CH_2Cl_2) to afford 3.9 mg (98.5%) of lactone **22**, mp 242–243 °C (recryst MeOH/Et_2O/CH_2Cl_2): ^1H NMR (270 MHz) (Me_2SO-d_6) δ TMS 2.044–2.378 (2 H, m), 3.141–3.239 (1 H, m), 3.687 (1 H, $^1/_2$ABq, J = 19.3 Hz), 3.790 (1 H, $^1/_2$ABq, J = 19.3 Hz), 4.123–4.394 (3 H, m), 8.237 (1 H, s), 8.357 (1 H, s); IR (NaCl, neat) 3180, 1750, 1670, 1535, 1455, 1370, 1325, 1165, 1085, 1015 cm^{-1}. Anal. ($C_8H_{10}N_2O_4$) C, H, N.

X-ray Structure Determination. For compound **20** ($C_{27}H_{25}N_3O_4S$) at 20 (1) °C, a = 7.929 (3) Å, b = 16.094 (9) Å, c = 18.891 (9) Å; space group $Pna2_1$, ρ_c = 1.34 g cm^{-3}, Z = 4, formula weight = 487.58 % mol^{-1}. The intensities of 2451 reflections (h, k, $l \geq 0$; $3.5° < 2\theta < 50°$) from a small crystal (0.28 mm × 0.22 mm × 0.38 mm) were measured (θ–2θ scans) on the Nicolet R3m/E diffractometer (Mo K_α radiation, graphite monochromator). Unique, observed reflections (1801 ($I > 2\sigma(I)$) were used in refinement of the structure. The structure was solved (using Sheldrick's direct methods routine RANT) and refined by using the SHELXTL crystallographic program library[18] supplied by Nicolet with the R3m/E computing system. The final structural model included anisotropic thermal parameters for all non-hydrogen atoms, together with placement of hydrogen atoms in idealized positions. A check of the correctness of the crystal enantiomorph provided a positive, albeit weak, indication that the reported enantiomorph was correct. Refinement of this structural model (317 least-squares parameters) converged to R = 0.038, R_w = 0.041, and GOF = 1.17.

Results of this structure determination have been provided as supplementary material (Table 1, atomic coordinates; Table 2, bond lengths; Table 3, bond angles; Table 4, anisotropic thermal parameters; Table 5, hydrogen atom positions; Table 6, structure factors).

Acknowledgment. Acknowledgement is made to the National Institutes of Health Grant 1R01 AI18957 for financial support of this work. NMR measurements at 360 MHz were obtained at the Colorado State University Regional NMR Center, funded by the National Science Foundation Grant CHE 78-18581. The Nicolet R3m/E diffractometer and computer system used in the X-ray structure determination was purchased with funds provided by the National Science Foundation (Grant CHE 8103011).

(18) Sheldrick, G. M. "SHELXTL User Manual"; Nicolet XRD Corp: Madison, WI, 1984.

Registry No. 8a, 95676-10-1; **8b**, 95676-11-2; **8c**, 95676-12-3; **8d**, 95676-13-4; (±)-major *syn*-**10a** (R_2R_3 = CH_2CH_2), 95676-14-5; (±)-minor *anti*-**10a** (R_2R_3 = CH_2CH_2), 95723-17-4; (±)-minor *syn*-**10a** (R_2R_3 = CH_2CH_2), 95723-18-5; (±)-major *anti*-**10a** (R_2R_3 = CH_2CH_2), 95723-19-6; (±)-*syn*-**10a** (R_2 = CH_3; R_3 = CO_2CH_3), 95676-15-6; (±)-*anti*-**10a** (R_2 = CH_3; R_3 = CO_2CH_3), 95676-16-7; (±)-major *syn*-**10a** (R_2R_3 = $(CH_2)_3$), 95676-17-8; (±)-minor *syn*-**10a** (R_2R_3 = $(CH_2)_3$), 95723-20-9; (±)-major *syn*-**10b** (R_2R_3 = CH_2CH_2), 92098-01-6; (±)-minor *syn*-**10b** (R_2R_3 = CH_2CH_2), 92216-23-4; (±)-*syn*-**10b** (R_2 = CH_3; R_3 = CO_2CH_3), 95676-18-9; (±)-*anti*-**10b** (R_2 = CH_3; R_3 = CO_2CH_3), 95676-19-0; (±)-major *syn*-**10b** (R_2R_3 = $(CH_2)_3$), 95676-20-3; (±)-minor *syn*-**10b** (R_2R_3 = $(CH_2)_3$), 95723-21-0; (±)-major *syn*-**10c** (R_2R_3 = CH_2CH_2), 92098-11-8; (±)-major *anti*-**10c** (R_2R_3 = CH_2CH_2), 92216-27-8; (±)-minor *syn*-**10c** (R_2R_3 = CH_2CH_2), 92216-26-7; (±)-minor *anti*-**10c** (R_2R_3 = CH_2CH_2), 92216-28-9; (±)-*anti*-**10c** (R_2 = CH_3, R_3 = CO_2CH_3), 95676-21-4; (±)-*syn*-**10c** (R_2 = CH_3; R_3 = CO_2CH_3), 95676-22-5; (±)-minor *syn*-**10c** (R_2R_3 = $(CH_2)_3$), 95676-23-6; (±)-major *syn*-**10c** (R_2R_3 = $(CH_2)_3$), 95723-22-1; (±)-major *anti*-**10c** (R_2R_3 = $(CH_2)_3$), 95723-23-2; (±)-*syn*-**10d** (R_2 = CH_3; R_3 = CO_2CH_3), 95676-24-7; (±)-*anti*-**10d** (R_2 = CH_3; R_3 = CO_2CH_3), 95693-57-5; **12b**, 42492-87-5; **12c**, 92097-99-9; **12d**, 21535-05-7; **13a**, 21579-45-3; **13b**, 89291-86-1; **13c**, 92098-10-7; **13d**, 30478-55-8; **15** (R_1 = CH_2Ph-*p*-OCH_3), 95676-09-8; (±)-**16** (R_1 = CH_2Ph-*p*-OCH_3), 95676-25-8; (±)-**17** (R_2R_3 = CH_2CH_2, major isomer), 95676-26-9; (±)-**17** (R_2R_3 = CH_2CH_2, minor isomer), 95676-27-0; **21** (R_1 = CH_2Ph; R, R_2 = CH_3; R_3 = CO_2CH_3), 95676-28-1; **22** (R_2R_3 = CH_2CH_2), 95676-29-2; 2-pySH, 73018-10-7; γ-butyrolactone ketone trimethylsilyl acetal, 51425-66-2; carbomethoxy ketene methyl trimethylsilyl acetal, 32346-10-4; δ-valerolactone trimethylsilyl ketene acetal, 71309-70-1; α-(trimethylsilyl)-γ-butyrolactone ketene trimethylsilyl acetal, 65946-60-3.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters and hydrogen atom positions for the crystal structure of **20** (15 pages). Ordering information is given on any current masthead page.

Stereocontrolled Total Synthesis of (±)- and (+)-Bicyclomycin†

Robert M. Williams,*‡ Robert W. Armstrong, and Jen-Sen Dung

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received October 10, 1984*

Abstract: The completely regio- and stereocontrolled total synthesis of bicyclomycin (**1**) is described in 12 chemical steps. A new carbon–carbon bond-forming reaction on 1,4-dibenzyl- and 1,4-bis(*p*-methoxybenzyl)-3,6-bis(2′-thiopyridyl)-2,5-piperazinediones (**10** and **46**) has been discovered involving complexation of **10** or **46** with silver(I) triflate followed by addition of the trimethylsilyl ketene acetal of γ-butyrolactone to afford 1,4-dibenzyl- and 1,4-bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-(2″-γ-butyrolactonyl)-2,5-piperazinediones (**11**, **12**, and **47**–**50**) in good yield. The reaction proceeds in THF at 25 °C with predominant syn stereospecificity. $LiAlH_4$ reduction of lactones **47**–**49** provides the corresponding diols **51**–**53** which are cyclized to the bicyclo[4.2.2] nucleus **54** in the presence of silver(I) triflate in THF at 25 °C. Dehydration of **54** in three steps affords the key olefinic intermediate 8,10-bis(*p*-methoxybenzyl)-8,10-diaza-5-methylene-2-oxabicyclo[4.2.2]-decane-7,9-dione (**42b**) which is regio- and stereoselectively elaborated at the bridgehead positions via (1) C-6-bridgehead carbanion formation followed by quenching with O_2, and (2) C-1-bridgehead carbanion formation followed by aldol condensation with 2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde to afford a single diastereomer (**44b**) possessing the correct relative configuration at C-1′, C-2′. Protection of the secondary hydroxyl at C-1′ as the trifluoroacetate followed by oxidative removal of all the protecting groups with ceric ammonium nitrate in $MeCN/H_2O$ affords directly, totally synthetic bicyclomycin. Condensation of the racemic bicyclic nucleus **43b** with optically active S-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (ee 83%) provides, after trifluoroacetylation and deprotection, (+)-bicyclomycin in ee 78%.

In 1972, two Japanese groups reported the independent isolation[1] of a structurally unique antibiotic from cultures of *Streptomyces sapporonensis* and *Streptomyces aizunensis*. The substance, named bicyclomycin or aizumycin (**1**), was found to exhibit antimicrobial activity against gram-negative bacteria and had the highly desirable property of displaying very low toxicity. The structure of bicyclomycin and the relative configuration were unambiguously established through X-ray crystallographic

† Taken in part from the Ph.D. Thesis of R. W. Armstrong, Colorado State University, 1984.

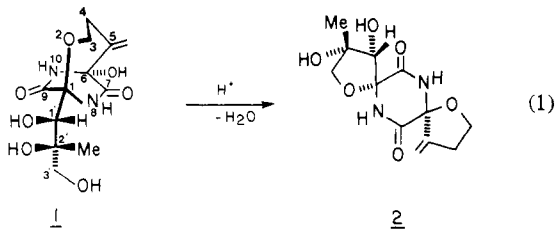
‡ NIH Research Career Development Awardee 1984–1989.

(1) For references to the isolation, structural elucidation biological activity, and mechanism of action of bicyclomycin, see ref 7 and 9.

0002-7863/85/1507-3253$01.50/0

analysis.[1] Preliminary studies by Iseki et. al., revealed that the mechanism of action of bicyclomycin seems to be distinct from the other known classes of antibiotics; the chemical mechanism of action of bicyclomycin and the nature of the bicyclomycin-binding proteins remain to be determined.[1] The efficient production of bicyclomycin from fermentation broths has led to the commercial introduction of this substance now named bicozamycin,[2] by the Fujisawa Co., on a worldwide basis.

Bicyclomycin is biosynthetically derived by the oxidative cyclodimerization of the amino acids leucine and isoleucine.[3] The novel 8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione nucleus containing the exomethylene moiety, primary, secondary, and two tertiary hydroxyl groups, and four asymmetric carbon atoms poses a substantial synthetic challenge. The history of synthetic approaches to bicyclomycin commenced with a landmark paper by Maag and associates at Hoffmann-La Roche in 1978[4] wherein the absolute stereochemistry of **1** was established through the synthesis and X-ray crystallographic structure determination of the bis spiro dehydration product (**2**) of **1** (eq 1). In this paper,



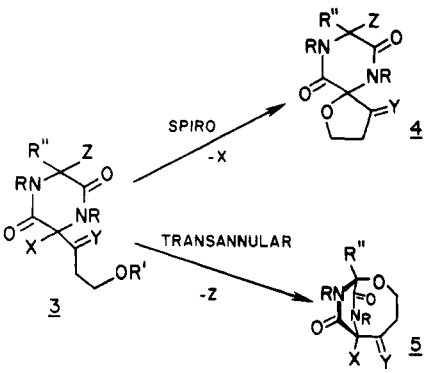
(1)

1 2

Maag points out that "synthesis schemes for bicyclomycin should probably be contrived in a way that circumvents the energy minimum represented by **2**".

A flurry of synthetic activity from numerous laboratories[5] followed and recently culminated in two total syntheses, one by the Goto group[6] and the other from these laboratories.[7] In addition, a successful synthesis of the bicyclomycin ring system bearing a bridgehead hydroxyl was achieved by Fukuyama and co-workers.[8] The strategy that has evolved from our laboratories[9] to construct the bicyclomycin ring system differs significantly from those mentioned above[6,8] in addressing the crucial spiro vs. transannular cyclization problem of a monocyclic precursor **3** (eq 2). For structure **3**, where X = Z = some heteroatom-bearing leaving group, one would expect the kinetically and thermodynamically favored spiro closure (**3** → **4**) to be the predominant reaction course as implicated by Maag[4] and is supported by experimental data.[5,6,8] Both the Fukuyama[8] and Goto[6] groups have similarly solved this problem by differentiating X and Z, so that Z is a more powerful leaving group than X, and the desired transannular cyclization can take place to furnish a structure **5** that contains the bridgehead alkoxy group (X = OH).

On the other hand, we have engineered a strategy[7,9] that completely sidesteps the potential formation of spiro structures (**4**) by constructing a precursor **3**, where X = H and Z = some leaving group. In this way, *only* the desired bicyclo[4.2.2] ring

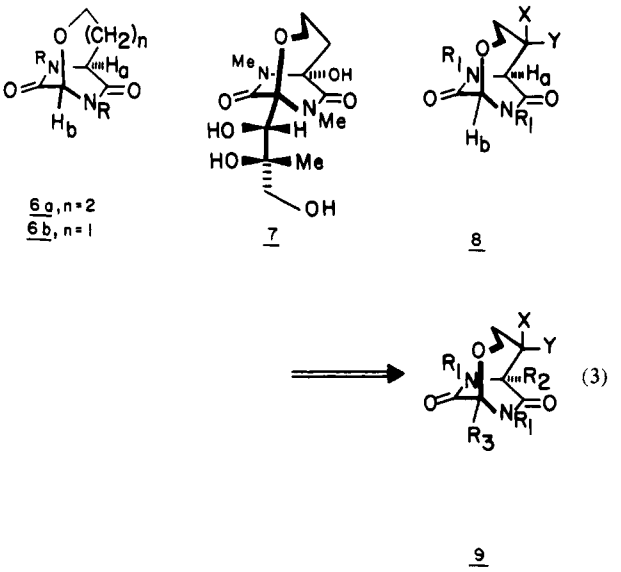


(2)

3 4 5

system **5** is formed (where X = H) and thus requires the subsequent introduction of the bridgehead hydroxyl (X = H → X = OH).

We have previously reported[9] on the synthesis and properties of the simple bicyclo[4.2.2] and bicyclo[3.2.2] nuclei **6a** and **6b** which can be regio- and stereoselectively elaborated at the bridgehead positions (H_a and H_b) via generation and electrophilic quenching of the corresponding bridgehead carbanions. Our



6a, n=2
6b, n=1

7 8

(3)

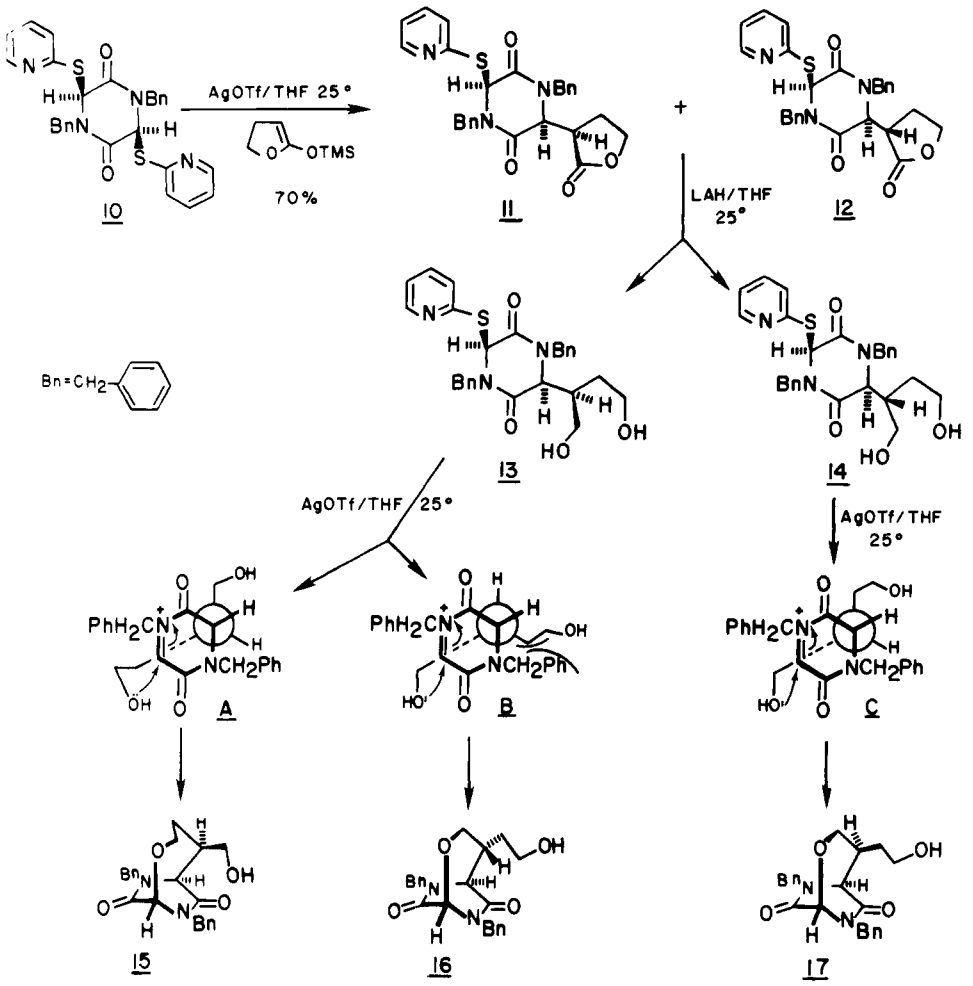
9

studies[9c] revealed that the carbanion derived by removal of H_a adjacent to the bridging CH_2 is thermodynamically more stable than the carbanion adjacent to the bridging oxygen atom (removal of H_b). In this way, an efficient regio- and stereocontrolled six-step synthesis of the bicyclomycin model **7** was realized.[9b] In order to reduce this efficient model study to a total synthesis of bicyclomycin, we had to overcome two difficult problems. Firstly, the most difficult problem involved is developing a means to introduce the C-5 exomethylene moiety which was devoid in the model systems. From our standpoint, this amounted to preparing a suitably oxidized isoleucine precursor containing the bridging isobutyl moiety. To our knowledge, no readily available amino acid or equivalent synthon existed that could be easily incorporated into our approach. Secondly, a suitable blocking group for the amides had to be selected that would withstand the strongly basic conditions required to generate the bridgehead carbanions and yet be removable under mild enough conditions that would not lead to the destruction of the labile final tetraol product. We have realized a significant extension of the inherent advantages of the desmethylene model series we have developed, in a program engineered for versatile and divergent access to structurally unique bicyclomycin analogues that cannot readily be prepared by manipulation of the abundantly available natural antibiotic. The cornerstone of this approach is the regiocontrolled elaboration of nuclei **8** → **9** (eq 3).

Herein is provided a full account of the total synthesis of bicyclomycin in racemic and optically active form.

(2) "Merck Index", 10th ed.; Merck: Rahway, NJ, 1984; No. 1213.
(3) (a) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *J. Antibiot.* **1980** *33*, 480. (b) Iseki, M.; Miyoshi, T.; Konomi, T.; Imanaka, H. *Ibid.* **1980** *33*, 488.
(4) Maag, H.; Blount, J. F.; Coffen, D. L.; Steppe, T. V.; Wong, F. *J. Am. Chem. Soc.* **1978** *100*, 6786.
(5) For synthetic approaches to **1**, see the references cited in ref 7 and 9: in addition, see: Sera, A.; Itoh, K.; Yamada, H.; Aoki, R. *Heterocycles* **1984** *22*, 713.
(6) (a) Nakatsuka, S.; Yuamada, K.; Yoshida, K.; Azano, O.; Murakami, Y.; Goto, T. *Tetrahedron Lett.* **1983** *24*, 5627. (b) Nakatsuka, S.; Goto, T. *Heterocycles* **1984** *21*, 61 and references cited therein.
(7) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1984** *106*, 5748.
(8) Fukuyama, T.; Robins, B. D.; Sachleben, R. A. *Tetrahedron Lett* **1981** *22*, 4155.
(9) (a) Williams, R. M. *Tetrahedron Lett* **1981** *22*, 2341. (b) Williams, R. M.; Anderson, O. P.; Armstrong, R. W.; Josey, J.; Meyers, H.; Eriksson, C. *J. Am. Chem. Soc.* **1982** *104*, 6092. (c) Williams, R. M.; Dung, J.-S.; Josey, J.; Armstrong, R. W.; Meyers, H. *Ibid.* **1983** *105*, 3214.

Scheme I



Results and Discussion

At the outset, we endeavored to construct a 2,5-piperazinedione **3**, where X = R″ = H and Y = a latent exomethylene carbon. We extensively investigated the enolate functionalization of N,N′-disubstituted 2,5-piperazinediones with a wide variety of electrophiles that would ultimately furnish the desired structure **3**. Unfortunately, we were unable to realize the reasonably efficient coupling of a secondary center to the piperazinedione α carbon by using enolate chemistry.[10] We were forced to conclude that the enolate anions are generally, poor nucleophiles toward carbon electrophiles other than aldehydes and primary halides. We then turned to an approach in which the polarity of the desired coupling was reversed; i.e., the piperazinedione α-carbon would serve as the *electrophile* rather than the nucleophile. This mode of reactivity for piperazinediones had previously been utilized toward heteroatom nucleophiles such as O[11] and S,[12] but no precedent for carbon nucleophiles existed in the literature.

As described in the preceeding paper[13] in this issue, 1,4-dibenzyl-2,5-piperazinedione was converted into the *syn*-3,6-bis(thiopyridyl) derivative **10**. Precomplexation of **10** with 1 equiv of silver(I) triflate in THF at 25 °C for 10 min, followed by addition of 1 equiv of γ-butyrolactone trimethylsilyl enol ether (2 h, 25 °C) furnished the syn-lactones **11** and **12** (2:1 ratio, epimeric at the lactone α carbon) in 70% yield (Scheme I). Reduction of each lactone with 1 equiv of $LiAlH_4$ in THF at 25 °C for 1 min followed by a rapid quench with $Na_2SO_4 \cdot 10H_2O$ afforded the diols **13** and **14**. It proved necessary to immediately purify the crude oils by chromatography; the purified materials were quite stable, but the crude decomposed rapidly.

Although unimportant ultimately, the stereochemistry obtained at the lactone α carbon proved to be significant in the cyclization of the corresponding diols **13** and **14**. When the diol **13** obtained from the "major" lactone **11** was treated with 1 equiv of AgOTf in THF at 25 °C, a 1:1 mixture of the desired bicyclo[4.2.2] ring system **15** and undesired bicyclo[3.2.2] system **16** was produced. When the corresponding "minor" diol **14** was similarly desulfurized, exclusive formation of the undesired bicyclo[3.2.2] diastereomer **17** (C-4 epimer of **16**) resulted. The product distribution from these two diastereomeric diols can be rationalized by examining the conformation of the putative precyclization iminium species that result from silver-assisted desulfurization of **13** and **14**. In the case of **14**, molecular models clearly show the preferred conformation of the 1′,4′-dihydroxybutyl moiety to be that depicted in structure C, where steric repulsion between the *N*-benzyl residue and the methylenes of the dihydroxybutyl group are minimized. This conformation places the hydroxymethyl moiety proximal to the electrophilic iminium carbon which, upon intramolecular alcoholysis, leads to the bicyclo[3.2.2] system **17**. For the "major" diol diastereomer **13**, the same conformational analysis as above dictates that structure A should be the most stable,[14] thus placing the hydroxyethyl group proximal to the iminium carbon to provide the desired bicyclo[4.2.2] system **15**. The roughly equimolar amount of **16** produced from this reaction, however, indicates that the *entropically favored* ring closure to the bicyclo[3.2.2] system

(10) Maag has realized the enolate condensation of *N,N′*-diacetylglycine anhydride with a ketone (ref 4); we were unable to effect this transformation on *N,N′*-dialkylpiperazinediones.

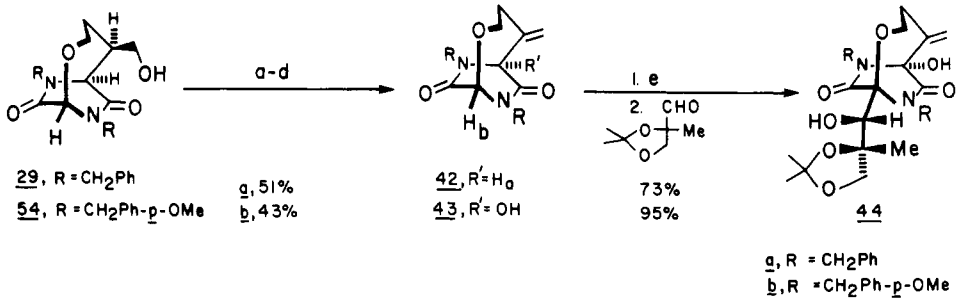
(11) See, for example: Ohler, E.; Tataruch, F.; Schmidt, U. *Chem. Ber.* **1973** *106*, 165. See also ref 9.

(12) Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968** *33*, 402.

(13) Williams, R. M.; Armstrong, R. W.; Maruyama, L. K.; Dung, J.-S.; Anderson, O. P. *J. Am. Chem. Soc.*, preceeding paper in this issue.

(14) The X-ray crystal structure of **12** also supports this arguement; see ref 13.

Scheme II



Reagents and conditions: (a) 2.5 equiv of methanesulfonyl chloride, Et_3N (2.5 equiv), THF, 25 °C, 12 h; (b) 2.2 equiv of $NaBH_3SePh$, THF, reflux, 2.2 h; (c) 30% H_2O_2 (5 equiv) THF, reflux, 20 min; (d) 1.5 equiv of *n*-BuLi, HMPA (2 equiv), $(Me_2N)_3P$ (2 equiv), THF, −100 °C, 1 min and then O_2 (gas) 15 min, −100 °C; (e) 2.3 equiv of *n*-BuLi, THF, −100 °C.

effectively competes via the more sterically encumbered structure B.

The undesirable regioselectivity preference for cyclization to the bicyclo[3.2.2] system could be effectively dealt with in the following manner. Selective silylation of diol **14** with *tert*-butyldimethylchlorosilane furnished a 4.7:1 mixture of silyl ethers **18** and **19** (76%). The major product was then converted into the *tert*-butyldiphenyl silyl ether **21** by silylation and selective HF·py removal of the more labile *tert*-butyldimethylsilyl group (75%, two steps). Cyclization of **21** with AgOTf in THF at 25 °C furnished the desired bicyclo[4.2.2] system **22** (80%). The minor silyl ether **19** was directly converted to the corresponding bicyclic silyl ether **23** (91%) by treatment with $AgOTf/K_2CO_3$[15] in THF at 25 °C. The same series of transformations could be applied to the minor diol **14** to afford silyl ethers **24** and **25** in a 4:1 ratio (58%). As above, the minor component **25** was directly cyclized to the bicyclo[4.2.2] system **27** (80%); HF·py treatment accordingly provided alcohol **29**. The major component **24** could either be subjected to the silylation/desilylation sequence as above for **18** or converted to the mesylate **26** and directly cyclized to the bicyclo[4.2.2] mesylate **28** by treatment with 3 equiv of $PhHgClO_4$[16] in THF at 25 °C (78%). In this way, complete conversion of the diols **14** and **15** to the desired bicyclo[4.2.2] nucleus was realized.

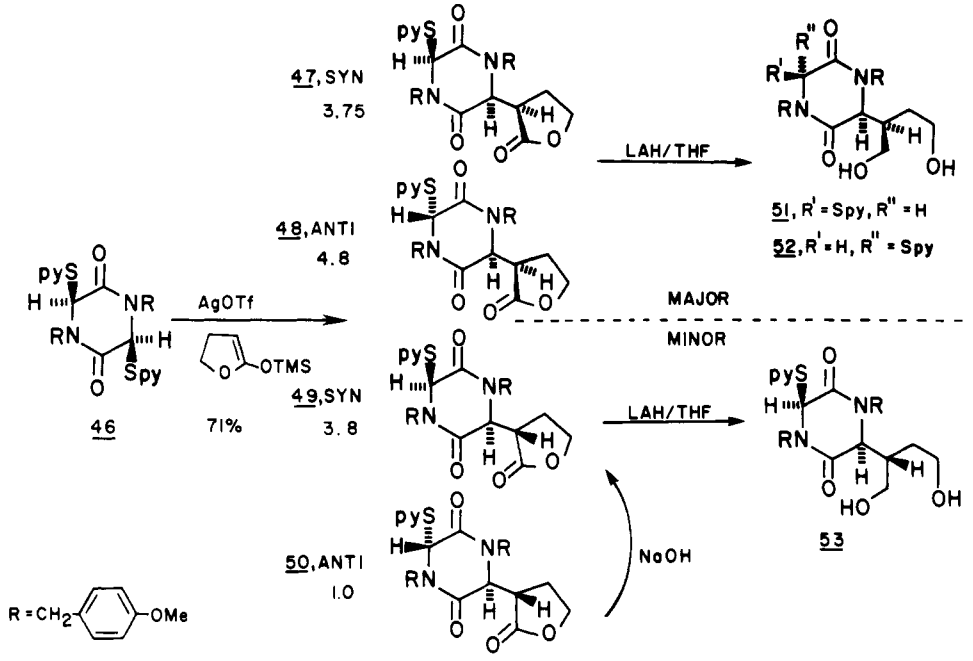
At this point, we examined the introduction of the required bridgehead hydroxyl and C-1′–C-3′ polyoxo side chain for the silyl derivative **23**, realizing that introduction of the exomethylene moiety would most likely have to occur after the reductive or oxidative removal of the *N*-benzyl protecting groups. We were surprised to find that treatment of **23** with *n*-BuLi in THF/HMPA at −100 °C followed by quenching with methyliodide afforded *exclusively* the methylated derivative **30**. This regioselectivity is in contradistinction with that we have observed for **6a** and **6b** as discussed above and may be due to steric and/or electronic effects of the silyloxymethyl group. The regioselectivity displayed by the carbanion quench of **23** dictated the *order* of introduction of C-1′–C-3′ via an aldol condensation followed by bridgehead hydroxylation at C-6. Thus, regio- and stereocontrolled aldol condensation of the bridgehead carbanion of **23** (LDA/THF, −100 °C) was achieved by quenching with 5 equiv of (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde[4] to afford a *single* diastereomer **31** (80%). Silylation (Bu^tMe_2SiOTf, 2,6-lutidine, CH_2Cl_2, 25 °C) of the secondary alcohol (**32**) followed by hydroxylation (*n*-BuLi/THF, −100 °C, O_2 quench) afforded the alcohol **33** (78%). Unfortunately, all attempts[17] to remove the *N*-benzyl groups on bicyclic derivatives **31–34**, **6a** (R = CH_2Ph), **16**, **22**, **23**, **27**, and **29** under a range of hydrogenolytic, dissolving metal, oxidative, and hydrolytic conditions[17] failed to produce any quantity of the desired deprotected *bicyclic* compounds. In particular, we found that under reductive conditions (H_2, 20% Pd/C, EtOH, 80 °C), cleavage of the C-1–O ether linkage and/or saturation[18] of the aromatic benzylic rings were the *only* types of reactivity observed. We were forced to conclude that the *N*-benzyl group does not constitute a generally useful protecting group for the bicyclomycin system.[19]

During the course of the above studies, we made two curious observations with substrates **23** and **32**. When compound **23** was treated with LDA in THF at −100 °C and quenched with *tert*-butyldimethylsilyl chloride, the expected C-silyl derivative **35** and the *unexpected* monodebenzylated compound **36** were isolated. The debenzylation of **23** is mechanistically difficult to rationalize based on the limited data we have; the precedent of Newcomb,[20] among others, however, would make it seem quite reasonable that LDA acts as the reducing agent by an electron-transfer process. An additionally interesting observation was made when the same substrate (**23**) was sequentially treated with LDA, TMSCl, and LDA; the C-silylated benzyl derivative **37** was isolated. Such a species presumably arose via trapping of the putative benzylic carbanion. This is the *first* case in our extensive bridgehead carbanion studies where we have apparently observed competing benzylic deprotonation over bridgehead carbanion formation. Excellent precedent in the literature describing "dipole-stabilized" amide N-carbanions exists;[21] thus, this result was not completely unexpected. It did suggest, however, that we might be able to successfully remove the recalcitrant *N*-benzyl groups by carbanionic oxidation. Treatment of **32**, with *tert*-butyllithium at −100 °C followed by an O_2 quench afforded a new compound that has been assigned structure **38** (35% or 68% based on **32**) based on spectroscopic data. Further attempts to oxidize both benzylic positions to benzoyl groups under more forcing conditions on **32** and **33** were unsuccessful. Apparently, *tert*-butyllithium is a strong enough base to form the benzylic carbanion but is too bulky to abstract a proton from the sterically encumbered N-8-benzylic moiety.

Just prior to embarking on a new strategy with another amide-protecting group, we decided to complete a synthesis of the *N*-benzylbicyclomycin system. A more efficient procedure for functionalizing the bridgehead positions was found by first introducing the exomethylene moiety onto the 1,6-unsubstituted bicyclo[4.2.2] nucleus. Dehydration of **29** to the bicyclic olefin **42** was readily accomplished in three steps: (1) mesylation (**39**); (2) selenide formation (**40**); and (3) oxidation/elimination (Scheme II). The corresponding diastereomeric mesylate **28** discussed above could similarly be transformed into olefin **42** via the selenide **41**.

(15) Anhydrous K_2CO_3 was found to preclude proton-catalyzed removal of the silyl ether by the triflic acid that is generated during cyclization.
(16) Dung, J.-S.; Armstrong, R. W.; Williams, R. M. *J. Org. Chem.* **1984** *49*, 3416.
(17) Among the conditions examined were: 20% Pd/C, H_2, 1 atm, EtOH, 80 °C; 20% Pd/C, H_2, 75 psi, EtOH, 25 °C → 80 °C; 20% PtO_2, H_2, 1 atm → 75 psi, EtOH, 25 °C → 80 °C; 20% $Pd(OH)_2$, H_2, 1 atm → 75 psi; EtOH, 25 °C → 80 °C; Li/NH_3/THF; Na/NH_3/THF; Al/Hg/THF; H_3PO_4/PhOH; DDQ; CrO_3; CAN; BCl_3/CH_2Cl_2; TMSI/CH_2Cl_2.
(18) Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971** *93*, 3478.
(19) The *N,N′*-dibenzoyl and *N,N′*-diacetyl-bis(thiopyridine) substrates (cf., **11**) were prepared but did not undergo the coupling reaction.
(20) Newcomb, M.; Williams, W. G. *Tetrahedron Lett.* **1984** *25*, 2723 and references cited therein.
(21) For example, see: Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981** *46*, 4108.

Scheme III



We were pleased to discover that the regioselectivity in the functionalization of the bridgehead carbanions of **42** was the *reverse* of that observed for **23** and in accordance with the behavior[9c] exhibited by the desmethylene nuclei **6a** and **6b**; i.e., H_a could be selectively deprotonated over H_b.[22] This order of regioselectivity is highly desirable since it diminshes the number of protecting group manipulations and, thus, overall number of steps.

Treatment of **42** with 1 equiv of *n*-BuLi in THF containing 2 equiv of HMPA and 2 equiv of hexamethylphosphorous triamide[23] at −78 °C followed by quenching with O_2 afforded the desired tertiary alcohol **43** (55%). Formation of the dianion of **43** (2.3 equiv of *n*-BuLi/THF, −98 °C) followed by addition of 5 equiv of (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde[4] afforded a *single* diastereoisomer **44** (73%). Although a correlation of **44** to bicyclomycin was not forthcoming,[24] the ^1H NMR spectrum of **44** clearly indicated that the aldol condensation rendered the correct relative configuration. Attempted removal of the *N*-benzyl groups of **44** again failed to produce the desired results. The only solace which was available from the now aborted *N*-benzyl series was the demonstrated feasibility of the overall synthetic plan that had emerged which, if a suitable amide protecting group could be selected, would lead to a considerably shorter synthesis of **1** than had been established by the Nagoya[6] group.

Due to the very favorable regio- and stereocontrol exhibited by the *olefinic* substrates **42** and **43**, we turned our attention toward potential protecting groups that could be removable under mild oxidative or hydrolytic conditions; reductive conditions would almost surely saturate the exomethylene. Following precedent from the β-lactam literature, we prepared[25] the simple *N*-*p*-methoxyphenyl and *N*-*p*-methoxybenzyl substrates **6a** (R = Ph-*p*-OCH_3 and R = CH_2Ph-*p*-OCH_3, respectively). Treatment of the *N*-*p*-methoxyphenyl derivative with a variety of oxidants (DDQ, CAN, CrO_3, O_3, electrochemical oxidation) failed to remove both *p*-methoxyphenyl rings; products resulting from the deblocking of one of the amides were realized with O_3 but further deprotection proved to be fruitless. We were pleased to discover that treatment of the *N*-*p*-methoxybenzyl derivative **6a** with ceric ammonium nitrate (CAN) according to the excellent conditions of Yoshimura[26] provided the desired lipophobic bicyclic compound **6a** (R = H) in 54% yield. To further test the feasibility of this approach, we examined the stability of natural bicyclomycin 2′,3′-acetonide (**45**)[27] toward this reagent. Treatment of **45** with 4 equiv of CAN (0.33 M) led to the complete destruction of **45** with no identifiable components being isolable. However, under slightly milder conditions (0.5 equiv of CAN, 0.04 M), the isopropylidene moiety of **45** was cleanly removed producing **1**. Unfortunately, these conditions failed to deblock **6a** (R = CH_2Ph-*p*-OCH_3). In a competition experiment, an equimolar mixture of **45** and **6a** (R = CH_2Ph-*p*-OCH_3) when treated with 4.5 equiv of CAN (0.3 M) fortuitously led to the clean deprotection of **6a** (R = CH_2Ph-*p*-OCH_3) → **6a** (R = H) and **45** → **1**. This result clearly established that the reaction of CAN with the *p*-methoxybenzyl groups at the required concentration was *faster* than the decomposition of the bicyclomycin nucleus. With this promising, yet narrow window apparent, we embarked on the total synthesis of bicyclomycin.

Total Synthesis of (±)-Bicyclomycin

Condensation of the *N*-(*p*-methoxybenzyl)-*syn*-3,6-bis(thiopyridyl) derivative[28] **46** with γ-butyrolactone trimethylsilyl enol ether in the presence of silver(I) triflate afforded the corresponding lactones **47**–**50** (Scheme III) in 71% combined yield.[13] The stereochemistry of each compound was readily assigned by correlation[13] to the *N*-benzyl analogues **11** and **12** as well as the behavior of the derived diols in the cyclizations. Reduction of the lactones **47**, **48**, and **49** to the corresponding diols **51**, **52**, and

(22) The J_{C-H} for the bridgehead methine protons of this nucleus (determined on **42b**) were 144 and 162 Hz for H_a and H_b, respectively. This compares with 144 and 168 Hz for H_a and H_b, respectively, for **6** (R = CH_3, ref 9c). The slightly diminished s character for C–H_b in **42b** as compared to **6** would indicate a slightly enhanced thermodynamic acidity for H_a in this system.

(23) We have found that inclusion of the phosphine results in higher yields of the alcohol which is presumably due to the reduction of the putative peroxide formed upon O_2 quench. LDA also effects the reduction of the peroxide: Williams, R. M.; Dung, J.-S. *Tetrahedron Lett.* **1985**, *26*, 37.

(24) Attempted N-benzylation of natural bicyclomycin and the corresponding acetonide **45** gave an array of products, none of which could be readily correlated to **44**; see also ref 6b.

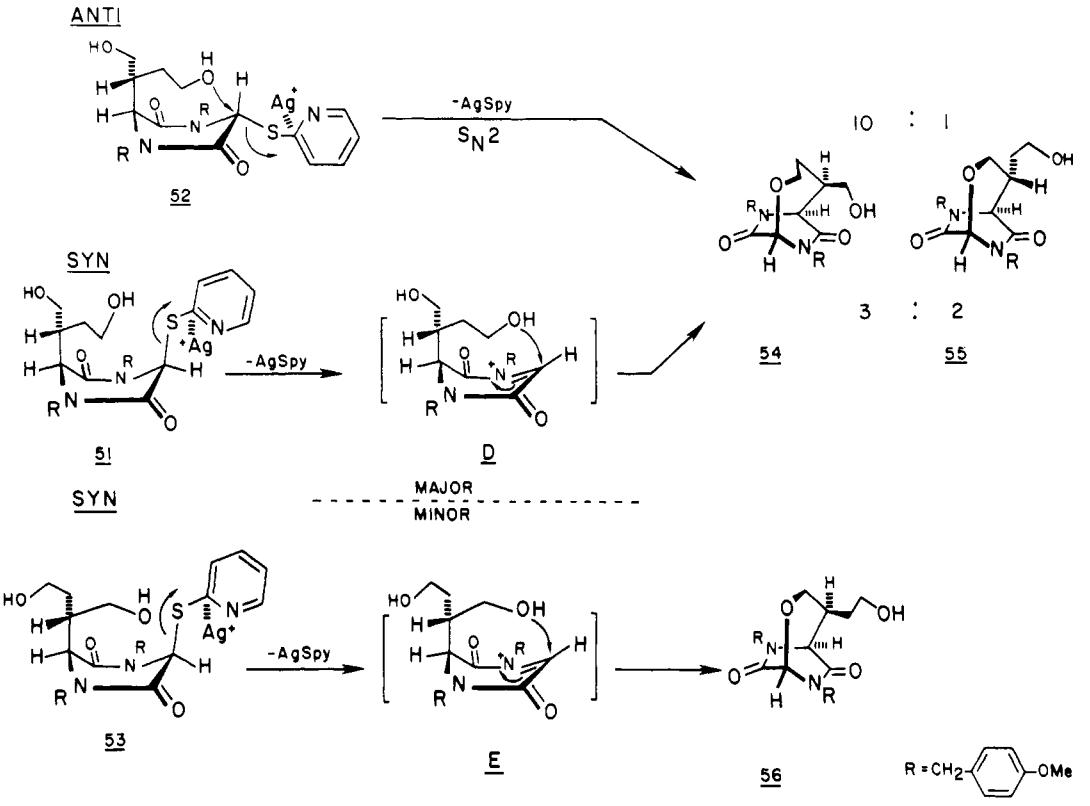
(25) (a) Krunethanl, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982** *47*, 2765. (b) Yanagisawa, H.; Ando, A.; Shiozaki, M.; Hiraoka, T. *Tetrahedron Lett.* **1983** *24*, 1037.

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

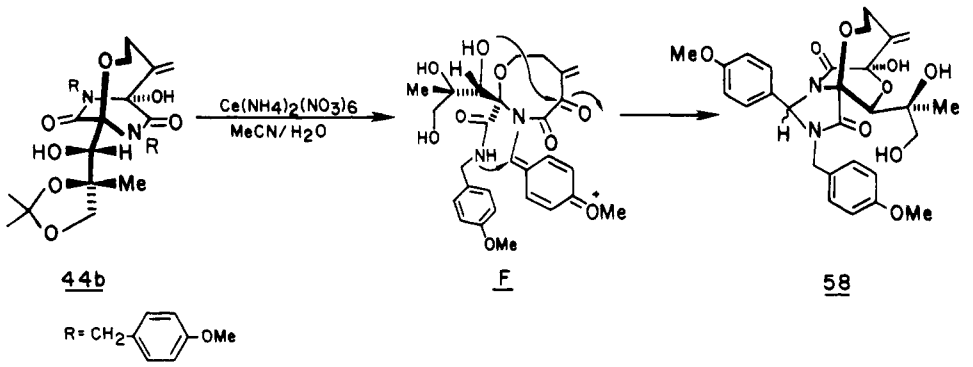
(27) Ger. Patent 2647322, April 28, 1977; *Chem. Abstr.* **1977** *87*, 102391*s*.

(28) Reference 6a indicates that 1,4-bis(*p*-methoxybenzyl)-2,5-piperazinedione underwent aromatic bromination and not bromination at the 3,6-positions of the piperazinedione. Under the conditions we utilize (NBS, CCl_4; see ref 13), a 98% yield of dibromide is obtained with no evidence for aromatic substitution.

Scheme IV



Scheme V



53, respectively, was accomplished with $LiAlH_4$ in THF at 25 °C. The minor *anti*-lactone **50** could not be effectively reduced to the corresponding diol and was, instead, epimerized to **49** in the presence of base.

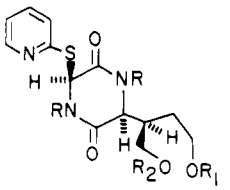
We were very intrigued to observe the product distribution resulting from cyclization of the major diols **51** and **52**. The syn diastereomer **51** afforded a 2:1 mixture of the desired bicyclo[4.2.2] alcohol **54** and undesired bicyclo[3.2.2] alcohol **55** upon treatment with AgOTf, in THF at 25 °C. On the other hand, the anti-diol **52** afforded a 10:1 ratio of **54**:**55**! This result clearly indicates that the transition states leading to the bicyclic products from the respective diols are distinct. The conformational analysis discussed above for the *N*-benzyl series also predicts that **54** should be the major product from both **51** and **52**. The syn disposition of **51**, however, mandates that removal of the thiopyridyl residue must precede C-1–O ether formation, and, thus, iminium species D is a reasonable intermediate. The anti-diol **52**, on the other hand, is capable of an intramolecular S_N2 alcoholysis of the Ag^+-coordinated thiopyridyl residue (see **52**, Scheme IV) and does not have to pass through the iminium species D to form the products. The relatively poor selectivity displayed by **51** when compared to **52** is readily rationalized on the assumption that iminium species D is highly reactive (early transition state), giving poor selectivity; the anti-diol **52**, then, would have a lower energy transition state farther along the reaction coordinate and thus displays greater selectivity consistent with the conformational analysis (vida infra). As expected, the minor diol diastereomer **53** gives exclusive formation (via E) of the bicyclo[3.2.2] system **56**.

The formation of the desired bicyclo[4.2.2] ring system from **51** and **53** was achieved in the same way as that described above for the *N*-benzyl series[29] (Chart I). The desired bicyclic olefin **42b** was obtained by dehydration of **54** (82%, cf. Scheme II) or from the diastereomeric mesylate **28b**. Hydroxylation of **42b** afforded **43b** (52%) which, upon aldol condensation as described above, afforded a *single* diastereomer (**44b**, 95%) that possessed the correct relative configuration.

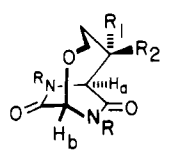
One curious observation was encountered during repeated trials of this remarkably diastereoselective aldol condensation. Typically, the reaction is performed at −100 °C and quenched with methanol at −80 °C. A variation in the procedure, where the reaction is allowed to warm to room temperature and then quenched with methanol, results in the isolation of a second diastereomer (1:1 ratio) that we have assigned as the C-1′ epimer[30] of **44b** (**57**).

(29) Except as specifically noted in the text, a series compounds contain R = CH_2Ph and b series compounds contain R = CH_2Ph-*p*-OMe (see Experimental Section for the preparation of each individual series).

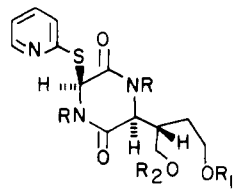
Chart I



18, $R_1 = SiMe_2Bu^t$, $R_2 = H$
19, $R_1 = H$, $R_2 = SiMe_2Bu^t$
20, $R_1 = SiMe_2Bu^t$, $R_2 = SiPh_2Bu^t$
21, $R_1 = H$, $R_2 = SiPh_2Bu^t$

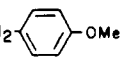


22, $R_1 = H$, $R_2 = CH_2OSiPh_2Bu^t$
23, $R_1 = H$, $R_2 = CH_2OSiMe_2Bu^t$
27, $R_1 = CH_2OSiMe_2Bu^t$, $R_2 = H$
28, $R_1 = CH_2OMs$, $R_2 = H$
29, $R_1 = CH_2OH$, $R_2 = H$
39, $R_1 = H$, $R_2 = CH_2OMs$
40, $R_1 = H$, $R_2 = CH_2SePh$
41, $R_1 = CH_2SePh$, $R_2 = H$



24, $R_1 = SiMe_2Bu^t$, $R_2 = H$
25, $R_1 = H$, $R_2 = SiMe_2Bu^t$
26, $R_1 = SiMe_2Bu^t$, $R_2 = Ms$

a SERIES, R = 

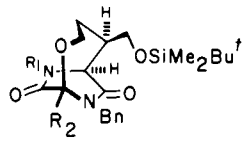
b SERIES, R = 

Since the desired aldol (**44b**) is formed and quenched under kinetic conditions, it is difficult to rationalize the formation of **57** upon warming to room temperature. It is possible that upon warming, the initially formed lithium alkoxide corresponding to **44b** undergoes a retro-Aldol condensation and recondenses, forming the observed diastereomeric mixture. Ample literature precedent for the retro-Aldol equilibrium of kinetic aldols can be cited.[31] The subtle electronic and steric effects of this particular bicyclic system that exhibit the remarkable degrees of stereoselectivities in both the kinetic and equilibrium processes are obscure. However, if the reaction is performed at −100 °C and quenched below −80 °C, the reliable, consistent, and exclusive formation of the desired isomer **44b** is realized.

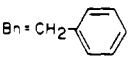
At this state, we turned to the crucial and final deblocking of **44b** to bicyclomycin. Disappointingly, subjecting **44b** to ceric ammonium nitrate in aqueous acetonitrile at the required concentration led to the rapid consumption of the starting material and the production of >10 unidentifiable products. The only identifiable component has been assigned structure **58** based on ^1H NMR, IR, and mass spectral data. The formation of **58** can be readily rationalized by consideration of a related rearrangement of N-alkylated bicyclomycin derivatives recently reported by Wacker[32] and associates. Tautomeric ring opening of **44b**, followed by intramolecular alcoholysis of the incipient ketone carbonyl by the C-1′–OH, loss of the isopropylidene moiety, and intramolecular trapping of the putative N-8-benzylic cation by N-10, furnishes **58** (illustrated as F, Scheme V).

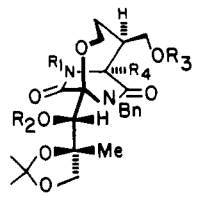
In an attempt to preclude this rearrangement, both the C-1′ and C-6 hydroxyl groups were converted into the corresponding trimethylsilyl and *tert*-butyl dimethylsilyl ethers. Treatment of these derivatives with CAN essentially led to the same product distribution as that obtained from **44b**, indicating the lability of

Chart II

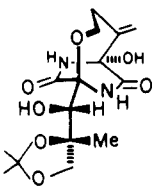


30, $R_1 = CH_2Ph$, $R_2 = CH_3$
35, $R_1 = CH_2Ph$, $R_2 = SiMe_2Bu^t$
36, $R_1 = R_2 = H$
37, $R_1 = CH(SiMe_3)Ph$, $R_2 = H$

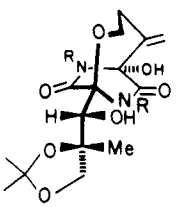
Bn = 

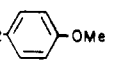


31, $R_1 = CH_2Ph$, $R_2 = R_4 = H$, $R_3 = SiMe_2Bu^t$
32, $R_1 = CH_2Ph$, $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = H$
33, $R_1 = CH_2Ph$, $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = OH$
34, $R_1 = CH_2Ph$, $R_2 = R_3 = H$, $R_4 = OH$
38, $R_1 = COPh$, $R_2 = R_3 = SiMe_2Bu^t$, $R_4 = H$



45



57, R = 

these silyl ethers to CAN. After extensive experimentation, we found that reaction of **44b** with trifluoroacetic anhydride in CH_2Cl_2 in the presence of DMAP led to the selective acetylation (**59**, Scheme VI) of the C-1′–OH in 95% yield. Treatment of **59** with 4 equiv of CAN in aqueous acetonitrile (0.3 M) followed by silica gel chromatography[33] *directly* afforded totally synthetic (±)-bicyclomycin in 35% yield (31% overall yield from **44b**). Comparison of ^1H NMR, IR, MS, TLC, and biological assay[34] confirmed the identity of synthetic **1**.

With the total synthesis of racemic bicyclomycin completed, we studied the resolution of the racemic bicyclic nucleus through the aldol condensation with optically active (−)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde.[35] The high degree of diastereodifferentiation displayed in the mutually racemic coupling indicated that an effective resolution could by realized by making either **44b** or the aldehyde optically active. When the asymmetric synthesis we recently reported[35] was used, the desired (−)-aldehyde was prepared (ca. ee 83%) and condensed with **43b**. We were gratified to isolate the optically active diastereomer of **44b** (9% or 49% based on consumed **43b**).[36] Conversion of this material to (+)-bicyclomycin exactly as described above furnished bicyclomycin with an optical rotation of +58° which corresponds to ca. ee 78%. It is apparent that the optical purity of the material obtained in the aldol condensation is limited by the optical purity

(30) The assignment is based on the ca. 1 ppm upfield shift of the C-1′–OH from δ 6.60(**44b**) to δ 5.78; the isopropylidene and C-2′–CH_3 resonances do not shift considerably (see Experimental Section).

(31) For a review, see: Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds. Elsevier: New York, 1981; Vol. II, Chapter 4.

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

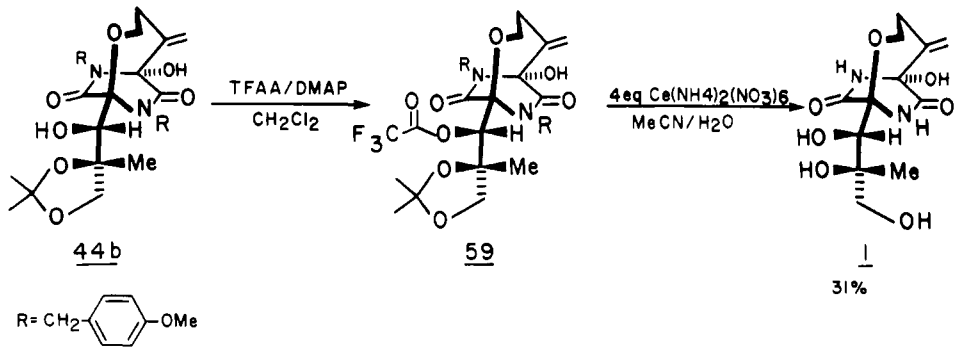
(33) We have found that the trifluoroacetate is stable to elution from silica gel with THF but is labile to elution with MeOH. Indeed, the final deprotonation does not produce **1** from the CAN reaction mixture; the trifluoroacetate is cleaved in the final purification with silica gel/MeOH.

(34) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Med. Chem.*, in press.

(35) Dung, J.-S.; Armstrong, R. W.; Anderson, O. P.; Williams, R. M. *J. Org. Chem.* **1983** *48*, 3592 and references cited therein.

(36) The unreacted **43b** was found to be optically enriched, $[\alpha]^{25}_D$ −6.2°.

Scheme VI



of the aldehyde employed. In principle, it would be possible to completely resolve[36] the *unreacted* **43b** (1*S*,6*R*) from this condensation by adjusting the reaction conditions such that complete consumption of (1*R*,6*S*)- **43b** occurred.

The totally synthetic (+)-bicyclomycin was identical with the natural sample by comparison of spectral properties.

Summary. The total synthesis of bicyclomycin has been achieved in 12 chemical steps (13 steps via **26b**) with complete regio- and stereocontrol. Since the natural product is now available commercially from an efficient fermentation process, the present total synthesis or, conceivably, any synthetic path is not likely to have any commercial import. The inherent value of the versatile unsubstituted bicyclic nuclei that we have employed in these studies and the interesting behavior of their derived bridgehead carbanions merit further application in elucidating the potentially valuable and unique mechanism of action of bicyclomycin. The *N*-*p*-methoxybenzyl derivatives allow for the preparation of a multitude of lipophilic and lipophobic bicyclic structures[34] that are not accessible by degradation of **1**. The search for mechanistically and functionally unique compounds based on the bicyclomycin nucleus is currently under investigation.

Experimental Section

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-(hydroxypropyl)]-2,5-piperazinedione (13).[37] To a stirred solution of **11** (899 mg, 1.88 mmol, 1.0 equiv) in THF (25 mL) at 0 °C over N_2 was added solid lithium aluminum hydride (35.02 mg, 0.943 mmol, 0.5 equiv), and the mixture was stirred for 30 min at 0 °C. The mixture was then quenched with excess $Na_2SO_4 \cdot 10H_2O$, filtered, concentrated, and separated by flash column silica gel (sequentially eluted with 1:1 EtOAc/hexanes to 100% EtOAc) to afford 380 mg (54%) of **13** as an oil: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 1.80–1.90 (1 H, m), 1.90–2.00 (1 H, m), 2.2–2.25 (1 H, m), 3.69 (1 H, t, J = 5.2 Hz, D_2O exch), 3.83 (5 H, m), 4.07 (1 H, $^1/_2$ABq, J = 15.4 Hz), 4.16 (1 H, $^1/_2$ABq, J = 15.1 Hz), 4.28 (1 H, s), 5.20 (1 H, $^1/_2$ABq, J = 15.1 Hz), 5.21 (1 H, $^1/_2$ABq, J = 15.4 Hz), 6.71 (1 H, s), 7.04–7.44 (11 H, m), 7.44–7.68 (2 H, m), 8.42 (1 H, br d, J = 5.5 Hz); IR (NaCl, neat) 3400, 2910, 1670, 1450, 1415, 1115, 720 cm^{-1}; mass spectrum, *m/e* 380 (2.4), 292 (1.8), 91 (100).

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-(hydroxypropyl)]-2,5-piperazinedione (14). To a stirred solution of **12** (652 mg, 1.34 mmol, 1.0 equiv) in THF (30 mL) at 0 °C was added a solution of lithium aluminum hydride (25.4 mg, 0.669 mmol, 0.5 equiv) in THF (2 mL). After stirring 20 min at 0 °C, excess $Na_2SO_4 \cdot 10H_2O$ was added, the mixture was stirred 10 min, and then warmed to room temperature, filtered, concentrated, and separated by PTLC silica gel (eluted with 4:1 MeOH/CH_2Cl_2) to afford 310 mg (47.3%) of **14** as an oil: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 1.60–2.08 (2 H, m), 2.20–2.36 (1 H, m), 3.60–3.96 (6 H, m, D_2O exch), 4.06 (1 H, $^1/_2$ABq, J = 15.1 Hz), 4.13 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.16 (1 H, br s), 5.25 (1 H, $^1/_2$ABq, J = 14.7 Hz), 5.39 (1 H, $^1/_2$ABq, J = 15.1 Hz), 6.73 (1 H, s), 7.02–7.68 (13 H, m), 8.46 (1 H, d, J = 4.2 Hz); ^{13}C NMR (25 MHz) ($CDCl_3$) δ 31.52 (t), 42.96 (d), 46.81 (t), 49.73 (t), 60.18 (d), 60.71 (2 C, t), 61.53 (d), 121.02 (d), 122.54 (d), 128.26 (d), 128.38 (d), 128.73 (d), 135.33 (s), 135.62 (s), 136.73 (d), 149.11 (d), 154.83 (s), 164.69 (s), 167.32 (s); mass spectrum, *m/e* 380 (M^+ – 111, 7.5), 362 (3.5), 297 (2.1), 292 (9.4), 274 (9.7), 111 (92.8), 91 (100).

8,10-Dibenzyl-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (15) and 7,9-Dibenzyl-7,9-diaza-4-[2′-(hydroxyethyl)]-2-oxabicyclo[3.2.2]nonane-6,8-dione (16). To a stirred solution of **13** (40 mg, 0.08 mmol, 1.0 equiv) in THF (1.5 mL) at room temperature was added solid silver triflate (24 mg, 0.12 mmol, 1.5 equiv). The mixture was stirred 10 min, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:9:89 NH_4OH/MeOH/CH_2Cl_2) to afford 25 mg (80%) of an inseparable mixture of **15** and **16**.

Compound 16: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.25 (2 H, m), 1.82 (1 H, D_2O exch), 2.38 (1 H, m), 3.60 (3 H, m), 3.82 (1 H, dd, J_{vic} = 5.33, J_{gem} = 12.47 Hz), 4.01 (1 H, s), 4.30 (1 H, $^1/_2$ABq, J = 15.1 Hz), 4.39 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.84 (1 H, $^1/_2$ABq, J = 15.1 Hz), 4.94 (1 H, $^1/_2$ABq, J = 14.7 Hz), 5.05 (1 H, s), 7.20–7.30 (10 H, m); IR (NaCl, neat) 3600–3200, 1670 cm^{-1}; mass spectrum, *m/e* 380 (4.5), 292 (11.6), 202 (4.4), 91 (100).

8,10-Dibenzyl-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (15). To a stirred solution of **22** (5 mg, 0.008 mmol, 1.0 equiv) in THF (0.5 mL at room temperature was added excess HF·pyridine complex. The solution was stirred for 30 min, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:1 EtOAc/hexane) to afford 3 mg (98%) of **15** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ TMS 1.58–1.65 (1 H, m), 1.70–1.85 (1 H, m), 2.19–2.28 (1 H, m), 2.46 (1 H, t, J = 5.5 Hz, D_2O exch), 3.58–3.70 (2 H, m), 3.72–3.81 (2 H, m), 4.21 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.25 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.28 (1 H, d, J = 3.4 Hz), 4.97 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.97 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.21 (1 H, s), 7.18–7.40 (10 H, m); ^{13}C NMR (25 MHz) ($CDCl_3$) δ 28.8 (t), 45.0 (d), 47.6 (t), 47.9 (t), 60.18 (d), 63.3 (t), 63.5 (t), 78.2 (d), 128.2 (d), 128.2 (d), 128.3 (d), 128.9 (d), 134.9 (s), 135.1 (s), 163.2 (s), 168.3 (s); IR (NaCl, neat) 3600–3150, 1675, 1450, 1160 cm^{-1}; mass spectrum, *m/e* 380 (0.6), 312 (1.1), 149 (6.9), 91 (11.4), 84 (100).

7,9-Dibenzyl-7,9-diaza-4-(2′-hydroxyethyl)-2-oxabicyclo[3.2.2]nonane-6,8-dione (17). To a stirred solution of **14** (43.6 mg, 0.089 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added solid silver triflate (36.8 mg, 0.177 mmol, 2.0 equiv), and the mixture was stirred at room temperature. After 20 min, the mixture was diluted with CH_2Cl_2, poured into 0.1 N NaOH, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:9:89 NH_4OH/MeOH/CH_2Cl_2) to give 26 mg (78%) of **17** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.20–1.35 (1 H, m), 1.35–1.60 (2 H, m), 1.82–1.95 (1 H, m), 3.26 (1 H, dd, J_{vic} = 8.7, J_{gem} = 11.5 Hz), 3.48 (2 H, br t, J = 6.2 Hz), 3.78 (1 H, dd, J_{vic} = 6.2, J_{gem} = 11.5 Hz), 3.93 (1 H, d, J = 2.3 Hz), 4.45 (1 H, $^1/_2$ABq, J = 14.9 Hz), 4.53 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.65 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.79 (1 H, $^1/_2$ABq, J = 14.9 Hz), 5.12 (1 H, s), 7.12–7.46 (10 H, m); IR (NaCl, neat) 3600–3200, 1670, 1450, 1150 cm^{-1}; mass spectrum, *m/e* 380 (M^+, 9.3), 292 (12.4), 274 (5.7), 183 (2.2), 91 (100).

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-[((*tert*-butyldimethylsilyl)oxy)propyl]]-2,5-piperazinedione (18), and 1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-[((*tert*-butyldimethylsilyl)oxy)methyl]-3″-(hydroxypropyl)]-2,5-piperazinedione (19). To a stirred solution of **13** (34 mg, 0.069 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (10.4 mg, 0.069 mmol, 1.0 equiv) and solid (dimethylamino)pyridine (1 mol %) followed by triethylamine (0.01 mL, 0.069 mmol, 1.0 equiv). The mixture was stirred for 30 min, evaporated to dryness, and separated by PTLC silica gel (eluted with 100% EtOAc) to afford 16 mg (63%) of **18** and 3.4 mg (13.5%) of **19**.

Compound 18: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.09 (6 H, s), 0.91 (9 H, s), 1.50–1.96 (2 H, m), 2.24–2.56 (2 H, m), 3.60–3.92 (4

(37) Melting points are uncorrected. See ref 13 for general experimental conditions, abbreviations, and instrumentation details.

H, m), 4.07 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.12 (1 H, $^1/_2$ABq, J = 13.9 Hz), 4.21 (1 H, d, J = 7.5 Hz), 5.18 (1 H, $^1/_2$ABq, J = 13.9 Hz), 5.38 (1 H, $^1/_2$ABq, J = 14.7 Hz), 6.68 (1 H, s), 7.02–7.62 (13 H, m), 8.39–8.45 (1 H, m); ^{13}C NMR (25 MHz) ($CDCl_3$) δ 5.32, 18.32, 25.97, 30.87, 41.73, 46.93, 48.50, 60.30, 60.59, 60.79, 61.59, 121.08, 122.48, 127.91, 128.38, 128.73, 135.56, 135.74, 136.73, 149.22, 155.00, 164.46, 167.03; IR (NaCl, neat) 3600–3200, 1675 cm^{-1}; mass spectrum, m/e 503 (M^+ – 102, 1.7), 437 (4.1), 355 (5.2), 281 (9.1), 149 (34.4), 105 (100), 91 (79.1).

Compound 19: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.12 (6 H, s), 0.92 (9 H, s), 1.6–2.0 (2 H, m), 2.10–2.42 (1 H, m), 3.60–3.96 (5 H, m), 4.10 (1 H, $^1/_2$ABq, J = 14.0 Hz), 4.22 (1 H, $^1/_2$ABq, J = 14.0 Hz), 4.23 (1 H, br s), 5.22 (1 H, $^1/_2$ABq, J = 14.0 Hz), 5.29 (1 H, $^1/_2$ABq, J = 14.0 Hz), 6.66 (1 H, s), 7.04–7.68 (14 H, m), 8.40–8.48 (1 H, m); IR (NaCl, neat) 3600–3300, 1675, 1450 cm^{-1}.

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-[((*tert*-butyldiphenylsilyl)oxy)methyl]-3″-[((*tert*-butyldimethylsilyl)oxy)propyl]]-2,5-piperazinedione (20). To a stirred solution of **18** (35 mg, 0.058 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at room temperature was added (dimethylamino)pyridine (1 mol %), *tert*-butyldiphenylsilyl chloride (0.038 mL, 0.145 mmol, 2.5 equiv), and triethylamine (0.01 mL, 0.07 mmol, 1.2 equiv). After stirring for 12 h, the mixture was evaporated to dryness and separated on PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 46 mg (94%) of **20** as an oil: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.048 (6 H, s), 0.835 (9 H, s), 1.093 (9 H, s), 1.40–1.80 (2 H, m), 2.08–2.22 (1 H, m), 3.00–3.55 (2 H, m), 3.80–3.96 (2 H, m), 4.15 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.16 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.37 (1 H, br s), 5.09 (1 H, $^1/_2$ABq, J = 14.7 Hz), 5.18 (1 H, $^1/_2$ABq, J = 14.7 Hz), 6.66 (1 H, s), 6.92–7.67 (23 H, m), 8.40–8.46 (1 H, m); IR (NaCl, neat) 1670, 1450, 1150 cm^{-1}; mass spectrum, m/e 732 (M^+ – CH_3, 0.3), 691 (2.3), 675 (9.6), 543 (3.2), 439 (4.4), 328 (65.0), 294 (7.7), 91 (100).

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-[((*tert*-butyldiphenylsilyl)oxy)methyl]-3″-(hydroxypropyl)]-2,5-piperazinedione (21). To a stirred solution of **20** (13 mg, 0.015 mmol, 1.0 equiv) in THF/CH_2Cl_2 (1:1, 2 mL) at room temperature was added all at once excess HF·pyridine complex. The mixture was stirred for 20 min, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, evaporated to dryness, and separated on PTLC silica gel (eluted with 1:9:89 NH_4OH/MeOH/CH_2Cl_2) to afford 9 mg (80%) of **21** as an oil which was carried on directly to **22**.

8,10-Dibenzyl-8,10-diaza-5-[((*tert*-butyldiphenylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (22). To a stirred solution of **21** (12 mg, 0.016 mmol, 1.0 equiv) in THF (0.5 mL) at room temperature was added solid silver triflate (21.1 mg, 0.08 mmol, 5.0 equiv). The mixture was stirred for 30 min at room temperature, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 100% EtOAc) to afford 8 mg (79%) of **22** as an oil: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 1.07 (6 H, s), 1.08 (3 H, s), 2.10 (3 H, m), 3.42 (1 H, dd, J_{vic} = 5.5, J_{gem} = 12.0 Hz), 3.54–3.88 (3 H, m), 4.10 (1 H, $^1/_2$ABq, J = 14.8 Hz), 4.15 (1 H, $^1/_2$ABq, J = 14.8 Hz), 4.40 (1 H, d, J = 1.9 Hz), 5.12 (1 H, $^1/_2$ABq, J = 14.8 Hz), 5.12 (1 H, $^1/_2$ABq, J = 14.8 Hz), 5.19 (1 H, s), 7.08–7.48 (15 H, m), 7.48–7.76 (5 H, m); IR (NaCl, neat) 1670, 1450, 1150 cm^{-1}; mass spectrum, m/e 561 (M^+ – *tert*-butyl, 74.0), 527 (39.1), 292 (2.7), 199 (17.5), 91 (100).

8,10-Dibenzyl-8,10-diaza-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (23). To a stirred solution of **19** (279 mg, 0.461 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added solid AgOTf (142.1 mg, 0.5532 mmol, 1.2 equiv), and the mixture was stirred at room temperature. After 20 min, the mixture was diluted with CH_2Cl_2, poured into 0.1 N NaOH, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 172 mg (91%) of **23** as an oil that was identical with that obtained from **15**.

8,10-Dibenzyl-8,10-diaza-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione from 15. To a stirred solution of **15** and **16** (274 mg, 0.741 mmol, 1.0 equiv) in THF (10 mL) at room temperature was added *tert*-butyldimethylsilyl triflate (0.599 mL, 2.16 mmol, 3.0 equiv), and the mixture was stirred at room temperature. After 12 h, the mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated on a silica gel flash column (eluted with 1:3 EtOAc/hexanes) to afford 170 mg (49%) of **23** as an oil.

Compound 23: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.06 (6 H, s), 0.89 (9 H, s), 1.9–2.3 (3 H, m), 3.41 (1 H, dd, J_{vic} = 5.5, J_{gem} = 9.8 Hz), 3.54 (1 H, d, J_{gem} = 9.8 Hz), 3.76 (1 H, m), 3.88 (1 H, m), 4.09 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.15 (1 H, $^1/_2$ABq, J = 14.9 Hz), 4.22 (1 H, d, J = 2.0 Hz), 5.10 (1 H, $^1/_2$ABq, J = 14.9 Hz), 5.12 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.18 (1 H, s), 7.30 (10 H, m); ^{13}C NMR (25 MHz) ($CDCl_3$) δ 5.32 (q), 18.32 (s), 25.97 (q), 29.06 (t), 46.93 (t), 47.63 (t), 59.30 (t), 63.45 (d), 65.09 (t), 83.48 (d), 127.79 (d), 127.97 (d), 128.26 (d), 128.73 (d), 135.27 (s), 162.47 (s), 166.97 (s); IR (NaCl, neat) 1670, 1445, 1052 cm^{-1}; mass spectrum, m/e 479 (M^+CH_3, 1.1), 437 (44.6), 292 (1.1), 208 (16.0), 91 (100).

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-[((*tert*-butyldimethylsilyl)oxy)methyl]-3″-(hydroxypropyl)]-2,5-piperazinedione (24) and 1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-[((*tert*-butyldimethylsilyl)oxy)propyl]]-2,5-piperazinedione (25). To a stirred solution of **14** (564 mg, 1.15 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at room temperature was added solid DMAP (2 mg), triethylamine (0.162 mL, 1.15 mmol, 1.0 equiv), and *tert*-butyldimethylsilyl chloride (174.6 mg, 1.15 mmol, 1.0 equiv), and the mixture was stirred at room temperature. After 24 h, the mixture was poured into H_2O and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and separated by radial chromatography on silica gel (eluted with 1:3 EtOAc/hexanes) to afford 87 mg (12.4%) of **25**, 318 mg (46%) of **24**, plus 132 mg (19.1%) of disilylated compound.

Compound 24: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.11 (6 H, s), 0.91 (9 H, s), 1.8 (2 H, m), 2.35 (1 H, m), 3.60–3.75 (5 H, m), 4.05 (1 H, $^1/_2$ABq, J = 15.1 Hz), 4.12 (1 H, $^1/_2$ABq, J = 14.8 Hz), 4.15 (1 H, d, J = 2 Hz), 5.19 (1 H, $^1/_2$ABq, J = 14.8 Hz), 5.35 (1 H, $^1/_2$ABq, J = 15.1 Hz), 6.65 (1 H, s), 7.20 (11 H, m), 7.35 (2 H, m), 8.40 (1 H, m); ^{13}C NMR (25 MHz) ($CDCl_3$) δ 5.15 (q), 18.3 (s), 26.03 (q), 31.22 (t), 42.55 (d), 46.87 (t), 49.73 (t), 60.50 (t), 61.62 (t), 120.96 (d), 122.77 (d), 127.79 (d), 128.32 (d), 128.67 (d), 129.02 (d), 135.56 (s), 135.91 (s), 136.31 (s), 149.22 (d), 155.23 (s), 164.46 (s), 166.68 (s); IR (NaCl, neat) 3600–3200, 1670, 1260 cm^{-1}.

Compound 25: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.14 (6 H, s), 0.97 (9 H, s), 1.80 (2 H, m), 2.30 (1 H, m), 3.01 (1 H, m), 3.65–3.75 (4 H, m), 4.10 (2 H, m), 4.17 (1 H, br s), 5.24 (1 H, $^1/_2$ABq, J = 14.65 Hz), 5.43 (1 H, $^1/_2$ABq, J = 14.89 Hz), 6.75 (1 H, s), 7.25 (11 H, m), 7.35 (2 H, m), 8.42 (1 H, d, J = 4.64 Hz); ^{13}C NMR (25 MHz) ($CDCl_3$) δ $CHCl_3$ 5.382 (q), 18.14 (s), 25.85 (q), 30.93 (t), 42.20 (d), 46.52 (t), 49.62 (t), 60.47 (t), 60.94 (t), 120.73 (d), 122.19 (d), 127.44 (d), 128.09 (d), 128.43 (d), 135.27 (s), 135.62 (s), 136.44 (d), 148.87 (d), 154.87 (s), 164.40 (s), 167.15 (s); IR (NaCl, neat) 3600–3200, 1670, 1260 cm^{-1}.

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-[1″-[(methylsulfonyl)oxy)methyl]-3″-[((*tert*-butyldimethylsilyl)oxy)propyl]]-2,5-piperazinedione (26). To a stirred solution of **24a** (22 mg, 0.526 mmol, 1.0 equiv) in THF (0.5 mL) was added Et_3N (0.11 mL, 0.789 mmol, 1.5 equiv) followed by methanesulfonyl chloride (0.06 mL, 0.789 mmol, 1.5 equiv) at room temperature. After 10 min, the mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 25 mg (98%) of **26** as an oil: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.10 (6 H, s), 0.93 (9 H, s), 2.60 (2 H, m), 2.80 (1 H, m), 3.64 (3 H, s), 3.73 (2 H, m), 3.92 (2 H, m), 3.93 (1 H, $^1/_2$ABq, J = 14.9 Hz), 4.02 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.43 (1 H, d, J = 3.2 Hz), 5.16 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.45 (1 H, $^1/_2$ABq, J = 14.6 Hz), 6.66 (1 H, s), 7.20–7.40 (11 H, m), 7.56 (2 H, m), 8.43 (1 H, d, J = 4.93 Hz); IR (NaCl, neat) 1670, 1450, 1045 cm^{-1}; mass spectrum, m/e 367 (M^+ – 91, 2.1), 272 (1.2), 181 (3.1), 91 (100).

8,10-Dibenzyl-8,10-diaza-5-methylene-2-oxabicyclo[4.2.2]decane-7,9-dione (42a). To a stirred solution of mesylate (**26a**) (18 mg, 0.026 mmol, 1.0 equiv) in THF (1 mL) was added a solution of $PhHgClO_4$ (0.058 mmol, 2.2 equiv) in THF (2 mL), and the mixture was stirred for 22 min at room temperature, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and passed through a silica plug. The crude **28a** was dissolved in THF (1.5 mL) at room temperature and $BH_3PhSeNa$ (0.03 mmol, 1.1 equiv, 1 mL of EtOH) was added, and the mixture was stirred 12 h and concentrated to dryness diluted with THF (5 mL) to afford crude **41a**. Hydrogen peroxide (30%, 0.03 mL, 1.0 equiv) was added, and the mixture was heated to reflux. After 20 min, the mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 4.1 mg (37% overall) of **42a** as an oil which was identical in every respect with that obtained from **40a** (see below).

8,10-Dibenzyl-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (29). To a stirred solution of **19** (82 mg, 0.135 mmol, 1.0 equiv) in $CHCl_3$ (1.5 mL) at room temperature was added solid AgOTf (34.8 mg, 0.135 mmol, 1.0 equiv), and the mixture was stirred at room temperature. After 35 min, the mixture was diluted with THF (1 mL)

and solid tetra-*n*-butylammonium fluoride (102 mg, 0.337 mmol, 5.0 equiv) was added. The mixture was stirred for 10 min, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and poured through a silica plug to afford 41.2 mg (80%) of **29** as an oil. This was carried on to the next step without further purification. The structure of the alcohol was established by conversion to the selenide (**41a**) via the mesylate (**28a**).

8,10-Dibenzyl-8,10-diaza-1-methyl-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (30). To a stirred solution of **23** (22 mg, 0.047 mmol, 1.0 equiv) in THF (2 mL) at −78 °C equipped with a constant N_2 flow was added HMPA (0.009 mL, 0.0517 mmol, 1.05 equiv) followed by a solution of LDA (0.0517 mmol, 1.05 equiv) in THF (1 mL). The yellow enolate was stirred for 65 min at −78 °C, at which time methyl iodide (0.014 mL, 0.235 mmol, 5 equiv) was added. After 5 min, the mixture was warmed to room temperature, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 12 mg (39%, 71% based on recovered starting material) of **30** as an oil: ^{1}H NMR (100 MHz) ($CDCl_3$) δ TMS 0.05 (6 H, s), 0.89 (9 H, s), 1.66 (3 H, s), 1.60–1.80 (2 H, m), 1.93–2.33 (1 H, m), 3.19–3.93 (4 H, m), 4.13 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.31 (1 H, br s), 4.40 (1 H, $^1/_2$ABq, J = 13.9 Hz), 5.08 (1 H, $^1/_2$ABq, J = 13.9 Hz), 5.26 (1 H, $^1/_2$ABq, J = 14.4 Hz), 7.26 (5 H, br s), 7.32 (5 H, br s); IR (NaCl, neat) 1670, 1450, 1150 cm^{-1}.

8,10-Dibenzyl-8,10-diaza-1-[1′-hydroxy-2′,3′-*O*-isopropylidene]-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (31). To a stirred solution of **23** (38 mg, 0.08 mmol, 1.0 equiv) in THF (1 mL) at −100 °C was added a solution of LDA (0.089 mmol, 1.1 equiv) in THF (1 mL). After stirring the dark yellow enolate at −100 °C for 5 min, (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (0.035 mL, 0.243 mmol, 3.0 equiv) was added, and the mixture was stirred 2 min at −100 °C and then warmed to room temperature. The mixture was then diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:5 EtOAc/hexanes) to give 6.3 mg (13%, 80% based on recovered starting material) of **31** as an oil. Compound **31** was very difficult to separate from starting material and was carried on as a mixture to the next step.

8,10-Dibenzyl-8,10-diaza-1-[1′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene]-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (32). To a stirred solution of **31** (7.8 mg, 0.012 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at room temperature was added 2,6-lutidine (0.003 mL, 0.024 mmol, 2.0 equiv) followed by *tert*-butyldimethylsilyl triflate (0.005 mL, 0.018 mmol, 1.5 equiv). After stirring 2 h at room temperature, the mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 9 mg (99%) of **32** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 0.021 (3 H, s), 0.026 (3 H, s), 0.029 (3 H, s), 0.104 (3 H, s), 0.855 (9 H, s), 0.918 (9 H, s), 1.020 (3 H, s), 1.284 (3 H, s), 1.297 (3 H, s), 1.40–1.655 (2 H, m), 2.16 (1 H, m), 3.39 (1 H, dd, J_{vic} = 5.9, J_{gem} = 10.1 Hz), 3.528–3.783 (3 H, m), 3.65 (1 H, $^1/_2$ABq, J = 8.6 Hz), 3.76 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.14 (1 H, $^1/_2$ABq, J = 8.6 Hz), 4.13 (1 H, s), 4.62 (1 H, $^1/_2$ABq, J = 15.2 Hz), 4.745 (1 H, s), 4.91 (1 H, $^1/_2$ABq, J = 15.2 Hz), 5.35 (1 H, $^1/_2$ABq, J = 14.5 Hz), 7.18–7.56 (10 H, m); IR (NaCl, neat) 1670, 1370, 1130, 1080 cm^{-1}; mass spectrum, *m/e* 737 (1.0), 696 (2.6), 637 (3.4), 581 (23.9), 517 (1.9), 436 (2.5), 201 (5.2), 145 (2.0), 91 (100).

8,10-Dibenzyl-8,10-diaza-1-[1′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene]-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (33). To a stirred solution of **32** (15 mg, 0.021 mmol, 1.0 equiv) in THF (1 mL) at −100 °C was added *tert*-butyllithium (0.005 mL, 0.023 mmol, 1.1 equiv), and the resulting dark enolate was stirred at −100 °C for 2 min. A steady stream of O_2 was bubbled through the mixture for 10 min. The mixture was stirred 10 min at −100 °C, allowed to warm to room temperature, diluted with CH_2Cl_2, poured into H_2O and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 12 mg (78%) of **33** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 0.03 (6 H, s), 0.10 (6 H, s), 0.85 (9 H, s), 0.92 (9 H, s), 1.02 (3 H, s), 1.20 (3 H, s), 1.30 (3 H, s), 2.15 (2 H, m), 3.32 (1 H, dd, J = 5.9, 10.1 Hz), 3.60 (2 H, m), 3.67 (1 H, $^1/_2$ABq, J = 8.6 Hz), 3.70 (2 H, m), 3.76 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.11 (1 H, $^1/_2$ABq, J = 8.6 Hz), 4.13 (1 H, s), 4.65 (1 H, $^1/_2$ABq, J = 15.2 Hz), 4.74 (1 H, s, D_2O exch), 4.91 (1 H, $^1/_2$ABq, J = 15.2 Hz), 5.34 (1 H, $^1/_2$ABq, J = 14.5 Hz), 7.20–7.50 (10 H, m); IR (NaCl, neat) 3500–3200, 1670, 1450, 1150 cm^{-1}; mass spectrum, *m/e* 754 ($M^+ - CH_3$, 1.3), 712 ($M^+ - C_4H_9$, 0.9), 638 ($M^+ - C_4H_9S$, 11.2), 581 (33), 437 (43.8), 129 (3), 91 (100).

8,10-Dibenzyl-8,10-diaza-1-[1′-hydroxy-2′,3′-*O*-isopropylidene]-5-(hydroxymethyl)-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (34). To a stirred solution of **33** (22 mg, 0.03 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added tetra-*n*-butylammonium fluoride (37.38 mg, 0.143 mmol, 5.0 equiv). The mixture was stirred for 2 h, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:9:89 NH_4OH/MeOH/CH_2Cl_2) to afford 11 mg (71%) of **34** as an oil: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 1.28 (3 H, s), 1.33 (3 H, s), 1.39 (3 H, s), 2.00–2.15 (3 H, m), 2.40 (1 H, m, D_2O exch), 3.23–3.39 (5 H, m), 3.56 (1 H, $^1/_2$ABq, J = 16.0 Hz), 3.90 (1 H, d, J = 9.1 Hz), 4.18 (1 H, d, J = 9.1 Hz), 4.65 (1 H, d, J = 10.2 Hz), 4.68 (1 H, $^1/_2$ABq, J = 16.0 Hz), 5.01 (1 H, $^1/_2$ABq, J = 15.0 Hz), 6.26 (1 H, d, J = 10.2 Hz, D_2O exch), 6.31 (1 H, s, D_2O exch), 7.40 (10 H, m); IR (NaCl, neat) 3600–3200, 1650, 1050 cm^{-1}.

8-Benzyl-8,10-diaza-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (36) and 8,10-Dibenzyl-8,10-diaza-1-[*tert*-butyldimethylsilyl]-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (35). To a stirred solution of **23** (109 mg, 0.233 mmol, 1.0 equiv) in THF (2 mL) at −78 °C was added a solution of LDA (0.267 mmol, 1.1 equiv) in THF (1 mL), and the dark brown enolate was stirred for 15 min. Solid *tert*-butyldimethylsilyl chloride (175.5 mg, 1.16 mmol, 5.0 equiv) was added, and the mixture was stirred at −78 °C. After 20 min, the mixture was warmed to room temperature, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:4 EtOAc/hexanes) to afford 32 mg (27%, 42% based on starting material) of **35** and 19 mg (22%, 41.26% based on recovered starting material) of **36** as an oil.

Compound 36: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 0.012 (3 H, s), 0.014 (3 H, s), 0.821 (9 H, s), 1.48–1.58 (1 H, m), 1.78–1.87 (1 H, m), 2.02–2.16 (1 H, m), 3.39 (1 H, dd, J_{vic} = 6.6, J_{gem} = 9.8 Hz), 3.62 (1 H, dd, J_{vic} = J_{gem} = 9.8 Hz), 3.81 (1 H, dd, J_{vic} = 8.9, J_{gem} = 13.6 Hz), 3.90 (1 H, dd, J_{vic} = 7.4, J_{gem} = 13.6 Hz), 4.06 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.23 (1 H, dd, J = 2.5, 4.3 Hz), 4.98 (1 H, s), 5.09 (1 H, $^1/_2$ABq, J = 14.7 Hz), 6.57 (1 H, br s), 7.19–7.29 (5 H, m); IR (NaCl, neat) 3400, 1670, 1050 cm^{-1}; mass spectrum, *m/e* 389 ($M^+ - CH_3$, 0.9), 347 (10.3), 317 (0.3), 241 (0.3), 179 (28.2), 135 (100), 91 (36.8).

Compound 35: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 0.11 (3 H, s), 0.025 (3 H, s), 0.054 (6 H, s), 0.57 (9 H, s), 0.924 (9 H, s), 1.74 (2 H, m), 1.95 (1 H, m), 3.43 (1 H, m), 3.53 (1 H, m), 3.63 (1 H, m), 3.73 (1 H, bs), 3.80 (1 H, m), 4.20 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.40 (1 H, $^1/_2$ABq, J = 15.1 Hz), 4.77 (1 H, $^1/_2$ABq, J = 15.1 Hz), 5.34 (1 H, $^1/_2$ABq, J = 14.4 Hz), 7.20–7.30 (10 H, m); IR (NaCl, neat) 1670, 1450, 1020 cm^{-1}; mass spectrum, *m/e* 609 (M^+, 609), 567 (19.0), 213 (1.6), 179 (3.4), 149 (25.5), 91 (83.1), 75 (100).

8-Benzyl-10-[(*tert*-butyldimethylsilyl)benzyl]-8,10-diaza-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (37). To a stirred solution of **23** (21 mg, 0.045 mmol, 1.0 equiv) in THF (2.5 mL) at −78 °C was added a solution of LDA (0.049 mmol, 1.1 equiv) in THF (1.5 mL). The dark yellow solution was stirred for 5 min at −78 °C and then solid trimethylsilyl chloride (6 mg, 0.049 mmol, 1.1 equiv) was added and the mixture was warmed to room temperature. The mixture was then cooled to −78 °C, a solution of LDA (0.049 mmol, 1.1 equiv) in THF (0.5 mL) was added followed by solid MoOPh (97 mg, 0.224 mmol, 5.0 equiv), the mixture was stirred 10 min at −78 °C, warmed to room temperature over 20 min, and then solid (n-Bu)$_4$NF (11.7 mg, 0.049 mmol, 1.0 equiv) was added. After 1 h at room temperature, the mixture was concentrated to dryness and separated by PTLC silica gel (eluted with 1:2 hexanes/EtOAc) to afford 12 mg (41.2%, 54.7% based on recovered starting material) of **37** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 0.007 (3 H, s), 0.12 (12 H, s), 0.86 (9 H, s), 1.42–1.60 (2 H, m), 1.77 (1 H, m), 3.21 (1 H, dd, J_{vic} = 9.8, J_{gem} = 9.8 Hz), 3.37 (1 H, s), 3.50 (1 H, dd, J_{vic} = 9.8, J_{gem} = 9.8 Hz), 3.83 (2 H, dd, J = 4.5 Hz), 4.06 (1 H, $^1/_2$ABq, J = 14.9 Hz), 4.42 (1 H, d, J = 1.8 Hz), 5.09 (1 H, s), 5.24 (1 H, $^1/_2$ABq, J = 14.9 Hz), 7.18–7.38 (10 H, m); IR (NaCl, neat) 1670, 1450 cm^{-1}; mass spectrum, *m/e* 566 (M^+, 22.4), 509 (22.1), 475 (11.8), 449 (18.3), 437 (18.3), 260 (10.1), 91 (100), 57 (35.3).

8-Benzyl-10-benzoyl-8,10-diaza-[1′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene]-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (38). To a stirred solution of **32** (62 mg, 0.085 mmol, 1.0 equiv) in THF (5 mL) at −100 °C was added *tert*-butyllithium (0.04 mL, 0.0941 mmol, 1.1 equiv), and the resulting yellow enolate was stirred for 10 min at −100 °C. A steady stream of O_2 was bubbled

through the mixture for 30 min at −100 °C and 30 min at room temperature. The mixture was then diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 1:5 EtOAc/hexanes) to afford 22 mg (35%, 68% based on starting material) of **38** as an oil. (NOTE: It is difficult by NMR to establish which of the two *N*-benzyl groups was oxidized. The structure chosen corresponds to the least hindered approach of the base.)

^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 0.092 (3 H, s), 0.067 (3 H, s), 0.056 (3 H, s), 0.116 (3 H, s), 0.079 (9 H, s), 0.932 (9 H, s), 1.26 (3 H, s), 1.350 (3 H, s), 1.33 (3 H, s), 1.50–2.00 (2 H, m), 2.56–2.70 (1 H, m), 2.99 (1 H, dd, J_{vic} = 9.1, J_{gem} = 9.8 Hz), 3.19 (1 H, dd, J_{vic} = 10.0, J_{gem} = 9.8 Hz), 3.45–3.70 (2 H, m), 3.82 (1 H, $^1/_2$ABq, J = 8.6 Hz), 4.08 (1 H, $^1/_2$ABq, J = 8.6 Hz), 4.36 (1 H, d, J = 1.9 Hz), 4.62 (1 H, $^1/_2$ABq, J = 15.2 Hz), 4.80 (1 H, s), 5.03 (1 H, $^1/_2$ABq, J = 15.2 Hz), 7.15–7.56 (10, m); IR (NaCl, neat) 1680, 1400, 1250, 1100 cm^{-1}.

8,10-Dibenzyl-8,10-diaza-5-[(methylsulfonyl)methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (39a). To a stirred solution of **15** and **16** (54 mg, 0.142 mmol, 1.0 equiv) in THF (2 mL) at 0 °C was added triethylamine (0.02 mL, 0.156 mmol, 1.1 equiv), and the mixture was stirred at 0 °C. After 10 min, mesyl chloride (0.018 mL, 0.156 mmol, 1.1 equiv) was added and the mixture was stirred an additional 10 min at 0 °C, diluted with ether, filtered, concentrated, and separated by PTLC silica gel (eluted with 4:1 EtOAc/hexanes) to afford 57 mg (87.5%) of mesylates as a mixture of oils. Pure **39a** was obtained by recovery from the subsequent selenide displacement on the mixture of mesylates: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.50–1.60 (1 H, m), 1.79–1.89 (1 H, m), 2.36–2.44 (1 H, m), 2.98 (3 H, s), 3.77 (1 H, dd, J_{vic} = 9.1, J_{gem} = 13.8 Hz), 3.95 (1 H, dd, J_{vic} = 7.3, J_{gem} = 13.8 Hz), 4.09 (1 H, dd, J_{vic} = 5.7, J_{gem} = 10.5 Hz), 4.13–4.16 (1 H, m), 4.19 (1 H, d, J = 2.3 Hz), 5.06 (2 H, twice, $^1/_2$ABq, J = 15.0 Hz), 5.10 (2 H, twice $^1/_2$ABq, J = 14.9 Hz), 5.21 (1 H, s), 7.20–7.38 (10 H, m); IR (NaCl, neat) 1672, 1450, 1150 cm^{-1}; mass spectrum, m/e 458 (M^+, 4.7), 363 (1.3), 353 (9.2), 261 (1.9), 218 (4.1), 167 (52.8), 121 (12.1), 91 (100).

8,10-Dibenzyl-8,10-diaza-5-[(phenylselenyl)methyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (40a). To a stirred solution of diphenyl diselenide (18 mg, 0.057 mmol, 1.05 equiv) in EtOH (1 mL) at room temperature was added solid sodium borohydride (43 mg, 0.115 mmol, 2.1 equiv), and the mixture was stirred until H_2 evolution had stopped. After 30 min, the selenide salt was transferred to a stirred solution of **39a** (25 mg, 0.055 mmol, 1.0 equiv) in EtOH (1 mL) at room temperature, and the mixture was warmed to 45 °C. After 20 min, it was cooled to room temperature, evaporated to dryness and separated by PTLC silica gel (1:1 EtOAc/hexanes) to afford 22 mg (78%) of **40a** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.60–1.78 (1 H, m), 1.90–2.01 (1 H, m), 2.00–2.17 (1 H, m), 2.80–2.94 (1 H, m), 3.00–3.11 (1 H, m), 3.66 (1 H, dd, J = 10.8, 14.4 Hz), 3.69 (1 H, dd, J = 7.2, 14.4 Hz), 4.32 (1 H, d, J = 2.5 Hz), 3.88 (1 H, $^1/_2$ABq, J = 16.7 Hz), 4.18 (1 H, $^1/_2$ABq, J = 16.7 Hz), 5.02 (1 H, $^1/_2$ABq, J = 16.7 Hz), 5.06 (1 H, $^1/_2$ABq, J = 16.7 Hz), 5.17 (1 H, s), 7.2–7.6 (15 H, m); IR (NaCl, neat) 1670, 1430, 1050 cm^{-1}; mass spectrum, m/e 520 (6.3), 429 (0.2), 363 (8.9), 292 (4.3), 91 (100); ^{13}C NMR (25 MHz) ($CDCl_3$) δ 30.46 (t), 32.92 (t), 43.89 (d), 47.28 (t), 47.58 (t), 61.57 (d), 64.10 (t), 83.36 (d), 127.04 (d), 127.80 (d), 127.97 (d), 128.20, 128.55 (d), 128.67 (d), 129.14 (d), 129.47 (d), 132.17 (s), 135.03 (s), 162.36 (s), 166.62 (s).

8,10-Dibenzyl-8,10-diaza-5-methylene-2-oxabicyclo[4.2.2]decane-7,9-dione (42a). To a stirred solution of **40a** (154 mg, 0.291 mmol, 1.0 equiv) in THF (3.5 mL) at room temperature was added 30% hydrogen peroxide (0.045 mL, 1.48 mmol, 5.0 equiv), and the temperature was brought to reflux. After 45 min, the mixture was cooled to room temperature, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 96 mg (90%) of **42a** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 2.18–2.28 (1 H, m), 2.35 (1 H, dd, J_{gem} = 16.4, J_{vic} = 6.9 Hz), 3.28 (1 H, dd, J_{gem} = 13.4, J_{vic} = 9.0 Hz), 3.77 (1 H, dd, J_{gem} = 13.4, J_{vic} = 6.9 Hz), 3.84 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.13 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.35 (1 H, s), 4.92 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.01 (1 H, s), 5.09 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.10 (1 H, s), 5.20 (1 H, s), 7.12–7.32 (10 H, m); ^{13}C NMR (25 MHz) ($CDCl_3$) δ 34.92 (t), 47.51 (t), 47.98 (t), 63.40 (t), 65.32 (d), 83.89 (d), 119.68 (t), 128.61 (d), 128.50 (d), 127.95 (d), 134.33 (s), 134.68 (s), 142.86 (s), 166.97 (s), 164.23 (s); IR (NaCl, neat) 1675, 1660, 1150 cm^{-1}; mass spectrum, m/e 362 (M^+, 11.5), 271 (2.3), 91 (100).

8,10-Dibenzyl-8,10-diaza-5-methylene-6-hydroxy-2-oxabicyco[4.2.2]-decane-7,9-dione (43a). To a stirred solution of **42a** (54 mg, 0.149 mmol, 1.0 equiv) in THF (2 mL) at −100 °C was added HMPA (0.54 mL, 0.298 mmol, 2.0 equiv) followed by *n*-butyllithium (0.09 mL, 0.179 mmol, 1.2 equiv), and the dark brown anion was stirred at −100 °C for 15 min. A steady flow of O_2 was bubbled through the mixture for 15 min at −100 °C, and then it was warmed to room temperature, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 20 mg (35.5%, 63.7% based on recovered starting material) of **43a** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 2.12 (1 H, dd, J_{vic} = 9.8, J_{gem} = 16.6 Hz), 2.31 (1 H, dd, J_{gem} = 16.6, J_{vic} = 7.2 Hz), 3.31 (1 H, dd, J_{gem} = 13.1, J_{vic} = 9.8 Hz), 3.84 (1 H, dd, J_{gem} = 13.1, J_{vic} = 7.2 Hz), 4.27 (1 H, $^1/_2$ABq, J = 14.1 Hz), 4.47 (1 H, $^1/_2$ABq, J = 14.1 Hz), 4.64 (1 H, $^1/_2$ABq, J = 14.1 Hz), 4.94 (1 H, s, D_2O exch), 4.99 (1 H, $^1/_2$ABq, J = 14.4 Hz), 5.09 (1 H, s), 5.24 (1 H, s), 5.60 (1 H, s), 7.20–7.50 (10 H, m); IR (NaCl, neat) 3600–3200, 1670, 1660, 1250 cm^{-1}; mass spectrum, m/e 378 (M^+, 1.0), 294 (2.2), 133 (12.1), 111 (24.1), 91 (72.6), 57 (100).

***N,N*-Dibenzyl-2′,3′-*O*-isopropylidenebicyclomycin (44a).** To a stirred solution of **43a** (24 mg, 0.063 mmol, 1.0 equiv) in THF (2 mL) at −100 °C was added *n*-BuLi (0.08 mL, 0.152 mmol, 2.4 equiv), and the dark enolate was stirred at −100 °C. After 10 min, (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (0.045 mL, 0.317 mmol, 1.5 equiv) was added, and the mixture was allowed to warm to room temperature, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 16 mg (48.2%, 67.7% based on recovered starting material) of **44a** as an oil: ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.34 (3 H, s), 1.35 (3 H, s), 1.54 (3 H, s), 1.98–2.12 (2 H, m), 2.79 (1 H, dd, J_{gem} = 13.7, J_{vic} = 1.8 Hz), 3.53 (1 H, dd, J_{gem} = 13.7, J_{vic} = 7.1 Hz), 3.77 (1 H, $^1/_2$ABq, J = 9.3 Hz), 4.10 (1 H, $^1/_2$ABq, J = 9.3 Hz), 4.32 (1 H, $^1/_2$ABq, J = 13.5 Hz), 4.58 (1 H, $^1/_2$ABq, J = 13.5 Hz), 4.62 (1 H, d, J = 9.9 Hz), 4.68 (1 H, $^1/_2$ABq, J = 15.3 Hz), 5.00 (1 H, s, D_2O exch), 5.13 (1 H, s), 5.17 (1 H, $^1/_2$ABq, J = 15.3 Hz), 5.56 (1 H, s), 6.50 (1 H, d, J = 9.9 Hz, D_2O exch), 7.20–7.58 (10 H, s); IR (NaCl, neat) 3600–3200, 1675, 1660, 1250 cm^{-1}.

***syn*-1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-(hydroxypropyl)]-2,5-piperazinedione (51).** To a stirred solution of major syn lactone **47**[13] (600 mg, 1.09 mmol, 1.0 equiv) in THF (60 mL) at 0 °C equipped with a constant N_2 flow was added all at once solid LiAlH (20.85 mg, 0.549 mmol, 2.0 equiv). Immediately following addition, the mixture was quenched with excess $Na_2SO_4 \cdot 10H_2O$, warmed to room temperature, and stirred for 1 h. The suspension was then filtered, concentrated, and separated on PTLC silica gel by using a chromatron (eluted with EtOAc) to afford 197 mg (33%, 40% by conversion) of **51** as an oil: ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 1.72 (1 H, m), 1.91 (1 H, m), 2.36 (1 H, m), 3.58–3.76 (6 H, m), 3.78 (3 H, s), 3.80 (3 H, s), 4.02 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.12 (1 H, $^1/_2$ABq, J = 15.4 Hz), 4.25 (1 H, d, J = 6.9 Hz), 5.18 (1 H, $^1/_2$ABq, J = 14.4 Hz), 5.28 (1 H, $^1/_2$ABq, J = 15.4 Hz), 6.70 (1 H, s), 6.83 (4 H, d, J = 8.7 Hz), 7.16 (4 H, d, J = 8.7 Hz), 7.26 (2 H, m), 7.60 (1 H, m), 8.52 (1 H, d, J = 3.4 Hz); IR (NaCl, neat) 3600–3100, 1660, 1510, 1240, 1025 cm^{-1}; mass spectrum, m/e 503 (M^+ − 48, 0.5), 429 (0.7), 198 (11.9), 121 (100), 111 (25.8).

***anti*-1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-(hydroxypropyl)]-2,5-piperazinedione (52).** To a stirred solution of **48** (850 mg, 1.58 mmol, 1.0 equiv) in THF (180 mL) at 0 °C was added solid $LiAlH_4$ (30.14 mg, 0.79 mmol, 2.0 equiv). The mixture was stirred for 30 min at 0 °C, quenched with $Na_2SO_4 \cdot 10H_2O$, warmed to room temperature, filtered, concentrated, and separated by silica gel flash column to afford 128 mg (15%, 21% based on recovered starting material) of **52** as an oil. NOTE: An alternative procedure was utilized in which the $LiAlH_4$ was added in 0.25-equiv portions over a period of an hour at 0 °C, resulting in substantial increase in the yield (51%): ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 1.80–1.90 (1 H, m), 1.90–1.92 (1 H, m, D_2O exch), 1.90–1.93 (1 H, m), 2.36–2.40 (1 H, m), 3.79 (3 H, s), 3.80 (3 H, s), 3.80–3.95 (4 H, m), 4.02 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.13 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.24 (1 H, d, J = 5.8 Hz), 4.25 (1 H, m, D_2O exch), 5.17 (1 H, $^1/_2$ABq, J = 14.3 Hz), 5.22 (1 H, $^1/_2$ABq, J = 14.8 Hz), 6.79 (1 H, s), 6.79 (2 H, d, J = 8.9 Hz), 6.82 (2 H, d, J = 8.9 Hz), 7.05–7.15 (2 H, m), 7.13 (2 H, d, J = 8.9 Hz), 7.17 (2 H, d, J = 8.9 Hz), 7.56 (1 H, m), 8.52 (1 H, m); IR (NaCl, neat) 3600–3100, 1660 cm^{-1}; mass spectrum, m/e 440 (M^+ − 111, 0.6), 198 (5.7), 111 (13.1), 84 (100).

***syn*-1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-(hydroxypropyl)]-2,5-piperazinedione (53).** To a stirred solution of **49** (1.102 g, 2.014 mmol, 1.0 equiv) in THF (100 mL) at 0 °C was added solid $LiAlH_4$ (38.2 mg, 1.0 mmol, 0.5 equiv) and the solution was stirred for 15 min at 0 °C, quenched with excess $Na_2SO_4 \cdot 10H_2O$, warmed to room temperature, filtered, concentrated, and separated by silica gel flash column (eluted with 100% EtOAc) to afford 185 mg (17%,

19% based on recovered starting material) of **53** as an oil: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.18–2.28 (2 H, m), 2.95–3.01 (1 H, m), 3.20–3.40 (1 H, m), 3.50–3.90 (5 H, m), 3.77 (3 H, s), 3.79 (3 H, s), 3.92 (1 H, $^1/_2$ABq, J = 14.8 Hz), 4.00 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.10 (1 H, d, J = 6.9 Hz), 5.11 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.34 (1 H, $^1/_2$ABq, J = 14.8 Hz), 6.65 (1 H, s), 6.79 (2 H, d, J = 8.7 Hz), 6.80 (2 H, d, J = 8.7 Hz), 7.11 (2H, d, J = 8.7 Hz), 7.10 (2 H, d, J = 8.7 Hz), 7.20–7.32 (2 H, m), 7.55 (1 H, m), 8.46 (1 H, d, J = 4.2 Hz); IR (NaCl, neat) 3600–3100, 1670, 1420, 1050 cm^{-1}; mass spectrum, m/e 441 (M^+ − 110, 0.8), 426 (2.1), 354 (0.9), 121 (100), 110 (43.2).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (54) and 7,9-Bis(*p*-methoxybenzyl)-7,9-diaza-4-(2′-(hydroxyethyl))-2-oxabicyclo[3.2.2]nonane-6,8-dione (55) from 51. To a stirred solution of major syn-diol **51** (316 mg, 0.573 mmol, 1.0 equiv) in THF (5 mL) at 25 °C was added AgOTf (294.7 mg, 1.147 mmol, 2.0 equiv) in one portion. The milky-white solution was stirred for 15 min, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, concentrated, and separated on PTLC silica gel (eluted with EtOAc) to afford 198 mg (78% yield) of a 3:2 mixture of eight-(**54**) and seven-membered (**55**) ring alcohols.

Compound 54: ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 1.80 (1 H, m), 2.08 (1 H, m), 3.70–3.90 (6 H, m), 3.79 (6 H, s), 4.16 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.21 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.28 (1 H, d, J = 3.2 Hz), 4.88 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.93 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.20 (1 H, s), 6.83 (4 H, d, J = 8.5 Hz), 7.18 (2 H, d, J = 8.5 Hz), 7.20 (2 H, d, J = 8.5 Hz); IR (NaCl, neat) 3600–3200, 1668, 1510, 1230 cm^{-1}; mass spectrum, m/e 440 (M^+, 1.9), 389 (2.0), 352 (1.6), 319 (1.7), 198 (1.4), 121 (100).

Compounbd 55: ^{1}H NMR (270 MHz) ($CDCl_3$ δ $CHCl_3$ 1.40–1.75 (2 H, m), 1.80–1.90 (1 H, m), 2.50 (1 H, m), 3.27 (1 H, dd, J_{vic} = 8.5, J_{gem} = 13.2 Hz), 3.53 (2 H, t, J = 6.6 Hz), 3.77 (1 H, dd, J_{vic} = 4.64, J_{gem} = 13.16 Hz), 3.78 (6 H, s), 3.94 (1 H, d, J = 3.0 Hz), 4.43 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.45 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.59 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.63 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.09 (1 H, s), 6.85 (2 H, d, J = 5.5 Hz), 6.86 (2 H, d, J = 8.5 Hz), 7.18 (2 H, d, J = 8.5 Hz), 7.21 (2 H, d, J = 8.5 Hz); IR (NaCl, neat) 3600–3200, 1668, 1510, 1230 cm^{-1}; mass spectrum, m/e 440 (M^+, 2.1), 389 (0.7), 121 (100).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-(hydroxymethyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (54) and 7,9-Bis(*p*-methoxybenzyl)-7,9-diaza-4-(2′-(hydroxyethyl))-2-oxabicyclo[3.2.2]nonane-6,8-dione (55) from 52. To a stirred solution of major anti-diol **52** (128 mg, 0.232 mmol, 1.0 equiv) in THF (2 mL) was added AgOTf (119 mg, 0.464 mmol, 2.0 equiv) at 25 °C. The milky-white solution was stirred for 15 min, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, concentrated, and separated on PTLC silica gel (eluted with EtOAc) to afford a mixture of the bicyclic alcohols (82 mg, 80% yield, 10:1 ratio of the eight-membered/seven-membered ring alcohols **54** and **55**, respectively) (calculated by NMR integration of bridgehead methine's adjacent to the bridging oxygen atom).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (27b). To a stirred solution of **25b** (20 mg, 0.03 mmol, 1.0 equiv) in THF (1.2 mL) at room temperature was added solid silver triflate (15 mg, 0.06 mmol, 2.0 equiv), and the mixture was stirred at room temperature. After 22 min, the mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2; the combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 11 mg (66%) of **27b** as an oil: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 0.09 (3 H, s), 0.10 (3 H, s), 0.92 (9 H, s), 1.60–1.80 (2 H, m), 2.20–2.40 (1 H, m), 3.38–3.48 (2 H, m), 3.56 (1 H, dd, J_{vic} = 6.4, J_{gem} = 10.7 Hz), 3.80 (6 H, s), 3.80–3.90 (1 H, m), 3.86 (1 H, $^1/_2$ABq, J = 14.2 Hz), 4.03 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.44 (1 H, d, J = 1.0 Hz), 4.96 (1 H, $^1/_2$ABq, J = 14.2 Hz), 5.17 (1 H, s), 5.23 (1 H, $^1/_2$ABq, J = 14.6 Hz), 6.82 (2 H, d, J = 8.8 Hz), 6.83 (2 H, d, J = 8.8 Hz), 7.11 (2 H, d, J = 8.8 Hz), 7.14 (2 H, d, J = 8.8 Hz); IR (NaCl, neat) 1680, 1515, 1247, 1030 cm^{-1}; mass spectrum, m/e 503 (M^+ − 48, 0.5), 429 (0.7), 198 (11.9), 121 (100), 111 (25.8).

1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-[1″-(hydroxymethyl)-3″-[((*tert*-butyldimethylsilyl)oxy)propyl]]-2,5-piperazinedione (24b) and 1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-[1″-[((*tert*-butyldimethylsilyl)oxy)methyl]-3″-(hydroxypropyl)]-2,5-piperazinedione (25b). To a stirred solution of **53** (298 mg, 0.541 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added Et_3N (0.750 mL, 0.541 mmol, 1.0 equiv) followed by *tert*-butyldimethylsilyl chloride (89.23 mg, 0.594 mmol, 1.15 equiv), and the mixture was stirred at room temperature. After 14 h, the mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by flash column silica gel (eluted with 1:1 EtOAc/hexanes) to afford 96 mg (27.0%, 35% based on recovered starting material) of **24b** and 45 mg (12.6%, 16.2% based on recovered starting material) of **25b** as oils.

Compound 24b: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 0.11 (3 H, s), 0.12 (3 H, s), 0.92 (9 H, s), 1.3 (1 H, m), 1.98 (2 H, m), 2.40 (1 H, m), 3.70–4.00 (4 H, m), 3.80 (3 H, s), 3.80 (3 H, s), 3.94 (1 H, $^1/_2$ABq, J = 14.7 Hz), 3.96 (1 H, $^1/_)$ABq, J = 14.3 Hz), 4.14 (1 H, d, J = 6.6 Hz), 5.12 (1 H, $^1/_2$ABq, J = 14.3 Hz), 5.31 (1 H, $^1/_2$ABq, J = 14.7 Hz), 6.62 (1 H, s), 6.79 (2 H, d, J = 8.5 Hz), 6.82 (2 H, d, J = 8.5 Hz), 7.12 (2 H, d, J = 8.5 Hz), 7.12–7.16 (2 H, m), 7.14 (2 H, $^1/_2$ABq, J = 8.5 Hz), 7.60 (1 H, dd, J = 10.8, 8.2 Hz), 8.48 (1 H, d, J = 8.5 Hz); IR (NaCl, neat) 3600–3200, 1671, 1248, 1030 cm^{-1}.

Compound 25b: ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 0.06 (6 H, s), 0.89 (9 H, s), 1.87 (1 H, m), 1.89 (1 H, m), 2.28–2.35 (1 H, m), 2.86–2.98 (1 H, m), 3.74 (3 H, s), 3.75 (3 H, s), 3.75–3.85 (4 H, m), 3.81 (1 H, $^1/_2$ABq, J = 14.7 Hz), 3.94 (1 H, $^1/_2$ABq, J = 14.5 Hz), 3.97 (1 H, d, J = 7.2 Hz), 5.09 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.33 (1 H, $^1/_2$ABq, J = 14.7 Hz), 6.61 (1 H, s), 6.75 (2 H, d, J = 8.6 Hz), 6.76 (2 H, d, J = 8.6 Hz), 7.05 (2 H, d, J = 8.6 Hz), 7.10 (2 H, d, J = 8.6 Hz), 7.10–7.20 (2 H, m), 7.51 (1 H, br t, J = 1.71, 8.1 Hz), 8.40 (1 H, br d, J = 4.7 Hz); IR (NaCl, neat) 3700–3200, 1665, 1240, 1030 cm^{-1}.

1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-[1″-[(methylsulfonyl)methyl]-3″-[((*tert*-butyldimethylsilyl)oxy)propyl]]-2,5-piperazinedione (26b). To a stirred solution of **24b** (154 mg, 0.231 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added Et_3N (0.035 mL, 0.254 mmol, 1.1 equiv) followed by mesyl chloride (0.019 mL, 0.254 mmol, 1.1 equiv). The mixture was stirred at room temperature for 35 min, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 117 mg (68%, 75% based on recovered starting material) of **26b** as an oil: ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 0.056 (3 H, s), 0.06 (3 H, s), 1.78–1.91 (1 H, m), 1.93–2.04 (1 H, m), 2.63–2.78 (1 H, m), 2.97 (3 H, s), 3.73 (3 H, s), 3.73 (3 H, s), 3.73–3.93 (4 H, m), 4.02–4.12 (2 H, m), 4.39 (1 H, d, J = 2.9 Hz), 5.05 (1 H, $^1/_2$ABq, J = 14.4 Hz), 5.32 (1 H, $^1/_2$ABq, J = 14.7 Hz), 6.74 (1 H, s), 6.74 (2 H, d, J = 8.6 Hz), 6.77 (2 H, d, J = 8.6 Hz), 7.05 (2 H, d, J = 8.6 Hz), 7.08 (2 H, d, J = 8.6 Hz), 7.08–7.20 (2 H, m), 7.50 (1 H, dd, J = 1.5, 7.7 Hz), 8.56 (1 H, br d, J = 4.0 Hz); IR (NaCl, neat) 1680, 1510, 1250, 1170 cm^{-1}.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-[(methylsulfonyl)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (28b). To a stirred solution of **26b** (16 mg, 0.23 mmol, 1.0 equiv) in THF (1 mL) at room temperature was added solid $Cu(ClO_4)_2$ (6.0 mg, 0.023 mmol, 1.0 equiv), and the mixture was stirred at room temperature. After 16 h, the mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 100% EtOAc) to afford 9.8 mg (83%) of **28b** as an oil: ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 1.78–1.94 (2 H, m), 1.48–1.62 (1 H, m), 3.07 (3 H, m), 3.31 (1 H, dd, J_{vic} = 6.9, J_{gem} = 12.4 Hz), 3.80–4.01 (3 H, m), 3.81 (3 H, s), 3.82 (4 H, s), 4.12 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.19 (1 H, br s), 4.97 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.16 (1 H, $^1/_2$ABq, J = 14.3 Hz), 5.23 (1 H, s), 6.86 (4 H, d, J = 8.6 Hz), 7.16 (2 H, d, J = 8.6 Hz), 7.20 (2 H, $^1/_2$ABq, J = 8.6 Hz); IR (NaCl, neat) 1670, 1608, 1512, 1240 cm^{-1}; mass spectrum, m/e 518 (M^+, 7.8), 422 (5.9), 397 (9.4), 301 (7.9), 136 (20.5), 121 (100).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-[(methylsulfonyl)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (39b). To a stirred solution of the alcohols **54** and **55** (obtained above as a 2:1 mixture) (198 mg, 0.45 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added Et_3N (0.157 mL, 1.125 mmol, 2.5 equiv) followed by mesyl chloride (0.087 mL, 1.125 mmol, 2.5 equiv). The solution was stirred for 12 h, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and separated on PTLC silica gel (eluted with 2:1 EtOAc/hexanes) to afford 208 mg (85% yield) of the mixture of mesylates **39b** and the bicyclo[3.2.2] isomer in the same ratio of ring sizes as the starting material mixture: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.50–1.70 (1 H, m), 1.78–1.96 (1 H, m), 2.32–2.46 (1 H, m), 3.03 (3 H, s), 3.80–4.30 (4 H, m), 3.80 (3 H, s), 3.81 (3 H, s), 4.08 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.13 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.22 (1 H, m), 4.96 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.97 (1 H, $^1/_2$ABq, J = 14.4 Hz), 5.20 (1 H, s), 6.84 (2 H, d, J = 8.6 Hz), 6.80 (2 H, J = 8.6 Hz), 7.17 (2 H, d, J = 8.6 Hz), 7.23 (2 H, d, J = 8.6 Hz); IR (NaCl, neat) 1675, 1510, 1460, 1240 cm^{-1}; mass spectrum, m/e 518 (M^+, 3.5), 422 (1.9), 397 (3.1), 352 (0.7), 301 (2.7), 232 (0.1), 121 (100).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-methylene-2-oxabicyclo-[4.2.2]decane-7,9-dione (42b) from 40b. To a stirred solution of the selenide **40b** (210 mg, 0.405 mmol, 1.0 equiv) in THF (4.2 mL) was added 30% hydrogen peroxide (0.124 mL, 0.405 mmol, 10 equiv). The solution was refluxed for 20 min, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, concentrated, and separated by PTLC silica gel (eluted with 50% EtOAc/hexanes) to afford 162 mg (95.5%) of the olefin **42b**: mp 112–113 °C (recryst. Et_2O/hexanes); ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 2.27 (1 H, dd, J_{gem} = 16.3, J_{vic} = 6.82 Hz), 2.40 (1 H, dd, J_{gem} = 16.3, J_{vic} = 9.0 Hz), 3.30 (1 H, dd, J_{gem} = 13.2, J_{vic} = 8.9 Hz), 3.78–3.82 (1 H, m), 3.79 (6 H, s), 3.87 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.39 (1 H, s), 4.16 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.88 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.97 (1 H, $^1/_2$ABq, J = 14.4 Hz, 5.07 (1 H, s), 5.16 (1 H, s), 5.24 (1 H, s), 6.85 (4 H, d, J = 8.1 Hz), 7.15 (2 H, d, J = 8.1 Hz), 7.22 (2 H, d, J = 8.1 Hz); IR (NaCl, neat) 1682, 1615, 1518, 1250, 1031 cm^{-1}; mass spectrum, m/e 422 (M^+, 3.6), 301 (2.7), 149 (4.1), 121 (100). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23%; H, 6.20%; N, 6.63. Found: C, 68.26; H, 6.30; N, 6.65.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-[(phenylselenyl)methyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (41b). To a stirred solution of **28b** (80 mg, 0.154 mmol, 1.0 equiv) in THF (2.5 mL) at room temperature was added a solution of $PhSeNaBH_3$ (0.169 mmol, 1.1 equiv) in EtOH (1.5 mL), and the mixture was heated to reflux. After 20 min, the mixture was cooled, poured into H_2O, and exhaustively extracted wtih CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:3 EtOAc/hexanes) to afford 82 mg (99%) of **41b** as an oil: ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 2.48–2.69 (1 H, m), 2.85–3.04 (1 H, m), 3.18–3.35 (1 H, m), 2.00 (1 H, d, J_{vic} = 8.6, J_{gem} = 12.6 Hz), 2.79 (1 H, dd, J_{vic} = 7.2, J_{gem} = 12.6 Hz), 3.24 (1 H, dd, J_{vic} = 9.4, J_{gem} = 13.7 Hz), 3.78 (6 H, s), 3.84 (1 H, dd, J_{vic} = 7.3, J_{gem} = 13.7 Hz), 4.01 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.03 (1 H, $^1/_2$ABq, J = 14.7 Hz), 4.54 (1 H, s), 4.94 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.05 (1 H, $^1/_2$ABq, J = 14.7 Hz), 5.17 (1 H, s), 6.83 (2 H, d, J = 8.1 Hz), 6.84 (2 H, d, J = 8.1 Hz), 7.12 (2 H, d, J = 8.1 Hz), 7.15 (2 H, d, J = 8.1 Hz), 7.27–7.29 (3 H, m), 7.50–7.53 (2 H, m); IR (NaCl, neat) 1725, 1670, 1608, 1512, 1240 cm^{-1}; mass spectrum, m/e 518 (M^+, 1.8), 422 (4.8), 397 (1.4), 382 (2.1), 301 (3.7), 121 (100).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-methylene-2-oxabicyclo-[4.2.2]decane-7,9-dione (42b) from 41b. To a stirred solution of **41b** (80 mg, 0.154 mmol, 1.0 equiv) in THF (2 mL) at room temperature was added 30% H_2O_2 (0.047 mL, 1.54 mmol, 10.0 equiv), and the mixture was heated to reflux. After 15 min, the mixture was cooled, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by silica gel flash column (eluted with 1:1 EtOAc/hexanes) to afford 54 mg (83%) of **42b** as a crystalline solid identical with that obtained from **40b**.

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-5-methylene-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (43b). To a stirred solution of **42b** (80 mg, 0.213 mmol, 1.0 equiv) in THF (2 mL) at −78 °C in THF (1 mL) was added HMPA (0.07 mL, 0.42 mmol, 2.0 equiv) hexamethylphosphorous triamide (0.077 mL, 0.42 mmol, 2.0 equiv) followed by *n*-BuLi (0.33 mL, 0.32 mmol, 1.5 equiv). The dark brown anion was stirred for 7 min, and O_2 was bubbled through the solution for 10 min at −78 °C, warmed to 0 °C over 3 min, and quenched with H_2O (50 mL). The mixture was diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and separated on PTLC silica gel (eluted with 50% EtOAc/hexanes) to afford 41 mg (49% yield, 52% by conversion) of the alcohol **43b**, mp 199–199.5 °C (recryst THF/ether): ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 2.27 (1 H, dd, J_{vic} = 9.2, J_{gem} = 16.6 Hz), 2.41 (1 H, dd, J_{vic} = 7.0, J_{gem} = 16.6 Hz), 3.31 (1 H, dd, J_{vic} = 9.2, J_{gem} = 13.6 Hz), 3.80 (3 H, s), 3.80–3.85 (1 H, m), 3.81 (3 H, s), 3.88 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.16 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.39 (1 H, s, D_2O exch), 4.89 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.97 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.07 (1 H, br s), 5.16 (1 H, br s), 5.23 (1 H, s), 6.85 (2 H, d, J = 8.5 Hz), 6.86 (2 H, d, J = 8.5 Hz), 7.15 (2 H, d, J = 8.5 Hz), 7.22 (2 H, d, J = 8.5 Hz); IR (NaCl, neat) 3500–3100, 1673, 1610, 1513, 1246, 1083 cm^{-1}; mass spectrum, m/e 438 (M^+, 0.9), 421 (0.5), 317 (1.2), 301 (0.6), 177 (5.0), 149 (2.0), 121 (100); exact mass calcd for $C_{24}H_{26}N_2O_6$ 438.179 18, found 438.1793.

***N,N'*-Bis(*p*-methoxybenzyl)-2',3'-*O*-isopropylidenebicyclomycin (44b).** To a THF (2 mL) solution of **43b** (13 mg, 0.029 mmol, 1.0 equiv) at −98 °C was added *n*-butyllithium (0.31 mL, 0.68 mmol, 2.3 equiv). The slightly yellow anion was stirred for 3 min and quenched with (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (0.021 mL, 0.148 mmol, 5.0 equiv). The mixture was stirred for 10 min at −98 °C, warmed to −80 °C, quenched with 50% H_2O/MeOH (0.2 mL), evaporated to dryness and separated on PTLC silica gel (eluted with 50% EtOAc/hexanes) to afford 6 mg of the desired diol **44b** (42% yield, 95% by conversion) plus 9 mg of the starting material **43a**: ^1H NMR (360 MHz) ($CDCl_3$) δ TMS 0.841 (3 H, s), 1.36 (3 H, s), 1.37 (3 H, s), 2.00–2.10 (1 H, m), 2.80–2.89 (1 H, m), 3.55–3.62 (1 H, m), 3.78–3.85 (1 H, m), 3.78 (6 H, s), 3.82 (1 H, $^1/_2$ABq, J = 9.3 Hz), 4.11 (1 H, $^1/_2$ABq, J = 9.3 Hz), 4.31 (1 H, $^1/_2$ABq, J = 13.5 Hz), 4.53 (1 H, $^1/_2$ABq, J = 13.5 Hz), 4.61 (1 H, d, J = 9.9 Hz), 4.64 (1 H, $^1/_2$ABq, J = 15.3 Hz), 4.99 (1 H, s), 5.08 (1 H, $^1/_2$ABq, J = 15.3 Hz), 5.15 (1 H, s), 5.56 (1 H, s), 6.59 (1 H, d, J = 9.9 Hz, D_2O exch), 6.79 (4 H, d, J = 8.5 Hz), 7.39 (2 H, d, J = 8.5 Hz), 7.44 (2 H, d, J = 8.5 Hz); IR (NaCl, neat) 3600–3150, 1670, 1660, 1515, 1245 cm^{-1}; mass spectrum, m/e 582 (M^+, 0.8), 468 (0.4), 451 (0.4), 241 (1.0), 149 (3.3), 121 (100); exact mass calcd for $C_{31}H_{38}N_2O_9$ 582.257 84; found 582.257 100.

***N,N'*-Bis(*p*-methoxybenzyl)-1'-*O*-(trifluoroacetyl)-2',3'-*O*-isopropylidenebicyclomycin (59).** To a stirred solution of **44b** (9 mg, 0.154 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at room temperature was added solid (dimethylamino)pyridine (20 mg, 0.169 mmol, 11.0 equiv) followed by trifluoroacetic anhydride (0.02 mL, 0.15 mmol, 10.0 equiv), and the mixture was stirred at room temperature. After 25 min, the mixture was evaporated to dryness and separated by PTLC silica gel (eluted with 1:1 EtOAc/hexanes) to afford 10 mg (95%) of **59** as an oil: ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 0.41 (3 H, s), 1.12 (3 H, s), 1.15 (3 H, s), 2.30 (1 H, dd, J_{vic} = 8.9, J_{gem} = 16.6 Hz), 2.40 (1 H, dd, J_{vic} = 7.3 Hz, J_{gem} = 16.6 Hz), 3.05 (1 H, d, J = 9.6 Hz), 3.24 (1 H, dd, J_{vic} = 8.9, J_{gem} = 13.6 Hz), 3.76 (3 H, s), 3.78 (3 H, s), 3.86 (1 H, dd, J_{vic} = 7.3, J_{gem} = 13.6 Hz), 4.22 (1 H, d, J = 9.6 Hz), 4.22 (1 H, $^1/_2$ABq, J = 13.8 Hz), 4.55 (1 H, $^1/_2$ABq, J = 13.6 Hz), 4.55 (1 H, $^1/_2$ABq, J = 13.8 Hz), 4.94 (1 H, s), 4.95 (1 H, $^1/_2$ABq, J = 13.6 Hz), 5.19 (1 H, s), 5.67 (1 H, br s), 6.09 (1 H, s, D_2O exch), 6.78 (2 H, d, J = 7.6 Hz), 6.83 (2 H, d, J = 7.9 Hz), 7.86 (2 H, d, J = 7.6 Hz), 8.184 (2 H, d, J = 7.9 Hz); IR (NaCl, neat) 3600–3200, 1790, 1680, 1665, 1660, 1510, 1250 cm^{-1}; exact mass calcd for $C_{33}H_{37}F_3N_2O_{10}$ 678.240 11, found 678.242 90.

(±)-Bicyclomycin (1). To a stirred solution of **59** (18 mg, 0.026 mmol, 1.0 equiv) in acetonitrile/H_2O (0.2 M) was added solid ceric ammonium nitrate (58.2 mg, 0.106 mmol, 4.0 equiv) and the mixture was stirred at room temperature. After 40 min, the mixture was diluted with MeOH and separated by PTLC silica gel (eluted with 1:1 MeOH/THF) to afford 2.6 mg (31%, 35% based on recovered starting material) of racemic bicyclomycin, that was identical with a natural sample by NMR, IR, TLC, and bioassay.[34]

(+)-*N,N'*-Bis(*p*-methoxybenzyl)-2',3'-*O*-isopropylidenebicyclomycin (44b). To a stirred solution of **43b** (40 mg, 0.091 mmol, 1.0 equiv) in THF (1 mL) at −100 °C was added *n*-BuLi (0.095 mL, 0.228 mmol, 2.5 equiv); the yellow enolate was stirred for 10 min, and then optically active aldehyde **18** (0.008 mL, 0.059 mmol, 0.65 equiv) was added and the mixture was stirred at −109 °C. After 20 min, the mixture was warmed to −50 °C, methanol (10 equiv) was added, and the mixture was warmed to room temperature, diluted with CH_2Cl_2, poured into H_2O, and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by PTLC silica gel (eluted with 1:2 EtOAc/hexanes) to afford 5 mg [9%, 49% based on recovered starting material, $[\alpha]^{25}_D$ −4.60 (c 2.5, CH_2Cl_2)] of **44b** as an oil, $[\alpha]^{25}_D$ +74.80 (c 5, CH_2Cl_2). **44b** was identical with racemic diol by NMR, IR, and TLC.

(+)-*N,N'*-Bis(*p*-methoxybenzyl)-1'-*O*-(trifluoroacetyl)-2',3'-*O*-isopropylidenebicyclomycin (59). To a stirred solution of (+)-**44b** (6 mg, 0.01 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at room temperature was added DMAP (14.4 mg, 0.11 mmol, 11.0 equiv) followed by trifluoroacetic anhydride (0.014 mL, 0.1 mmol, 10.0 equiv), and the mixture was stirred at room temperature. After 20 min, the mixture was evaporated to dryness and separated by PTLC silica gel (eluted with 1:2 EtOAc/hexanes) to afford 7 mg (99%) of **32b** as an oil, $[\alpha]^{24}_D$ +41.18 (c 6, CH_2Cl_2). Compound (+)-**59** was found to be identical by NMR and TLC with the racemic material.

(+)-Bicyclomycin (Synthetic). To a stirred solution of (+)-**59** (7 mg, 0.01 mmol, 1.0 equiv) in CH_3CN (0.3 mL) and H_2O (0.1 mL) at room temperature was added CAN (33.9 mg, 0.06 mmol, 6.0 equiv), the mixture was stirred 42 min, diluted with MeOH, and separated by PTLC silica gel (eluted with 1:5 MeOH/$CHCl_3$) to afford 1 mg (32.07%) of **1** as a white powder, $[\alpha]^{24}_D$ +49.0° (c 0.1, CH_3OH), ee 78%. The synthetic material was identical by NMR and TLC with an authentic sample of naturally occurring bicyclomycin.

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Registry No. (±)-**1**, 89362-24-3; (+)-**1**, 38129-37-2; **10**, 92098-00-5; **11**, 92098-01-6; **12**, 92216-23-4; **13**, 92098-02-7; **14**, 95782-30-2; **15**, 92216-24-5; **16**, 95694-56-7; **17**, 95782-31-3; **18a**, 95694-57-8; **19a**, 95694-58-9; **20a**, 95694-59-0; **21a**, 95694-60-3; **22a**, 95694-61-4; **23a**, 92098-06-1; **24a**, 95782-32-4; **24b**, 95694-62-5; **25a**, 95782-33-5; **25a** ($R_1 = R_2 = SiMe_2Bu$-*t*), 95694-74-9; **25b**, 95694-63-6; **26a**, 95782-34-6; **26b**, 95782-35-7; **27a**, 95782-36-8; **27b**, 95694-64-7; **28a**, 95782-37-9; **28b**, 95782-38-0; **29a**, 95782-39-1; **30**, 92098-07-2; **31**, 92125-39-8; **32**, 95739-42-7; **33**, 92125-40-1; **34**, 92125-41-2; **35**, 95694-65-8; **36**, 95694-66-9; **37**, 95694-67-0; **38**, 95739-44-9; **39a**, 95782-40-4; **39a** ([3.2.2] isomer), 95694-68-1; **39b**, 95782-41-5; **39b** ([3.2.2] isomer), 95694-69-2; **40a**, 92098-05-0; **40b**, 92098-14-1; **41a**, 95782-42-6; **41b**, 95782-43-7; **42a**, 92216-25-6; **42b**, 92098-15-2; **43a**, 92098-08-3; **43b**, 92098-16-3; **44a**, 92098-09-4; **44b**, 92098-17-4; (+)-**44b**, 95694-70-5; **45**, 63777-16-2; **46**, 92125-61-6; **47**, 92098-11-8; **48**, 92216-27-8; **49**, 92216-26-7; **50**, 92216-28-9; **51**, 92098-03-8; **52**, 92216-29-0; **53**, 95782-44-8; **54**, 92098-12-9; **55**, 95739-48-3; **57**, 95694-71-6; **58**, 95694-72-7; **59**, 92125-62-7; (+)-**59**, 95694-73-8; (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde, 81600-36-4; (−)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde, 79243-92-8; γ-butyrolactone trimethylsilyl enol ether, 51425-66-2.

Synthesis of Skeletally Labeled 3-Methylhexaborane(12) and 2-Methylpentaborane(9): ^{10}B and ^{11}B NMR Spectral Studies of Base-Catalyzed Intramolecular Rearrangements in 2-Methylpentaborane(9)

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Abstract: Selectively ^{10}B labeled 3-MeB_6H_{11} has been synthesized from 1-MeB_5H_8 and 96% ^{10}B labeled B_2H_6 by modification of a previously published procedure. Positions B(1), B(2), and B(6) of the labeled 3-MeB_6H_{11} each contain 46 ± 5% ^{10}B while B(3), B(4), and B(5) are isotopically normal (19% ^{10}B). Reaction of this compound with dimethyl ether produces 2-MeB_5H_8 which is ^{10}B enriched at B(4) (47 ± 5% ^{10}B) and, to a lesser extent, at B(3,5) (30 ± 5% ^{10}B). In the presence of 2,6-lutidine the ^{10}B label in the 2-MeB_5H_8 equilibrates into all boron positions except the methyl-substituted B(2). These are the first direct observations of the movement of cluster boron atoms in the isomerization of pentaborane(9) derivatives. Several proposed isomerization mechanisms are examined in light of these results.

Interest in the chemistry of cluster compounds is rapidly expanding.[1] Internal cluster rearrangement and exchange processes are an important area of cluster chemistry, though there are few examples of experimentally verified mechanisms of such rearrangements. A number of different types of intramolecular cluster rearrangements and exchange processes have been observed. For example, a cluster may undergo internal site exchange of terminal or bridging groups (or atoms) attached to the periphery of the cluster while the cluster framework atoms remain intact and static. Such exchange has been studied extensively in metal carbonyl clusters[2,3] and in metallaborane clusters.[4] A cluster may also undergo internal atom rearrangements that change the cluster shape or produce a different geometric isomer but that do not involve movement of terminal substituents to different cluster atoms. A classic example of this type of rearrangement is the isomerization of the icosahedral carboranes (eq 1).[5,6] Intramolecular cluster rearrangements may also involve a combination of terminal substituent movement and cluster atom movement.

$$1,2\text{-}C_2B_{10}H_{12} \xrightarrow{450\ ^\circ C} 1,7\text{-}C_2B_{10}H_{12} \xrightarrow{620\ ^\circ C} 1,12\text{-}C_2B_{10}H_{12} \quad (1)$$

Extending our interest in intramolecular exchange processes in boranes and metallaborane clusters, we address in this paper several aspects of the isomerization mechanism of the square-pyramidal pentaborane(9), B_5H_9, framework. Pentaborane(9) derivatives have long been known to undergo isomerization reactions in the presence of Lewis bases. The most complete example, though not the first, is trimethylsilylpentaborane(9)[7] (eq 2). The μ-$(Me_3Si)B_5H_8$ contains the Me_3Si group in a bridging position, analogous to a bridging hydrogen atom, between two adjacent boron atoms in the base of the pentaborane pyramid.

$$\mu\text{-}(Me_3Si)B_5H_8 \xrightarrow{Et_2O} 2\text{-}(Me_3Si)B_5H_8 \underset{}{\overset{HMTA}{\rightleftharpoons}} 1\text{-}(Me_3Si)B_5H_8 \quad (2)$$

The silicon is considered to be bonded to the two adjacent boron atoms by a boron–silicon–boron, three-center, two-electron bond.[8] Isomerization of the μ-$(Me_3Si)B_5H_8$ occurs in diethyl ether to form 2-$(Me_3Si)B_5H_8$, in which the Me_3Si group occupies a terminal substituent position on the base of the pentaborane pyramid. Further isomerization to 1-$(Me_3Si)B_5H_8$ occurs at elevated temperatures or in the presence of stronger bases such as hexamethylenetetramine. The mechanisms of these processes in various pentaborane(9) derivatives have been studied in our laboratories[9] and elsewhere.[10]

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