 (m, 4 H); IR (NaCl, neat) 3500–3100 (br), 1686, 1610, 1583, 1512 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 422 (M$^+$, 34), 183 (29), 166 (20), 136 (100), 121 (95).

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-1-hydroxy-4-methyl-2-ethenylbicyclo[2.2.2]octane-5,7-dione (9b) and 6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-1-hydroxy-4-methyl-2-ethenylbicyclo[3.2.1]octane-5,7-dione (10b). To **6b** (21 mg, 0.048 mmol, 1.0 equiv) in tetrahydrofuran (1 mL) at −100 °C under a nitrogen atmosphere was added *n*-butyllithium in hexane (0.045 mL, 0.072 mmol, 1.5 equiv). The solution was stirred for 20 min, and then quenched with 2 mL of a saturated ammonium chloride solution. The mixture was diluted with 40 mL of dichloromethane, washed with two 10-mL portions of water, and dried over anhydrous sodium sulfate. The crude product was chromatographed by PTLC (eluted with 50% ethyl acetate in hexane) to afford two products.

9b: 6.3 mg (30%) as an oil, R_f 0.43; ^{1}H NMR (270 MHz, CDCl$_3$) δ 1.49–1.55 (m, 1 H), 1.53 (s, 3 H), 2.10 (dd, J = 13.9, 10.1 Hz, 1 H), 2.58–2.63 (m, 1 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.40 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 4.59 (s, 2 H), 4.71 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 4.74 (s, 1 H, D$_2$O exchange), 5.12–5.19 (m, 2 H), 5.48–5.60 (m, 1 H), 6.75–7.22 (m, 8 H); IR (NaCl, neat) 3500–3050, 1690, 1678, 1608, 1580, 1510 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 437 (M$^+$, 15), 317 (2), 183 (5), 121 (100).

10b: 6.6 mg (31%) as an oil, R_f 0.67; mp 99–100 °C (recrystallized from CH$_2$Cl$_2$–hexane); ^{1}H NMR (270 MHz, CDCl$_3$) δ 1.29 (s, 3 H), 1.67 (dd, J = 13.7, 5.7 Hz, 1 H), 2.18 (dd, J = 13.7, 11.3 Hz, 1 H), 2.96–3.08 (m, 1 H), 3.23 ($^1/_2$ AB q, J = 14.8 Hz, 1 H), 3.69 ($^1/_2$ AB q, J = 14.9 Hz, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.28 (s, 1 H), 4.80 (s, 2 H), 4.97–5.06 (m, 2 H), 5.19–5.33 (m, 1 H), 6.78–7.34 (m, 8 H); IR (NaCl, neat) 3550–3200, 1724, 1671, 1635, 1603, 1576, 1500 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 437 (M$^+$, 15), 423 (9), 317 (4), 121 (100). Anal. Calcd for C$_{25}$H$_{28}$N$_2$O$_5$ (436.51): C, 68.79; H, 6.46; N, 6.42. Found: C, 68.57; H, 6.43; N, 6.36.

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-1,4-dihydroxy-2-ethenylbicyclo-[2.2.2]octane-5,7-dione (9c). To alcohol **6c** (40 mg, 0.091 mmol, 1.0 equiv) in tetrahydrofuran (2 mL) at −100 °C under a nitrogen atmosphere was added *n*-butyllithium in hexane (0.114 mL, 0.18 mmol, 2.0 equiv). The resulting rose solution was stirred for 15 min and quenched with 2 mL of a saturated ammonium chloride solution. The crude mixture was diluted with 50 mL of dichloromethane, washed with two 20-mL portions of water, and dried over anhydrous sodium sulfate. The crude product was chromatographed by PTLC (eluted with 50% ethyl acetate in hexane) to afford 29 mg (72%) of **9c**: mp 88–89 °C (recrystallized from CH$_2$Cl$_2$–hexane); ^{1}H NMR (270 MHz, CDCl$_3$) δ 1.55–1.61 (m, 1 H), 2.19–2.28 (m, 1 H), 2.46–2.54 (m, 1 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.41 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.59 (s, 2 H), 4.69 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.76 (s, 1 H, D$_2$O exchange), 4.84 (s, 1 H, D$_2$O exchange), 5.09–5.17 (m, 2 H), 5.42–5.55 (m, 1 H), 6.76–6.83 (m, 4 H), 7.08–7.21 (m, 4 H); IR (KBr) 3600–3100, 1678, 1614, 1588, 1514 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 438 (M$^+$, 10), 208 (10), 166 (11), 121 (100). Anal. Calcd for C$_{24}$H$_{26}$N$_2$O$_6$ (438.48): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.94; H, 6.01; N, 6.30.

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-4-[(*tert*-butyldimethylsilyl)-oxy]-2-ethenyl-1-hydroxybicyclo[2.2.2]octane-5,7-dione (9d) and 6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-4-[(*tert*-butyldimethylsilyl)oxy]-2-ethenyl-1-hydroxybicyclo[3.2.1]octane-5,7-dione (10d). To silyl ether **6d** (25 mg, 0.045 mmol, 1.0 equiv) in tetrahydrofuran (1 mL) at −100 °C under a nitrogen atmosphere was added *n*-butyllithium in hexanes (0.028 mL, 0.045 mmol, 1.0 equiv). The reaction was stirred for 15 min and then quenched with 2 mL of a saturated ammonium chloride solution. The mixture was diluted with 50 mL of dichloromethane, washed with two 20-mL portions of water, and dried over anhydrous sodium sulfate. The crude product was chromatographed by PTLC (eluted with 33% ethyl acetate in hexane) to afford two products. **9d**: 12 mg (48%) as an oil, R_f 0.54; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.20 (s, 3 H), 0.23 (s, 3 H), 0.94 (s, 9 H), 1.75–1.88 (m, 1 H), 2.24–2.32 (m, 1 H), 2.55–2.63 (m, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.34 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 4.55 ($^1/_2$ AB q, J = 15.0 Hz, 1 H), 4.57 (s, 1 H, D$_2$O exchange), 4.69 ($^1/_2$ AB q, J = 15.0 Hz, 1 H), 4.69 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 5.11–5.20 (m, 2 H), 5.49–5.62 (m, 1 H), 6.70 (d, J = 8.5 Hz, 2 H), 6.77 (d, J = 8.6 Hz, 2 H), 7.01 (d, J = 8.5 Hz, 2 H), 7.07 (d, J = 8.6 Hz, 2 H); IR (NaCl, neat) 3500–3100, 1698, 1612, 1586, 1510 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 552 (M$^+$, 1), 400 (1), 372 (1), 154 (27), 136 (75), 121 (35). **10d**: 8 mg (32%) as an oil, R_f 0.63; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.14 (s, 3 H), 0.27 (s, 3 H), 0.83 (s, 9 H), 1.72 (dd, J = 13.7, 6.1 Hz, 1 H), 2.30–2.39 (m, 1 H), 2.97–3.08 (m, 1 H), 3.48 ($^1/_2$ AB q, J = 15.2 Hz, 1 H), 3.66 ($^1/_2$ AB q, J = 15.2 Hz, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.07 (s, 1 H), 4.69 (AB q, J = 7.6 Hz, 2 H), 4.92–5.21 (m, 3 H), 6.77–7.31 (m, 8 H).

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-1-[(*tert*-butyldimethylsilyl)-oxy]-2-ethenylbicyclo[2.2.2]octane-5,7-dione (11). To alcohol **9a** (132 mg, 0.312 mmol, 1.0 equiv) in dichloromethane (2 mL) at 25 °C was added 2,6-lutidine (50 mg, 0.47 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl triflate (1.0 M in CH$_2$Cl$_2$, 0.64 mL, 0.64 mmol, 2.0 equiv). The reaction was stirred at 25 °C for 30 h, diluted with dichloromethane (80 mL), washed with brine, and dried over anhydrous sodium sulfate. Radial chromatography (2-mm thickness, eluted with 50% ethyl acetate in hexane) afforded 147 mg (88%) of **11** as a foam: ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.07 (s, 3 H), 0.24 (s, 3 H), 0.87 (s, 9 H), 1.51–1.65 (m, 1 H), 1.93–2.04 (m, 1 H), 2.60–2.71 (m, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 3.92 (dd, J = 3.7, 2.0 Hz, 1 H), 4.41 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.43 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 4.66 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.79 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 5.07–5.21 (m, 2 H), 5.59–5.69 (m, 1 H), 6.75–7.19 (m, 8 H); IR (NaCl, neat) 1705, 1687, 1608, 1580, 1507 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 536 (M$^+$, 29), 406 (4), 136 (100), 121 (74).

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-4-[(*tert*-butyldimethylsilyl)-oxy]-3-(hydroxymethyl)bicyclo[2.2.2]octane-5,7-dione (12). Into a solution of olefin **11** (181 mg, 0.38 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (25 mL) at −78 °C was bubbled ozone until a pale blue color persisted. The reaction was purged with O$_2$ to remove excess ozone, and NaBH$_4$ (64 mg, 1.7 mmol, 5.0 equiv) in methanol (2 mL) was added. The reaction was warmed to room temperature and stirred for 5 h. The crude mixture was diluted with dichloromethane (100 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (2-mm thickness, eluted with 33% hexane in EtOAc) to afford 137 mg (75%) of **12** as a foam: mp 127–129 °C (recrystallized from methanol); ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.05 (s, 3 H), 0.25 (s, 3 H), 0.92 (s, 9 H), 1.64 (br s, 1 H, D$_2$O exchange), 1.67–1.75 (m, 1 H), 1.86–1.96 (m, 1 H), 2.14–2.24 (m, 1 H), 3.48–3.58 (m, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 3.92–3.98 (m, 2 H), 4.38 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 4.38 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 4.66 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 4.72 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 6.76–7.18 (m, 8 H); IR (NaCl, neat) 3600–3100, 1686, 1678, 1609, 1580, 1509 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 540 (M$^+$, 77), 482 (18), 136 (61), 121 (100). Anal. Calcd for C$_{29}$H$_{40}$N$_2$O$_6$Si (540.73): C, 64.42; H, 7.46; N, 5.18. Found: C, 64.24; H, 7.57; N, 5.06.

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-4-[(*tert*-butyldimethylsilyl)-oxy]-3-[(phenylselenyl)methyl]bicyclo[2.2.2]octane-5,7-dione (13). To alcohol **12** (228 mg, 0.42 mmol, 1.0 equiv), in THF (4 mL) at 0 °C was added triethylamine (128 mg, 1.26 mmol, 3.0 equiv) and methanesulfonyl chloride (97 mg, 0.84 mmol, 2.0 equiv), The mixture was stirred at 0 °C for 1 h and filtered. The white precipitate was washed with cold THF, and the filtrate and washings were combined. In a separate flask, NaBH$_4$ (64 mg, 1.68 mmol, 4.0 equiv) was added to a solution of diphenyl diselenide (263 mg, 0.84 mmol, 2.0 equiv) in ethanol (3 mL). The mixture was stirred until H$_2$ evolution ceased, and it was then added to the crude mesylate solution. The reaction was stirred at 65 °C for 1 h, diluted with CH$_2$Cl$_2$ (80 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (2-mm thickness, eluted with 33% EtOAc in hexane) to afford 252 mg (88%) of **13** as a foam: mp 165–166 °C (recrystallized from ethanol); ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.90 (s, 9 H), 1.63 (dd, J = 11.5, 2.3 Hz, 1 H), 1.92–2.17 (m, 2 H), 2.24–2.32 (m, 1 H), 3.43 (dd, J = 11.5, 2.3 Hz, 1 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 3.92–3.94 (m, 1 H), 4.41 ($^1/_2$ AB q, J = 15.3 Hz, 1 H), 4.42 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.59 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.79 ($^1/_2$ AB q, J = 15.3 Hz, 1 H), 6.76–7.16 (m, 8 H), 7.24–7.33 (m, 3 H), 7.44–7.48 (m, 2 H); IR (KBr) 1695, 1612, 1586, 1513 cm^{-1}; mass spectrum (CI(NH$_3$)), m/e (relative intensity) 679 (M$^+$, 45), 620 (11), 522 (19), 121 (100). Anal. Calcd for C$_{35}$H$_{44}$N$_2$O$_5$SeSi (679.79): C, 61.84; H, 6.52; N, 4.12. Found: C, 61.72; H, 6.67; N, 4.09.

6,8-Bis(*p*-methoxybenzyl)-6,8-diaza-4-[(*tert*-butyldimethylsilyl)-oxy]-3-methylenebicyclo[2.2.2]octane-5,7-dione (14). To selenide **13** (200 mg, 0.29 mmol, 1.0 equiv) in THF (15 mL) was added 30% H$_2$O$_2$ (333 mg, 2.94 mmol, 10 equiv), and the mixture was refluxed for 40 min. The mixture was diluted with CH$_2$Cl$_2$ (80 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (2-mm thickness, eluted with 50% EtOAc in hexane) to afford 146 mg (95%) of **14**: mp 75–76 °C (recrystallized from methanol); ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.12 (s, 3 H), 0.28 (s, 3 H), 0.92 (s, 9 H), 2.34–2.56 (m, 2 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.00 (t, J = 2.2 Hz, 1 H), 4.35 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.47 ($^1/_2$ AB q, J = 15.6 Hz, 1 H), 4.65 ($^1/_2$ AB q, J = 15.6 Hz, 1 H), 4.76 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 5.10 (br s, 1 H), 5.55 (br s, 1 H), 6.75–7.18 (m, 8 H); IR (KBr) 1695, 1612, 1586, 1513 cm^{-1}; mass

spectrum (CI(NH_3)), *m/e* (relative intensity) 522 (M^+, 42), 465 (4), 360 (19), 136 (51), 121 (100). Anal. Calcd for $C_{29}H_{38}N_2O_5Si \cdot {}^1/_2H_2O$ (531.73): C, 65.51; H, 7.39; N, 5.27. Found: C, 65.29; H, 7.41; N, 5.27.

1,4-Bis(*p*-methoxybenzyl)-3-methoxy-2,5-piperazinedione (18). To sodium (1.93 g, 84.1 mmol, 2.3 equiv) in methanol (200 mL) was added dichloride **17** (15.54 g, 36.5 mmol, 1.0 equiv). The mixture was refluxed for 6 h, and the reaction was quenched with saturated ammonium chloride solution. The methanol was evaporated, and the residue was dissolved in CH_2Cl_2 (600 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by flash column chromatography (eluted with 33% hexane in EtOAc) and recrystallized from EtOAc–hexane to afford 9.07 g (65%) of **18**: mp 78 °C (recrystallized from EtOAc–hexane); ^1H NMR (270 MHz, $CDCl_3$) δ 3.40 (s, 3 H), 3.78 ($^1/_2$ AB q, J = 17.5 Hz, 1 H), 3.80 (s, 6 H), 4.01 ($^1/_2$ AB q, J = 17.5 Hz, 1 H), 4.10 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.33 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 4.67 (s, 1 H), 4.69 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 5.07 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 6.85–6.89 (m, 4 H), 7.15–7.21 (m, 4 H); IR (KBr) 1675, 1659, 1613, 1514 cm^{-1}; mass spectrum (EI), *m/e* (relative intensity) 384 (M^+, 1), 352 (20), 231 (38), 121 (100). Anal. Calcd for $C_{21}H_{24}N_2O_5$ (384.43): C, 65.61; H, 6.29; N, 7.29. Found: C, 65.64; H, 6.19; N, 7.31.

(*Z*)-1,4-Bis(*p*-methoxybenzyl)-3-[6′-(tetrahydropyranyloxy)-4′-hexenyl]-6-methoxy-2,5-piperazinedione (20). To diketopiperazine **18** (330 mg, 0.86 mmol, 1.0 equiv) and iodide **19** (293 mg, 0.94 mmol, 1.1 equiv) in THF (4 mL) at −78 °C under nitrogen was added hexamethylphosphoramide (0.2 mL) and 1 M lithium hexamethyldisilazide in THF (0.9 mL, 0.90 mmol, 1.05 equiv). The mixture was stirred for 2 h, quenched with saturated aqueous ammonium chloride solution (4 mL), and extracted with EtOAc (200 mL). The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by radial chromatography (2-mm thickness, eluted with 50% EtOAc in hexane) to afford 375 mg (77%) of **20** as a mixtuire of 2,5-syn and 2,5-anti diastereomers: ^1H NMR (270 MHz, $CDCl_3$) δ 1.47–1.63 (m, 6 H), 1.70–1.81 (m, 2 H), 1.84–1.96 (m, 2 H), 2.02–2.13 (m, 2 H), 3.36 and 3.50 (s, 3 H), 3.48–3.57 (m, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 3.76–3.84 (m, 1 H), 3.87–3.94 (m, 1 H), 3.95 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 4.04–4.13 (m, 1 H), 4.07 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 4.21–4.29 (m, 1 H), 4.57 and 4.79 (s, 1 H), 4.63–4.68 (m, 1 H), 5.07 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.09 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 5.46–5.65 (m, 2 H), 6.83–6.88 (m, 4 H), 7.12–7.25 (m, 4 H); IR (NaCl, neat) 2996, 2939, 2868, 2836, 1667, 1613, 1585, 1513, 1454 cm^{-1}.

Preparation of 19: 5-[(*tert*-Butyldimethylsilyl)oxy]-1-pentyne. To 4-pentyn-1-ol (5.53 g, 65.7 mmol, 1.0 equiv), triethylamine (7.3 g, 72.3 mmol, 1.1 equiv), and 4-(dimethylamino)pyridine (80 mg, 0.66 mmol, 0.01 equiv) in dichloromethane (100 mL) at 0 °C was added dropwise over 15 min a solution of *tert*-butyldimethylsilyl chloride (10.9 g, 72.3 mmol, 1.1 equiv) in dichloromethane (100 mL). The reaction was stirred at 0 °C for 1 h and at 25 °C for 20 h. The reaction mixture was diluted with dichloromethane (200 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Distillation of the crude product yielded 12.15 g (93%) as a clear, colorless liquid: bp 88–89 °C (17 mmHg); ^1H NMR (270 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.68–1.77 (m, 2 H), 1.93 (t, J = 2.6 Hz, 1 H), 2.28 (dt, J = 7.1, 2.6 Hz, 2 H), 3.70 (t, J = 6.0 Hz, 2 H); IR (NaCl, neat) 3310, 2100, 1250, 1098 cm^{-1}; mass spectrum (CI(NH_3)), *m/e* (relative intensity) 199 (M^+, 100), 158 (10), 132 (12). **6-(*tert*-Butyldimethylsilyloxy)-2-hexyn-1-ol.** To the acetylene obtained above (6.00 g, 30.2 mmol, 1.0 equiv) in tetrahydrofuran (60 mL) at −78 °C under a nitrogen atmosphere was added *n*-butyllithium in hexanes (22.2 mL, 33.3 mmol, 1.1 equiv). The solution was stirred for 30 min, then paraformaldehyde (1.09 g, 36.2 mmol, 1.2 equiv) suspended in tetrahydrofuran (20 mL) was added, and the reaction was stirred for 1 h at −78 °C and for 3 h at 25 °C. The reaction was quenched with the addition of saturated aqueous ammonium chloride solution, diluted with ethyl acetate (300 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The crude product was distilled to yield 5.92 g (86%) as a clear, colorless liquid: bp 107–109 °C (0.9 mm); ^1H NMR (270 MHz, $CDCl_3$): δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.52–1.64 (br s, 1 H, D_2O exchange), 1.66–1.76 (m, 2 H), 2.30 (tt, J = 7.1, 2.1 Hz, 2 H), 3.68 (t, J = 6.0 Hz, 2 H), 4.25 (br s, 2 H); IR (NaCl, neat) 3600–3100 (br), 2205, 1463 cm^{-1}; mass spectrum (CI(NH_3)), *m/e* (relative intensity) 229 (M^+, 45), 213 (23), 199 (92), 132 (27). Anal. Calcd for $C_{12}H_{24}O_2Si$ (228.41): C, 63.10; H, 10.59. Found: C, 62.94; H, 10.60. **(*Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-hexen-1-ol.** To the alkyne obtained above (1.86 g, 8.13 mmol) in methanol (18 mL) was added synthetic quinoline (0.1 mL) and 5% palladium on calcium carbonate poisoned with lead (36 mg). The reaction was stirred under a hydrogen atmosphere at 25 °C for 8 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. Distillation of the crude product afforded 1.48 g (79%) as a clear, colorless, liquid: bp 103–104 °C (0.95 mmHg); ^1H NMR (270 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.53–1.64 (m, 2 H), 1.80–1.88 (br s, 1 H, D_2O exchange), 2.15–2.24 (m, 2 H), 3.63 (t, J = 6.1 Hz, 2 H), 4.16 (d, J = 6.7 Hz, 2 H), 5.48–5.58 (m, 1 H), 5.65–5.76 (m, 1 H); IR (NaCl, neat) 3600–3100 (br), 3000, 1458 cm^{-1}; mass spectrum (CI(NH_3)), *m/e* (relative intensity) 230 (M^+, 100), 213 (34), 130 (34). Anal. Calcd for $C_{12}H_{26}O_2Si$ (230.42): C, 62.55; H, 11.37. Found: C, 62.88; H, 11.11. **(*Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-(tetrahydropyranyloxy)-2-hexene.** To the alcohol obtained above (781 mg, 3.4 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) was added 3,4-dihydro-2*H*-pyran (342 mg, 4.1 mmol, 1.2 equiv) and pyridinium *p*-toluenesulfonate (85 mg, 0.34 mmol, 0.1 equiv). The mixture was stirred for $4^1/_2$ h and diluted with EtOAc (200 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by distillation under reduced pressure to afford 846 mg (79%) as a clear, colorless liquid: bp 136 °C (0.75 mmHg); ^1H NMR (270 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 1.51–1.88 (m, 8 H), 2.09–2.18 (m, 2 H), 3.46–3.54 (m, 1 H), 3.63 (t, J = 6.1 Hz, 2 H), 3.83–3.94 (m, 1 H), 4.04–4.12 (m, 1 H), 4.22–4.30 (m, 1 H), 4.62–4.66 (m, 1 H), 5.56–5.63 (m, 2 H); IR (NaCl, neat) 2939, 2850, 1253 cm^{-1}; mass spectrum (CI(NH_3)), *m/e* (relative intensity) 331 ($M^+ + NH_3$, 3), 231 (70), 229 (30), 213 (30), 102 (100), 85 (100). **(*Z*)-1-(Tetrahydropyranyloxy)-2-hexen-6-ol.** To the silyl ether obtained above (793 mg, 2.52 mmol, 1.0 equiv) in THF (3 mL) was added 1.0 M tetrabutylammonium fluoride in THF (3.8 mL, 3.8 mmol, 1.5 equiv). The mixture was stirred at 25 °C for 2 h and diluted with ether (80 mL). The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (4-mm thickness, eluted with 33% hexane in EtOAc) to afford 461 mg (91%) as an oil: bp 115–120 °C (Kugelrohr oven temperature @ 1.0 mmHg); ^1H NMR (270 MHz, $CDCl_3$) δ 1.50–1.82 (m, 8 H), 2.18–2.28 (m, 2 H), 2.67 (br s, 1 H, D_2O exchange), 3.49–3.57 (m, 1 H), 3.61 (t, J = 6.2 Hz, 2 H), 3.83–3.94 (m, 1 H), 4.07–4.14 (m, 1 H), 4.22–4.32 (m, 1 H), 4.62–4.67 (m, 1 H), 5.56–5.66 (m, 2 H); IR (NaCl, neat) 3600–3100 (br), 2940, 2869 cm^{-1}; mass spectrum (CI(NH_3)), *m/e* (relative intensity) 217 ($M^+ + NH_3$, 1), 102 (20), 85 (100). Anal. Calcd for $C_{11}H_{20}O_3$ (200.28): C, 65.97; H, 10.07. Found: C, 66.05; H, 10.17. **(*Z*)-1-(Tetrahydropyranyloxy)-6-iodo-2-hexene (19).** To the alcohol obtained above (3.11 g, 15.5 mmol, 1.0 equiv) in THF (60 mL) at 0 °C was added triethylamine (2,4 g, 23.3 mmol, 1.5 equiv) and methanesulfonyl chloride (2.1 g, 18.6 mmol, 1.2 equiv). The mixture was stirred for 1 h at 0 °C and filtered. The white precipitate was washed with cold THF, and the washings and filtrate were combined and evaporated. The residue was dissolved in 2-butanone (100 mL), NaI (7.0 g, 46.6 mmol, 3.0 equiv) was added, and the mixture was refluxed (80 °C) for 1.5 h. The crude product was diluted with EtOAc (600 mL), washed successively with 1 M $Na_2S_2O_3$ and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by flash column chromatography (eluted with 33% EtOAc in hexane) to afford 4.37 g (91%) of **19** as an oil: bp 95–100 °C (Kugelrohr oven temperature @ 0.5 mmHg); ^1H NMR (270 MHz, $CDCl_3$) δ 1.51–1.95 (m, 8 H), 2.17–2.27 (m, 2 H), 3.19 (t, J = 6.9 Hz, 2 H), 3.48–3.57 (m, 1 H), 3.85–3.94 (m, 1 H), 4.03–4.14 (m, 1 H), 4.24–4.32 (m, 1 H), 4.63–4.68 (m, 1 H), 5.50–5.69 (m, 2 H); IR (NaCl, neat) 2940, 2869, 1164 cm^{-1}; mass spectrum (CI(NH_3)), *m/e* (relative intensity) 327 ($M^+ + NH_3$, 1), 225 (2), 114 (12), 102 (58), 85 (100). Anal. Calcd for $C_{11}H_{19}O_2I$ (310.18): C, 42.60; H, 6.17. Found: C, 42.52; H, 6.36.

(*Z*)-1,4-Bis(*p*-methoxybenzyl)-3-(6′-hydroxy-4′-hexenyl)-6-methoxy-2,5-piperazinedione (21). To **20** (193 mg, 0.34 mmol) in methanol (4 mL) was added *p*-toluenesulfonic acid (20 mg, 0.10 mmol). The mixture was stirred at 25 °C for 2 h and diluted with CH_2Cl_2 (80 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (2-mm thickness, eluted with 33% EtOAc in hexane) to afford 136 mg (83%) of **21** as a mixture of 2,5-syn and 2,5-anti diastereomers: ^1H NMR (270 MHz, $CDCl_3$) δ 1.43–1.54 (m, 2 H), 1.75 (br s, 1 H), 1.86–2.12 (m, 4 H), 3.37 and 3.51 (s, 3 H), 3.79–3.88 (m, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 4.00 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 4.08 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 4.14 (d, J = 6.7 Hz, 2 H), 4.58 and 4.81 (s, 1 H), 5.04 ($^1/_2$ AB q, J = 14.7 Hz, 12 H), 5.06 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.36–5.48 (m, 1 H), 5.57–5.67 (m, 1 H), 6.84–6.88 (m, 4 H), 7.12–7.22 (m, 4 H); IR (NaCl, neat) 3600–3100 (br), 1669, 1613, 1585, 1514 cm^{-1}; mass spectrum (CI(NH_3)), *m/e* (relative intensity) 482 (M^+, 26), 450 (100), 136 (57), 121 (93). Anal. Calcd for $C_{27}H_{34}N_2O_6$ (482.58): C, 67.20; H, 7.10; N, 5.81. Found: C, 67.09; H, 6.95; N, 5.73.

(*Z*)-11,13-Bis(*p*-methoxybenzyl)-11,13-diaza-2-oxabicyclo[7.2.2]tridec-4-ene-10,12-dione (22). To alcohol **21** (692 mg, 1.43 mmol, 1.0 equiv) in 1,2-dichloroethane (150 mL) was added *p*-toluenesulfonic acid (14 mg, 0.072 mmol, 0.05 equiv) and pyridinium *p*-toluenesulfonate (269

mg, 1.07 mmol, 0.75 equiv). The mixture was refluxed for 70 h, diluted with CH_2Cl_2 (300 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (4-mm thickness, eluted with 50% ethyl acetate in hexane) to afford 236 mg (37%) of **22** as a foam: mp 116–117 °C (recrystallized from ethanol–diethyl ether) and 122 mg of unreacted **21**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.67–1.76 (m, 1 H), 1.90–2.15 (m, 5 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.91 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 3.98–4.13 (m, 3 H), 4.10 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 4.86 (s, 1 H), 5.16 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.18 ($^1/_2$ AB q, J = 14.7 Hz, 1 H), 5.74–5.82 (m, 2 H), 6.82–6.87 (m, 4 H), 7.11–7.16 (m, 4 H); IR (KBr) 1675, 1612, 1585, 1513 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 450 (M^+, 9), 167 (18), 136 (18), 121 (17), 104 (100). Anal. Calcd for $C_{26}H_{30}O_5N_2$ (450.54): C, 69.31; H, 6.71; N, 6.22. Found: C, 69.33; H, 6.80; N, 6.23.

(*Z*)-11,13-Bis(*p*-methoxybenzyl)-11,13-diaza-9-methyl-2-oxabicyclo-[7,2,2]tridec-4-ene-10,12-dione (23). To **22** (440 mg, 0.98 mmol, 1.0 equiv) in THF (5 mL) at −78 °C under a nitrogen atmosphere was added 1.0 M lithium hexamethyldisilazide in THF (0.4 mL, 0.40 mmol, 2.0 equiv) and HMPA (72 mg, 0.40 mmol, 2.0 equiv). The mixture was stirred for 10 min, and then methyl iodide (556 mg, 3.92 mmol, 4.0 equiv) was added. The reaction was stirred for 1.5 h and quenched with saturated aqueous ammonium chloride solution. The mixture was diluted with ethyl acetate (150 mL), washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (4-mm thickness, eluted with 50% ethyl acetate in hexane) to afford 410 mg (99%) of **23** as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.47 (s, 3 H), 1.53–1.69 (m, 1 H), 1.91–2.14 (m, 5 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 4.01 (dd, J = 10.7, 5.0 Hz, 1 H), 4.10 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.19 (dd, J = 10.7, 5.0 Hz, 1 H), 4.27 ($^1/_2$ AB q, J = 15.6 Hz, 1 H), 4.90 ($^1/_2$ AB q, J = 15.6 Hz, 1 H), 4.95 (s, 1 H), 5.26 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 5.72–5.79 (m, 2 H), 6.79–6.90 (m, 4 H), 7.11–7.21 (m, 4 H); IR (KBr) 1668, 1612, 1512 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 464 (M^+, 100), 449 (10), 136 (43), 121 (56). Anal. Calcd $C_{27}H_{32}N_2O_5$ (464.56): C, 69.81; H, 6.94; N, 6.03. Found: C, 70.00; H, 7.00; N, 6.18.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-hydroxy-1-methyl-5-ethenylbicyclo[4,2,2]decane-7,9-dione (24). To **23** (348 mg, 0.75 mmol, 1.0 equiv) in THF (55 mL) at −78 °C under a nitrogen atmosphere was added 1.50 M *n*-butyllithium in hexane (0.94 mL, 1.50 mmol, 2.0 equiv). The mixture was stirred for 20 min, quenched with saturated aqueous ammonium chloride solution, and diluted with CH_2Cl_2 (200 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by radial chromatography (2-mm thickness, eluted with 50% ethyl acetate in hexane) to afford 294 mg (84%) of **24** as a foam: mp 124–125 °C (recrystallized from methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.12–1.38 (m, 2 H), 1.48 (s, 3 H), 1.69–2.04 (m, 4 H), 2.71–2.82 (m, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.43 ($^1/_2$ AB q, J = 15.3 Hz, 1 H), 4.46 ($^1/_2$ AB q, J = 14.0 Hz, 1 H), 4.72 ($^1/_2$ AB q, J = 14.0 Hz, 1 H), 4.76 (s, 1 H, D_2O exchange), 4.88 ($^1/_2$ AB q, J = 15.3 Hz, 1 H), 5.13–5.23 (m, 2 H), 6.02–6.15 (m, 1 H), 6.77–6.85 (m, 4 H), 7.18–7.30 (m, 4 H); IR (KRr) 3600–3100, 1651, 1610, 1513 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 464 (M^+, 22), 136 (100), 121 (45). Anal. Calcd $C_{27}H_{32}N_2O_5$ (464.56): C, 69.81; H, 6.94; N, 6.03. Found: C, 69.89; H, 6.98; N, 5.96.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-1-methyl-5-ethenylbicyclo[4,2,2]decane-7,9-dione. To alcohol **24** (257 mg, 0.55 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (89 mg, 0.83 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl triflate (218 mg, 0.83 mmol, 1.5 equiv). The mixture was stirred for 1.5 h, diluted with CH_2Cl_2 (80 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (2-mm thickness, eluted with 50% ethyl acetate in hexane) to afford 305 mg (95%) as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.42 (s, 3 H), 0.69 (s, 9 H), 1.23–1.38 (m, 2 H), 1.42 (s, 3 H), 1.74–1.82 (m, 2 H), 1.90–1.97 (m, 2 H), 2.87–2.96 (m, 1 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.18 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 4.71 (s, 2 H), 5.11 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 5.10–5.22 (m, 2 H), 5.96–6.10 (m, 1 H), 6.76–6.89 (m, 4 H), 7.05–7.26 (m, 4 H); IR (KBr) 1666, 1615, 1514, 1247 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 578 (M^+, 99), 520 (12), 463 (15), 446 (13), 136 (49), 121 (100). Anal. Calcd for $C_{33}H_{46}N_2O_5Si$ (578.83): C, 68.48; H, 8.01; N, 4.84. Found: C, 68.47; H, 8.13; N, 4.80.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-5-(hydroxymethyl)-1-methylbicyclo[4,2,2]decane-7,9-dione (25). Into a solution of the olefin obtained above (250 mg, 0.43 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at −78 °C was bubbled ozone until a pale blue color persisted. The reaction was purged with nitrogen to remove excess ozone, and $NaBH_4$ (98 mg, 2.58 mmol, 6.0 equiv) in methanol (3 mL) was added. The reaction was warmed to room temperature, stirred for 7 h, and diluted with CH_2Cl_2 (150 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by radial chromatography (2-mm thickness, eluted with 33% hexane in ethyl acetate) to afford 183 mg (73%) of **25** as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.40 (s, 3 H), 0.73 (s, 9 H), 1.14–1.28 (m, 2 H), 1.43 (s, 3 H), 1.71–2.08 (m, 5 H), 2.30–2.42 (m, 1 H), 3.49–3.56 (m, 1 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 4.16–4.22 (m, 2 H), 4.49 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 4.67 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.08 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 6.78–6.88 (m, 4 H), 7.05–7.25 (m, 4 H); IR (KBr) 3600–3200 (br), 1665, 1617, 1514 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 582 (M^+, 10), 136 (100), 121 (41). Anal. Calcd for $C_{32}H_{46}N_2O_6Si$ (582.82): C, 65.95; H, 7.95; N, 4.81. Found: C, 65.65; H, 8.05; N, 4.61.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-5-[(phenylselenyl)methyl]-1-methylbicyclo[4,2,2]decane-7,9-dione (26). To alcohol **25** (173 mg, 0.30 mmol, 1.0 equiv) in THF (1.5 mL) at 0 °C was added triethylamine (90 mg, 0.90 mmol, 3.0 equiv) and methanesulfonyl chloride (68 mg, 0.60 mmol, 2.0 equiv). The mixture was stirred at 0 °C for 1 h and filtered. The white precipitate was washed with cold THF, and the filtrate and washings were combined. In a separate flask, $NaBH_4$ (45 mg, 1.19 mmol, 4.0 equiv) was added to a solution of diphenyl diselenide (185 mg, 0.60 mmol, 2.0 equiv) in ethanol (2 mL). The mixture was stirred until hydrogen evolution ceased, and was added to the crude mesylate solution. The reaction was stirred at 80 °C for 7.5 h and diluted with CH_2Cl_2 (80 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by radial chromatography (2-mm thickness, eluted with 33% ethyl acetate in hexane) to afforded 175 mg (82%) of **26** as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.18 (s, 3 H), 0.66 (s, 9 H), 1.12–1.25 (m, 2 H), 1.42 (s, 3 H), 1.63–1.75 (m, 2 H), 1.85–1.94 (m, 2 H), 2.11–2.23 (m, 1 H), 2.38–2.49 (m, 2 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.18 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 4.65 and 4.73 (AB q, J = 14.3 Hz, 2 H), 5.06 ($^1/_2$ AB q, J = 15.4 Hz, 1 H), 6.76–6.88 (m, 4 H), 7.05–7.23 (m, 4 H), 7.25–7.29 (m, 3 H), 7.51–7.54 (m, 2 H); IR (KBr) 1666, 1616, 1514 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 721 (M^+, 9), 566 (9), 174 (30), 151 (64), 136 (76), 121 (100). Anal. Calcd for $C_{38}H_{50}N_2O_5SiSe$ (721.87): C, 63.23; H, 6.98; N, 3.88. Found: C, 63.18; H, 7,09; N, 3.78.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-5-methylene-1-methylbicyclo[4,2,2]decane-7,9-dione. To selenide **26** (183 mg, 0.25 mmol, 1.0 equiv) in THF (2 mL) was added 30% H_2O_2 (287 mg, 2.5 mmol, 10 equiv). The mixture was heated at reflux for 60 min, cooled to room temperature, and diluted with CH_2Cl_2 (80 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (2-mm thickness, eluted with 33% ethyl acetate in hexane) to afford 140 mg (98%): mp 168–169 °C (recrystallized from methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.39 (s, 3 H), 0.82 (s, 9 H), 1.17–1.30 (m, 1 H), 1.55–1.68 (m, 2 H), 1.57 (s, 3 H), 1.82–1.92 (m, 2 H), 2.18–2.27 (m, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 4.26 ($^1/_2$ AB q, J = 15.3 Hz, 1 H), 4.55 and 4.63 (AB q, J = 14.5 Hz, 2 H), 4.96 ($^1/_2$ AB q, J = 15.3 Hz, 1 H), 5.08 (br s, 1 H), 5.50 (br s, 1 H), 6.75–6.88 (m, 4 H), 7.22–7.28 (m, 4 H); IR (KBr) 1670, 1612, 1514 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 564 (M^+, 45), 506 (8), 449 (25), 432 (11), 136 (100), 121 (64). Anal. Calcd for $C_{32}H_{44}N_2O_5Si$ (564.80): C, 68.05; H, 7.85; N, 4.96. Found: C, 67.98; H, 7.97; N, 4.87.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-hydroxy-5-methylene-1-methylbicyclo[4,2,2]decane-7,9-dione (27). To the silyl ether obtained above (91 mg, 0.16 mmol, 1.0 equiv) in THF (1 mL) was added 1.0 M tetrabutylammonium fluoride solution in THF (0.19 mL, 0.19 mmol, 1.2 equiv). The mixture was stirred at 25 °C for 15 min and diluted with ethyl acetate (80 mL). The organic phase was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by radial chromatography (2-mm thickness, eluted with 50% ethyl acetate in hexane) to afford 72 mg (100%) of **27** as a foam: mp 161–162 °C (recrystallized from methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06–1.19 (m, 1 H), 1.59 (s, 3 H), 1.74–1.84 (m, 2 H), 1.90–2.02 (m, 2 H), 2.31–2.36 (m, 1 H), 3.78 (s, 6 H), 4.26 ($^1/_2$ AB q, J = 13.9 Hz, 1 H), 4.53 ($^1/_2$ AB q, J = 15.2 Hz, 1 H), 4.66 ($^1/_2$ AB q, J = 13.9 Hz, 1 H), 4.76 ($^1/_2$ AB q, J = 15.2 Hz, 1 H), 5.08 (s, 1 H, D_2O exchange), 5.15 (br s, 1 H), 5.60 (br s, 1 H), 6.78–6.86 (m, 4 H), 7.20–7.42 (m, 4 H); IR (KBr) 3600–3100 (br), 1657, 1613, 1514 cm^{-1}; mass spectrum (CI(NH_3)), m/e (relative intensity) 450 (M^+, 100), 136 (86), 121 (55). Anal. Calcd for $C_{26}H_{30}N_2O_5$ (450.54): C, 69.31; H, 6.71; N, 6.22. Found: C, 69.09; H, 6.71; N, 6.13.

8,10-Diaza-6-hydroxy-5-methylene-1-methylbicyclo[4,2,2]decane-7,9-dione (28). To **27** (50 mg, 0.11 mmol, 1.0 equiv) in 0.5 mL of 1:4 water/acetonitrile was added ceric ammonium nitrate (243 mg, 0.44

mmol, 4.0 equiv). The mixture was stirred for 50 min, diluted with 30 mL of 15% methanol in chloroform, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by PTLC silica gel (eluted with 15% methanol in chloroform) to afford 11.5 mg (50%) of **28** as a white powder: mp 266–267 °C (recrystallized from methanol); ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.27 (s, 3 H), 1.76–1.84 (m, 2 H), 2.05–2.17 (m, 2 H), 2.22–2.34 (m, 2 H), 4.97 (br s, 1 H), 5.28 (br s, 1 H), 6.51 (s, 1 H), 8.35 (br s, 1 H), 8.47 (br s, 1 H); IR (KBr) 3414 (br), 3200 (br), 1677 cm^{-1}; mass spectrum (CI(NH$_3$)), *m/e* (relative intensity) 210 (M$^+$, 10), 195 (13), 165 (20), 152 (29), 139 (100). Anal. Calcd for $C_{10}H_{14}N_2O_3$ (210.23): C, 57.13; H, 6.71; N, 13.33. Found: C, 57.07; H, 6.69; N, 13.15.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-hydroxy-5-vinylbicyclo-[4.2.2]decane-7,9-dione (29) and 7,9-Bis(*p*-methoxybenzyl)-7,9-diaza-6-hydroxy-5-vinylbicyclo[4.3.1]decane-8,10-dione (30). To diisopropylamine (32 mg, 0.32 mmol, 1.2 equiv) in THF (3 mL) at −78 °C under an argon atmosphere was added a 1.60 M *n*-butyllithium solution in hexane (0.20 mL, 0.32 mmol, 1.2 equiv). The solution was stirred for 15 min, and then a solution of **22** (120 mg, 0.27 mmol, 1.0 equiv) in THF (3 mL) was added. The amber solution was stirred for 10 min, trimethylsilyl chloride (35 mg, 0.32 mmol, 1.2 equiv) was added, and the reaction was stirred for 20 min. To this mixture was added a second portion of 1.60 M *n*-butyllithium solution in hexane (0.25 mL, 0.40 mmol, 1.5 equiv), and the reaction was stirred at −78 °C for 30 min. To this mixture was added a 1.0 M tetrabutylammonium fluoride solution (0.54 mL, 0.54 mmol, 2.0 equiv), and the reaction was warmed to 25 °C and stirred under argon for 40 min. The reaction was diluted with 80 mL of CH_2Cl_2, washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by radial chromatography (2-mm thickness, eluted with 50% ethyl acetate in hexane) to afford two products.

29: (15 mg, 12%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.98–1.32 (m, 2 H), 1.71–2.05 (m, 4 H), 2.63–2.75 (m, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.02–4.07 (m, 1 H), 4.19 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 4.42 ($^1/_2$ AB q, J = 14.1 Hz, 1 H), 4.70 ($^1/_2$ AB q, J = 14.1 Hz, 1 H), 4.80 (s, 1 H), 4.93 ($^1/_2$ AB q, J = 14.4 Hz, 1 H), 5.13–5.23 (m, 2 H), 5.95–6.08 (m, 1 H), 6.73–6.87 (m, 4 H), 7.12–7.30 (m, 4 H); IR (TF) 3600–3200, 1664, 1613, 1586, 1513 cm^{-1}; mass spectrum (CI(NH$_3$)), *m/e* (relative intensity) 450 (M$^+$, 57), 136 (75), 121 (100); X-ray analysis mp 138–138.5 °C (recrystallized from EtOAc/hexanes). Anal. Calcd for $C_{26}H_{30}O_5N_2$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.40; H, 6.79; N, 6,27.

30: (53 mg, 44%); mp 93–94 °C (recrystallized from methanol); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92–1.08 (m, 1 H), 1.52–1.63 (m, 1 H), 1.65–1.88 (m, 2 H), 2.04–2.15 (m, 2 H), 2.53–2.64 (m, 1 H), 3.77 (s, 6 H), 3.78–3.81 (m, 1 H), 3.92 and 3.97 (AB q, J = 13.6 Hz, 2 H), 4.11 (s, 1 H), 4.82 and 4.89 (AB q, J = 13.7 Hz, 2 H), 4.87–4.98 (m, 2 H), 5.33–5.46 (m, 1 H), 6.77–6.85 (m, 4 H), 7.14–7.39 (m, 4 H); IR (TF) 3600–3200 (br), 1729, 1674, 1612, 1585, 1513 cm^{-1}; mass spectrum (CI(NH$_3$)), *m/e* (relative intensity) 450 (M$^+$, 99), 136 (75), 121 (100). Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.08; H, 6.92; N, 6.22.

Synthesis of 29 and 31 with NaH. To a stirred solution of **22** (250 mg, 0.55 mmol) in dimethoxyethane (DME) (50 mL) was added NaH (250 mg of a 50% oil dispersion, 9 equiv) and the mixture was stirred at room temperature for 3.5 h. (Note: Prolonged reaction times result in an increased amount of **31** at the expense of the **29** produced.) The reaction was quenched by pouring the reaction mixture into an ice-cold suspension of toluene-saturated aqueous NH_4Cl. The organic phase was washed with watr, brine, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by silica gel column chromatography (EtOAc–hexanes, 1:1) to yield 153 mg (61%) of **29** and 42 mg (17%) of **31** (see data above). On smaller scales the yield of **29** improved up to 87% with only a trace of **31**. The scale reported here is consistently reproducible.

31: ^{1}H NMR (270 MHz, $CDCl_3$) δ TMS, 0.95–1.11 (m, 1 H), 1.22–1.34 (m, 1 H), 1.64 (d, J = 6.8 Hz, 3 H), 1.68–1.82 (m, 1 H), 1.94–2.04 (m, 2 H), 2.51 (dd, J = 15.4, 9.4 Hz, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.09–4.14 (m, 1 H), 4.18 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.30 ($^1/_2$ AB q, J = 14.0 Hz, 1 H), 4.58 ($^1/_2$ AB q, J = 14.0 Hz, 1 H), 4.84 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 5.07 (s, 1 H), 6.17 (q, J = 6.8 Hz, 1 H), 6.78 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 8.6 Hz, 2 H), 7.35 (d, J = 8.6 Hz, 2 H); IR (NaCl, neat) 3100–3600 (br), 1668, 1612, 1585, 1513 cm^{-1}; mass spectrum, (CI/NH$_3$), *m/e* (relative intensity) 450 (M$^+$, 100), 136 (54), 121 (41).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-5-vinylbicyclo[4.2.2]decane-7,9-dione. To alcohol **29** (23 mg, 0.05 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) was added 2,6-lutidine (11 mg, 0.10 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl triflate (27 mg, 0.10 mmol, 2.0 equiv). The mixture was stirred for 40 min and diluted with CH_2Cl_2 (50 mL). The organic phase was washed with cold 1 M HCl solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by PTLC (eluted with 50% ethyl acetate in hexane) to afford 26 mg (90%) of the silyl ether as an oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.16 (s, 3 H), 0.43 (s, 3 H), 0.68 (s, 9 H), 1.29–1.43 (m, 2 H), 1.75–1.87 (m, 2 H), 1.96–2.08 (m, 2 H), 2.81–2.93 (m, 1 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 3.83 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 3.96–3.99 (m, 1 H), 4.66 (s, 2 H), 5.10–5.20 (m, 2 H), 5.27 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 5.90–6.03 (m, 1 H), 6.74–7.20 (m, 8 H); IR (KBr) 1675, 1613, 1514 cm^{-1}; mass spectrum (CI(NH$_3$)), *m/e* (relative intensity) 564 (M$^+$, 61), 506 (14), 136 (25), 121 (100).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-5-(hydroxymethyl)bicyclo[4.2.2]decane-7,9-dione (32). Into a solution of the silyl ether obtained above (42 mg, 0.074 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at −78 °C was bubbled ozone until a pale blue color persisted. The reaction was purged with nitrogen to remove excess ozone, and $NaBH_4$ (17 mg, 0.45 mmol, 6.0 equiv) in methanol (0.4 mL) was added. The reaction was warmed to room temperature, stirred for 7 h, and filtered through Celite. The filtrate was evaporated and the residue was chromatographed by PTLC (33% hexane in ethyl acetate) to afford 29 mg (69%) of **32**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.16 (s, 3 H), 0.42 (s, 3 H), 0.74 (s, 9 H), 1.24–1.37 (m, 2 H), 1.45–1.53 (br s, 1 H), 1.76–1.89 (m, 1 H), 1.92–2.09 (m, 3 H), 2.27–2.38 (m, 1 H), 3.47–3.58 (m, 1 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 3.85 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 3.97–4.00 (m, 1 H), 4.13–4.17 (m, 1 H), 4.50 ($^1/_2$ AB q, J = 14.8 Hz, 1 H), 4.63 ($^1/_2$ AB q, J = 14.8 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.00 (d, J = 8.6 Hz, 2 H), 7.18 (d, J = 8.6 Hz, 2 H); IR (KBr) 3600–3100, 1677, 1614, 1586, 1514 cm^{-1}; mass spectrum (CI(NH$_3$)), *m/e* (relative intensity) 568 (M$^+$, 28), 510 (12), 136 (100), 121 (92), 58 (19).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-5-[(phenylselenyl)methyl]bicyclo[4.2.2]decane-7,9-dione. To alcohol **32** (500 mg, 0.88 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (0.25 mL, 1.6 mmol, 2.0 equiv) and methanesulfonyl chloride (0.1 mL, 1.3 mmol, 1.5 equiv). The mixture was stirred at 0 °C for 30 min, quenched with $NaHCO_3$ (aq), and diluted with ether. The organic phase was washed sequentially with H_2O, cold 0.1 N HCl, H_2O, and brine. The organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude mesylate was directly used for the subsequent selenide displacement. In a separate flask, $NaBH_4$ (199 mg, 5.28 mmol, 6.0 equiv) was added to a solution of diphenyl diselenide (824 mg, 2.64 mmol, 3.0 equiv) in ethanol (6.0 mL). The mixture was stirred until hydrogen evolution ceased and was then added to the crude mesylate solution. The reaction was stirred at 80 °C for 3 h and diluted with EtOAc. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by radial silica gel chromatography (2-mm thickness, eluted with 33% ethyl acetate in hexane) to afford 603 mg (97%) of the selenide as a foam: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.19 (s, 3 H), 0.66 (s, 9 H), 1.18–1.33 (m, 2 H), 1.63–1.77 (m, 2 H), 1.90–2.04 (m, 2 H), 2.06–2.20 (m, 1 H), 2.31–2.47 (m, 2 H), 3.61 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 3.94–3.99 (m, 1 H), 4.66 (s, 2 H), 5.23 ($^1/_2$ AB q, J = 14.6 Hz, 1 H), 6.75 (d, J = 8.5 Hz, 2 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.27–7.35 (m, 3 H), 7.49–7.52 (m, 2 H); IR (KBr) 1675, 1613, 1586, 1514 cm^{-1}; mass spectrum (CI(NH$_3$)), *m/e* (relative intensity) 707 (M$^+$, 1), 650 (1), 550 (10), 136 (15), 121 (100), 77 (14).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-[(*tert*-butyldimethylsilyl)-oxy]-5-methylenebicyclo[4.2.2]decane-7,9-dione (33). To the selenide obtained above (560 mg, 0.79 mmol, 1.0 equiv) in THF (10 mL) was added 30% H_2O_2 (450 mg, 4.0 mmol, 5.0 equiv). The mixture was heated at reflux for 30 min and diluted with EtOAc (250 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by silica gel column chromatography (eluted with 50% ethyl acetate in hexane) to afford 424 mg (97%) of **33**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.13 (s, 3 H), 0.43 (s, 3 H), 0.88 (s, 9 H), 1.16–1.30 (m, 1 H), 1.46–1.62 (m, 1 H), 1.82–2.09 (m, 2 H), 2.13–2.24 (m, 2 H), 3.76 (s, 3 H), 3.81 (s, 3 H), 3.87 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.05–4.09 (m, 1 H), 4.51 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 4.67 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 5.05 (br s, 1 H), 5.17 ($^1/_2$ AB q, J = 14.5 Hz, 1 H), 5.49 (br s, 1 H), 6.75 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H); IR (KBr) 1684, 1656, 1613, 1586, 1514 cm^{-1}; mass spectrum (CI(NH$_3$)), *m/e* (relative intensity) 550 (M$^+$, 48), 492 (19), 418 (13), 136 (18), 121 (100); mp 133–134 °C (recrystallized from hexanes). Anal. Calcd for $C_{31}H_{42}O_5N_2Si$: C, 67.6; H, 7.69; N, 5.09. Found: C, 67.51; H, 7.72; N, 5.12.

Compound 35. To **33** (20.6 mg, 0.037 mmol, 1.0 equiv) in THF (2.0 mL) at −78 °C under an argon atmosphere containing TMEDA (8.7 mg, 2.0 equiv) was added *n*-butyllithium in hexane (0.05 mL, 1.6 N, 2.2 equiv). The pale yellow solution was stirred for 10 min, and then (±)-aldehyde **34** (11 mg, 0.074 mmol, 2.0 equiv) was added. The re-

action was stirred for 20 min at −78 °C and was quenched by the addition of saturated aqueous sodium chloride solution (1 mL, −78 °C), diluted with EtOAc (25 mL), washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was chromatographed by PTLC (eluted with ethyl acetate in hexane, 1:3) to afford 13.1 mg (50.4%; 79% based on recovered starting material) of **35** as an oily film: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.24 (s, 3 H), 0.54 (s, 3 H), 0.94 (s, 9 H), 1.10 (s, 3 H), 1.38–1.52 (m, 1 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.76–1.88 (m, 2 H), 1.92–2.07 (m, 2 H), 2.22–2.38 (m, 1 H), 3.78 ($^1/_2$ AB q, J = 9.1 Hz, 1 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.01 ($^1/_2$ AB q, J = 9.1 Hz, 1 H), 4.39–4.45 (m, 3 H), 4.62 ($^1/_2$ AB q, J = 13.6 Hz, 1 H), 4.97 (br s, 1 H), 5.33 ($^1/_2$ AB q, J = 15.0 Hz, 1 H), 5.44 (br, s 1 H), 6.10 (d, J = 10.6 Hz, 1 H), 6.74–6.79 (m, 4 H), 7.29–7.43 (m, 4 H); IR (TF) 3600–3100 (br), 1673, 1611, 1583, 1513 cm^{-1}; high-resolution mass spectrum calcd for $C_{38}H_{54}N_2O_8Si$ 695.3729, found 695.3740. 3.1 mg (12%, or 18% based on recovered **33**) of the C-1′ diastereomer was also isolated.

C-1′ Diastereomer of 35: ^{1}H NMR (270 MHz, $CDCl_3$, TMS) δ 0.13 (s, 3 H), 0.50 (s, 3 H), 0.85 (s, 9 H), 1.06 (s, 3 H), 1.28 (s, 3 H), 1.37 (s, 3 H), 1.20–1.50 (m, 1 H), 1.50–1.80 (m, 2 H), 2.00–2.30 (m, 2 H), 2.30–2.50 (m, 1 H), 3.29 ($^1/_2$ AB q, J = 7.8 Hz, 1 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 3.91 ($^1/_2$ AB q, J = 7.8 Hz), 4.05 ($^1/_2$ AB q, J = 12.6 Hz, 1 H), 4.43–4.54 (m, 3 H), 4.74 ($^1/_2$ AB q, J = 12.6 Hz, 1 H), 4.79 (d, J = 9.8 Hz, 1 H), 5.06 (br s, 1 H), 5.46 (br s, 1 H), 6.74 (d, J = 8.3 Hz, 2 H), 6.82 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.44 (d, J = 8.3 Hz, 2 H); IR (neat) 3471 (br), 2983, 2959, 2933, 2858, 1668, 1613, 1513, 1247, 1180, 1112, 1040 cm^{-1}; mass spectrum [CI(NH_3)], m/e (relative intensity) 695 (M^+, 32), 637 (12), 551 (14), 493 (4), 435 (9), 419 (4), 373 (4), 121 (100).

Preparation of 36. To a stirred solution of **35** (101.3 mg, 0.146 mmol) in THF (3 mL) at room temperature was added a 1 M THF solution of tetra-*n*-butylammonium fluoride trihydrate (0.5 mL, 3.4 equiv). After stirring for 1 h, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluted with 1:1 hexanes–EtOAc) to afford 79.9 mg (99.9%) of the corresponding diol as a white solid: mp 162–163 °C (recrystallized from hexanes–EtOAC); ^{1}H NMR (270 MHz, $CDCl_3$, TMS) δ 0.79 (s, 3 H), 1.3 (m, 2 H), 1.36 (s, 3 H), 1.6 (m, 1 H), 1.8 (m, 1 H), 2.2 (m, 1 H), 2.4 (m, 1 H), 3.72 ($^1/_2$ AB q, J = 9.2 Hz, 1 H), 3.98 (s, 5 H), 4.08 ($^1/_2$ AB q, J = 9.2 Hz, 1 H), 4.25 ($^1/_2$ AB q, J = 13.5 Hz, 1 H), 4.37 (d, J = 10.5 Hz, 1 H), 4.45 ($^1/_2$ AB q, J = 15.5 Hz, 1 H), 4.52 ($^1/_2$ AB q, J = 13.5 Hz, 1 H), 5.10 (s, 1 H), 5.36 (s, 1 H), 5.39 ($^1/_2$ AB q, J = 15.5 Hz, 1 H), 5.56 (s, 1 H), 6.33 (d, J = 10.5 Hz, 1 H), 6.78 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 7.37 (d, J = 8.7 Hz, 2 H), 7.40 (d, J = 8.7 Hz, 2 H); IR (NaCl, $CHCl_3$ soln) 3390 (br), 2997, 2937, 1655, 1635, 1613, 1512, 1440, 1248, 1216 cm^{-1}. Anal. Calcd for $C_{32}H_{40}O_8N_2$: C, 66.19; H, 6.94; N, 4.82. Found: C, 65.97; H, 7.18; N, 4.71.

To a stirred, 0 °C solution of the diol obtained above (70 mg, 0.1276 mmol) in CH_2Cl_2 (5 mL) was added DMAP (96 mg, 6 equiv), followed by slow addition of TFAA (0.072 mL, 4 equiv). After 40 min, the reaction solution was diluted with Et_2O (150 mL) and then was washed sequentially with H_2O, saturated $CuSO_4$ (aq), H_2O, and saturated NaCl (aq), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. This crude (yet essentially pure) compound was directly used in the next reaction (if crude **36** was subjected to PTLC, decomposition resulted): ^{1}H NMR (270 MHz, $CDCl_3$, TMS) δ 0.93 (s, 3 H), 1.18 (s, 3 H), 1.2 (m, 1 H), 1.24 (s, 3 H), 1.8 (m, 2 H), 2.1 (m, 2 H), 2.6 (m, 1 H), 3.52 ($^1/_2$ AB q, J = 9.4 Hz, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 3.81 ($^1/_2$ AB q, J = 14.9 Hz, 1 H), 4.31 ($^1/_2$ AB q, J = 9.4 Hz, 1 H), 4.41 ($^1/_2$ AB q, J = 14.9 Hz, 1 H), 5.07 ($^1/_2$ AB q, J = 9.9 Hz, 1 H), 5.12 ($^1/_2$ AB q, J = 9.9 Hz, 1 H), 5.42 (s, 1 H), 5.74 (s, 1 H), 6.25 (s, 1 H), 6.80 (d, J = 8.5 Hz, 2 H), 6.86 (d, J = 8.5 Hz, 2 H), 7.10 (d, J = 8.5 Hz, 2 H), 7.36 (s, 1 H), 7.53 (d, J = 8.5 Hz, 2 H); IR ($NaCl/CDCl_3$) 3400 (br), 2936, 1788, 1681, 1613, 1513, 1226, 1179, 1129, 1034, 909, 735 cm^{-1}.

2-Desoxy-2-methylenebicyclomycin (3). To a stirred solution of **36** (84 mg, 0.125 mmol) in acetonitrile/H_2O (0.8 mL/0.4 mL) was added solid ceric ammonium nitrate (428 mg, 6 equiv) at room temperature. After 1.5 h, the mixture was diluted with 20% MeOH in $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated to give the crude product. This crude compound was purified by PTLC twice (20% MeOH in $CHCl_3$) to give 16.3 mg (45% from **34**) of **3** as waxy oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ TMS 1.15 (s, 3 H), 1.0–2.5 (m, 6 H), 3.32 (s, 2 H), 3.50 (s, 2 H), 4.97 (s, 1 H, D_2O exchange), 5.04 (s, 1 H), 5.29 (s, 1 H), 5.34 (s, D_2O exchange, 1 H), 5.35 (s, D_2O exchange, 1 H), 6.82 (s, D_2O exchange, 2 H), 8.52 (s, D_2O exchange, 1 H), 9.05 (s, D_2O exchange, 1 H); ^{13}C NMR (75.47 MHz) (CD_3OD) δ 25.21, 25.31, 33.77, 38.15, 38.35, 66.61, 67.05, 82.91, 83.08, 99.38, 99.85, 115.27, 151.27, 151.73, 151.79, 171.51, 171.74, 172.09, 172.22; mass spectrum, m/e 300 (M^+, 16), 242 (4), 160 (100), 136 (10); IR (NaCl, THF-d_8) 3244 (br), 2735, 1682, 1415, 1097, 1034 cm^{-1}.

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Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen coordinates for compounds **27** and **29** (12 pages), Ordering information is given on any current masthead page,