(K_2CO_3) and evaporating in vacuo. Crystallization of the orange free base was accomplished from 2-PrOH. The dihydrochloride salt was prepared from the base in EtOAc solution by addition of anhydrous HCl in Et_2O. Ten grams (38%) of pale yellow needles gave mp 231-233 °C (with intumescence). Anal. ($C_{14}H_{17}N_3O_2$·2HCl) C, H, N.

3,4,5,6-Tetrahydro-4-(2-propenyl)-2H-1,5-methano-1,4-benzodiazocin-9-amine Diethanesulfonate Hemihydrate (12). Reduction of the nitro group of 11 was accomplished by the addition (without the application of external heat) of four 2-g portions of Fe powder to a solution of 10 g (0.03 mol) of the HCl salt of 11 in 100 mL of HOAc and 10 mL of H_2O. After overnight stirring and then evaporation to dryness, the residue was partitioned between dilute aqueous NaOH solution and $CHCl_3$. Evaporation of the dried (K_2CO_3) $CHCl_3$ left a tan powder, which was converted into the diethanesulfonate in 2-PrOH. Recrystallization from 2-PrOH gave 1.0 g (7%), mp 218-220 °C, of product 12. Anal. ($C_{14}H_{19}N_3$·2$C_2H_5SO_3H$·$^1/_2H_2O$) C, H, N.

Acknowledgment. We thank Dr. Stephen D. Clemans for interpretation of NMR protonation and chiral shift

Registry No. (±)-**1a**, 80769-97-7; (−)-**1a**, 80770-08-7; (−)-**1a**·*l*-mandelate, 95763-76-1; (+)-**1a**, 80770-13-4; (+)-**1a**·*d*-mandelate, 95763-77-2; (±)-**3a**, 80769-98-8; (±)-**3b**, 80770-20-3; (±)-**4a**, 80770-00-9; (±)-**4b**, 80770-21-4; (±)-**5**, 80770-01-0; (±)-**5a**, 80770-31-6; (±)-**6**, 80770-03-2; (+)-**6**, 80770-16-7; (−)-**6**, 80770-12-3; (±)-**6** (diazonium sulfate), 95763-82-9; (±)-**7**, 95763-78-3; (±)-**8**, 80770-30-5; (±)-**9a**, 80770-28-1; (±)-**9a**·2HCl, 80770-29-2; (±)-**9b**, 80770-32-7; (±)-**10**, 80770-23-6; (±)-**10**·2HCl, 95763-79-4; (±)-**11**·2HCl, 95763-80-7; (±)-**12**, 80770-25-8; (±)-**12**·2$C_2H_5SO_3H$, 80770-26-9; cyclopropanecarboxylic acid anhydride, 33993-24-7.

Synthesis and Antimicrobial Evaluation of Bicyclomycin Analogues

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The synthesis and antimicrobial evaluation of novel bicyclomycin analogues are described. The series of analogues were prepared from the basic 8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (8), 7,9-diaza-2-oxabicyclo[3.2.2]nonane-6,8-dione (9), 8,10-diaza-5-methylene-2-oxabicyclo[4.2.2]decane-7,9-dione (10), and 7,9-diaza-4-methylene-2-oxabicyclo[3.2.2]nonane-6,8-dione (11) nuclei. For compounds where R_1 = *p*-methoxybenzyl, deprotection of the lipophilic amides with ceric ammonium nitrate affords the corresponding lipophobic free amides. The basic bicyclic nucleus of bicyclomycin (**8h**, $R_1 = R_2 = R_3 = R_4 = H$) has been synthesized for the first time as well as increasingly more complex congeners bearing the C-6 OH, 5-methylene; C-1'–C-3' trihydroxyisobutyl group. In general, it has been found that the bicyclic nucleus of bicyclomycin is devoid of antimicrobial activity, the entire structure of bicyclomycin being generally obligate for activity. In one instance, the racemic analogue **10c** (R_1 = CH_2Ph, R_2 = OH, R_3 = H) showed interesting antimicrobial activity against several Gram-positive organisms; the minimum inhibitory concentrations were of the same order of magnitude as bicyclomycin displays toward Gram-negative organisms. Totally synthetic (±)-bicyclomycin was half as active as the natural antibiotic. The design, synthesis, and antimicrobial activity (and/or lack thereof) of bicyclomycin and the analogues are discussed in the context of a proposed chemical mechanism of action.

Bicyclomycin[1] (bicozamycin, 1) is an antibiotic obtained from cultures of *Streptomyces sapporonensis*[2] and *Streptomyces aizunensis*.[3] Bicyclomycin is biosynthesized[4] from leucine and isoleucine and possesses a unique chemical structure amongst the known classes of antibiotics. The low toxicity and ready availability of bi-

1
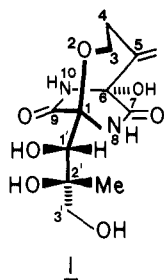
cyclomycin from fermentation have resulted in the recent commercial introduction of bicozamycin[5] as an effective agent against nonspecific diarrhea for humans and bacterial diarrhea of calves and pigs.[6] The mechanism of action of bicyclomycin is also thought to be unique and has been the subject of several accounts.[7]
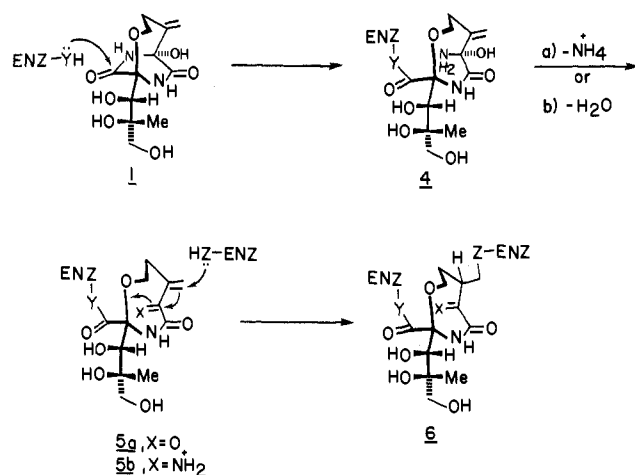
Scheme I
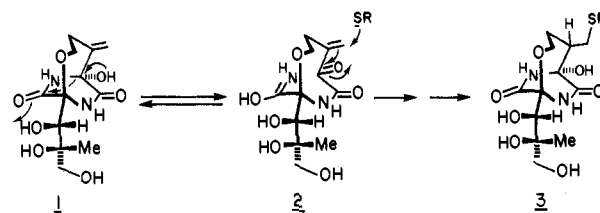
Bicyclomycin is active against Gram-negative bacteria such as *Escherichia coli*, *Klebsiella*, *Shigella*, *Salmonella*,

(1) (a) Miyoshi, T.; Miyairi, N.; Aoki, H.; Kohsaka, M.; Sakai, H.; Imanaka, H. *J. Antibiot.* **1972**, *25*, 569. (b) Kamiya, T.; Maeno, S.; Hashimoto, M.; Mine, Y. *Ibid.* **1972**, *25*, 576. (c) Nishida, M.; Mine, Y.; Matsubara, T. *Ibid.* **1972**, *25*, 582. (d) Nishida, M.; Mine, Y.; Matsubara, T.; Goto, S.; Kuwahara, S. *Ibid.* **1972**, *25*, 594. (e) Miyamura, S.; Ogasawara, N.; Otsuka, H.; Niwayama, S.; Tanaka, H.; Take, T.; Uchiyama, T.; Ochiai, H.; Abe, K.; Koizumi, K.; Asao, K.; Matsuki, K.; Hoshino, T. *Ibid.* **1972**, *25*, 610. (f) Miyamura, S.; Ogasawara, N.; Otsuka, H.; Niwayama, S.; Tanaka, H.; Take, T.; Uchiyama, T.; Ochiai, H. *Ibid.* **1973**, *26*, 479.

(2) References 1a–d.

(3) References 1e and 1f.

(4) (a) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 480; **1980**, *33*, 488.

Scheme II

$$\underline{5a}, X = O$$
$$\underline{5b}, X = NH_2$$

Scheme III

Scheme IV[a]

[a] (a) 2 equiv of $LiAlH_4$/THF, 25 °C, 1 min; $Na_2SO_4 \cdot 10H_2O$ quench; (b) 1 equiv of $AgClO_4$, THF, 25 °C; (c) MsCl, Et_3N, THF; (d) $NaBH_3SePh$, THF; (e) 30% H_2O_2, THF, 55 °C; (f) O_3, CH_2Cl_2; (g) $NaBH_4$, MeOH.

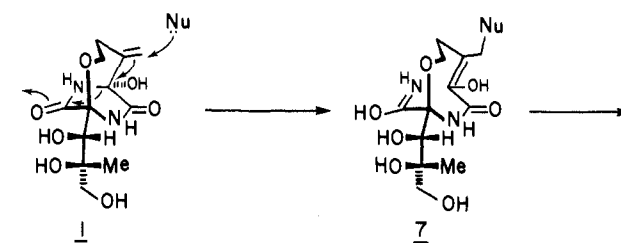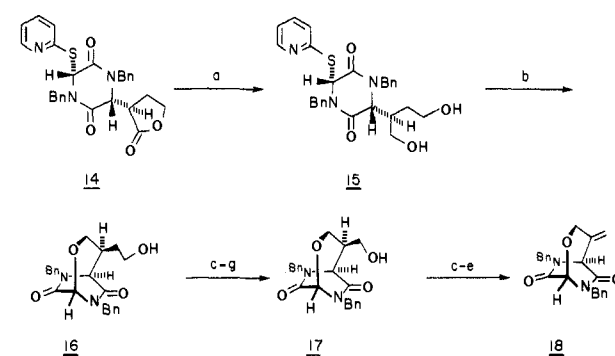*Citrobacter, Enterobacter cloacae,* and *Neisseria* but is inactive against *Proteus, Pseudomonas aeruginosa,* and Gram-positive bacteria. Iseki et al.[7] have shown that bicyclomycin irreversibly and covalently binds inner-membrane proteins (BBP's) of *E. coli* that are distinct from penicillin-binding proteins. The function of the bicyclomycin-binding proteins (BBP's) and the chemical mechanism by which bicyclomycin binds to these proteins remains to be determined. The stoichiometry of the bicyclomycin–BBP complex has been shown[7] to be 1:1, and further, the binding is inhibited by the addition of thiols.[8]

A Ciba-Geigy group[9] has prepared a large number of semisynthetic bicyclomycin derivatives and found that most structural modifications result in reduction or loss of biological activity. Unfortunately, a clear structure–activity relationship has not emerged from the above-mentioned studies. Iseki and co-workers[7] reported on the reaction of the C-5 *exo*-methylene moiety of bicyclomycin with methanethiol at high pH and suggested that the C-5 double bond may be the active functionality that could irreversibly alkylate a sulfhydryl residue on the BBP.[8] Careful inspection of the bicyclomycin structure and consideration of the regiochemistry of the mercaptan addition suggest that bicyclomycin may act as a "latent" α,β-unsaturated pyruvamide (2), which should undergo facile Michael-type addition at C-5=CH$_2$ (1 → 2 → 3, Scheme I). Such a general-base-catalyzed mechanism readily accounts for the regiochemistry of the mercaptan adduct (3, R = CH$_3$) reported by Iseki et al.[7]

Alternatively, bicyclomycin may irreversibly alkylate the BBP's by a distinctly different but related "latent" Michael-acceptor mechanism in vivo. Being itself a peptide, bicyclomycin may be interacting with a protease or transpeptidase type protein that functions by catalytically cleaving a peptide bond during the biosynthesis of the bacterial cell envelope. As proposed in Scheme II, cleavage of the 9,10-amide bond by the protein produces acyl en-

zyme derivative 4. The amide-derived NH$_2$ (at C-6, 4) should be rapidly expelled as NH$_3$[10] at physiological pH, forming the α,β-unsaturated pyruvamide 5a, which may similarly undergo conjugate addition resulting in the "suicide" inactivation of the BBP.

Finally, it is possible that a nucleophile may undergo allylic addition at C-5 that does not per se require the intermediacy of a ring-opened α,β-unsaturated species such as 2 or 5 (Scheme III, 1 → 7).
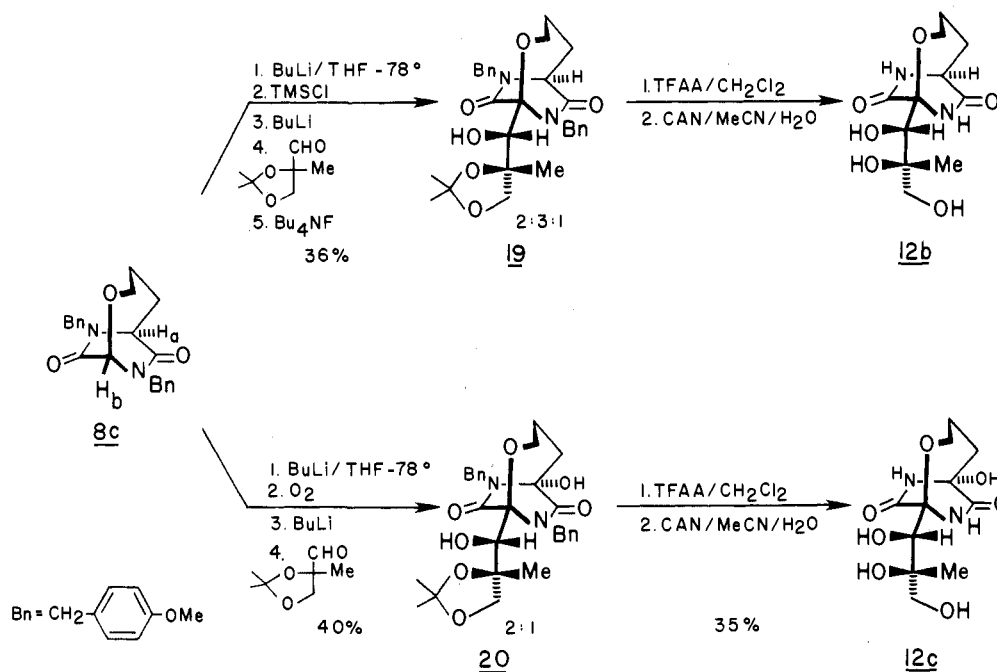
In order to gain some insight into the chemical mechanism of action of bicyclomycin, vis-a-vis the proposals outlined above, we have designed and synthesized a series of bicyclomycin analogues and have evaluated them for biological activity. We were primarily interested in probing the obligate partnership of the C-5 *exo*-methylene moiety and the C-6 hydroxyl group as a minimal structural requirement for biological activity rather than making more random peripheral structural changes. Furthermore, all of our synthetic analogues were specifically prepared in racemic form to allow for the greatest versatility in identifying intrinsic biological activity; all previously reported semisynthetic analogues possessed only the natural configuration.

Recently, we have reported[11-14] on the development of a versatile and efficient synthesis of the bicyclo[4.2.2] nucleus (8 and 10, R$_2$ = R$_3$ = H) that can be regioselec-

(5) Merck Index, 10th ed., No. 1213. Bicozamycin is the commercial name licensed to Fujisawa Pharmaceutical Co., Japan; aizumycin and bicyclomycin are synonyms; "bicyclomycin" shall be used throughout this paper.

(6) Private communication, Fujisawa Pharmaceutical Co., Japan.

(7) (a) Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiotics* **1978**, *31*, 712. (b) Tanaka, N.; Iseki, M.; Miyoshi, T.; Aoki, H.; Imanaka, H. *Ibid.* **1976**, *29*, 155.

(8) Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.* **1979**, *32*, 402. A detailed mechanism for the thiolate addition has not been suggested.

(9) Muller, B. W.; Zak, O.; Kump, W.; Tosch, W.; Wacker, O. *J. Antibiot.* **1979**, *32*.

(10) Depending upon the localized pH, it is also possible that the C-6 OH is lost as H$_2$O from 4, forming the corresponding α,β-unsaturated imino pyruvamide 5b that may either hydrolyze to 5a or directly undergo conjugate addition.

(11) Williams, R. M.; Anderson, O. P.; Armstrong, R. W.; Josey, J.; Meyers, H.; Eriksson, C. *J. Am. Chem. Soc.* **1982**, *104*, 6092.

(12) Williams, R. M.; Dung, J.-S.; Josey, J.; Armstrong, R. W.; Meyers, H. *J. Am. Chem. Soc.* **1983**, *105*, 3214.

(13) Armstrong, R. W.; Dung, J.-S.; Williams, R. M. 185th National Meeting of the American Chemical Society, Division of Organic Chemistry, Seattle, WA, March 1983; Abst. 10.

(14) Dung, J.-S.; Armstrong, R. W.; Williams, R. M. *J. Org. Chem.* **1984**, *49*, 3416.

Scheme V

1. BuLi/THF −78°
2. TMSCl
3. BuLi
4. CHO
5. Bu₄NF
36%

19 2:3:1

1. TFAA/CH₂Cl₂
2. CAN/MeCN/H₂O

12b

8c

Bn = CH₂⟨⟩OMe

1. BuLi/THF −78°
2. O₂
3. BuLi
4. CHO
40%

20 2:1

1. TFAA/CH₂Cl₂
2. CAN/MeCN/H₂O
35%

12c

Chart I

8   **9**

10   **11**

12   **13**

tively elaborated into a multitude of structurally diverse bicyclomycin analogues via carbanion substitution at the C-1 and C-6 bridgehead positions. This methodology has allowed making deepseated functional group modifications in the bicyclo[4.2.2] nucleus from a few simple bicyclic precursors. In increasing order of complexity, we have examined analogues both bearing and lacking the following: (a) substitution of N-8 and N-10, (b) the C-6 hydroxyl group, (c) the C-5 exo-methylene moiety, and (d) the C-1′-C-3′ trihydroxyisobutyl side chain. In addition, we have developed a parallel series of analogues based on the homologous bicyclo[3.2.2] ring system (9 and 11) whose anticipated increased ring strain was hoped to impart increased biological activity.

Results and Discussion

The bicyclic precursors 8 and 9 (R_1 = alkyl, aryl; R_2 = R_3 = R_4 = H) were prepared as previously described.[11,12,14,15] Substrates 10 were prepared according to the methods we have recently disclosed[13,16], in our total synthesis of bicyclomycin.

The homologous bicyclo[3.2.2] nucleus 11 was prepared as outlined in Scheme IV. The syn lactone 14 or its syn diastereomer could be converted into bicyclic olefin 18 by the procedure that is outlined. It is significant to point out that the bicyclo[3.2.2] nucleus 18 contains considerable strain energy as evidenced by the 1695-cm⁻¹ infrared absorbtion of the amide carbonyls relative to the bicyclo-[4.2.2] nucleus 10a (1660–1675 cm⁻¹).

These common bicyclic nuclei 8–11 (R_2 = R_3 = H, Chart I) served as the substrates from which the analogues were regioselectivity elaborated according to the protocol we have developed.[11,12] Table I provides a tabulation of the compounds synthesized that have been evaluated for antimicrobial activity.

It is significant to point out that, of the amide N-protecting groups we have evaluated (CH_3, CH_2OCH_3, CH_2Ph,
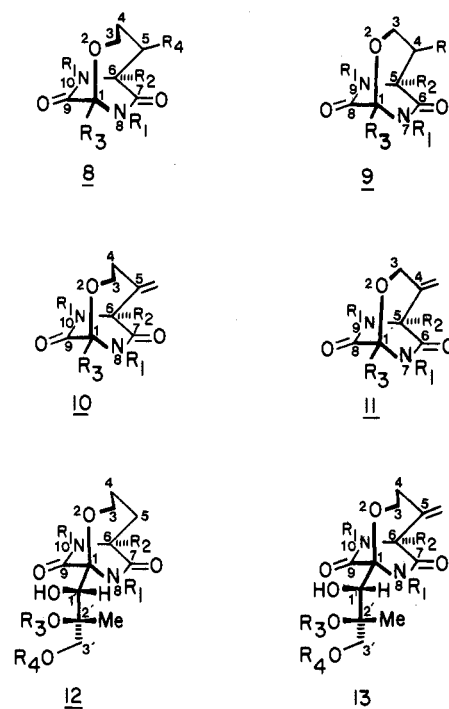
Ph-p-OCH₃, CH₂Ph-p-OCH₃), only the N-(p-methoxybenzyl) amides could be deprotected (N–R → N–H) under sufficiently mild conditions (ceric ammonium nitrate (CAN), MeCN, H_2O, 25 °C) for the bicyclic structure and attendant functionality to remain intact. The identification of a suitable and generally useful blocking group for the amides turned out to be a crucial element for the present study as well as our related studies on the total synthesis of bicyclomycin.[13,16] The corresponding N-benzyl protecting group, which has been utilized in a recently communicated[17] total synthesis, was found to be uniformly unsuitable for making bicyclic structures bearing free-NH

(15) Satisfactory combustion analytical data were reported for 8 and 9.

(16) (a) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1984**, *106*, 5748 and references cited therein. (b) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.*, in press.

(17) Nakatsuka, S.; Yamada, K.; Yoshida, K.; Asano, O.; Murakami, Y.; Goto, T. *Tetrahedron Lett.* **1983**, *24*, 5627.

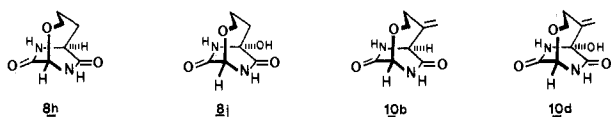**Table I.** Synthetic Bicyclomycin Analogues Submitted for Antimicrobial Assay[a]

compd	R_1	R_2	R_3	R_4	ref[b]
8a	CH_3	H	H	H	11
8b	CH_2Ph	H	H	H	11
8c	CH_2Ph-p-OCH_3	H	H	H	14
8d	Ph-p-OCH_3	H	H	H	14
8e	CH_3	SCH_3	H	H	12
8f	CH_3	CH_3	SCH_3	H	12
8g	CH_3	CHOHPh	H	H	12
8h	H	H	H	H	c
8i	H	OH	H	H	c
8j	CH_2Ph	OH	H	H	c
9a	CH_3	H	H	H	12
9b	CH_3	COPh	H	H	12
9c	H	H	H	$CH=CH_2$	c
9d	CH_2Ph	H	H	$CH=CH_2$	c
17	CH_2Ph	H	H	CH_2OH	c
10a	CH_2Ph	H	H		16
10b	H	H	H		b
10c	CH_2Ph	OH	H		16
10d	H	OH	H		c
18	CH_2Ph	H	H		c
12a	CH_2Ph	OH	$(Me)_2C$		c
12b	H	H	H	H	c
12c	H	OH	H	H	c
13a	H	OH	H	H	16

[a] See Table II for the standard 20 microorganism assay used. [b] See indicated reference for experimental preparation. [c] New compound not previously reported; experimental procedure appears in the Experimental Section.

amides. In our hands, numerous oxidative (CAN, CrO_3, DDQ), reductive (Li/NH_3, Na/NH_3, 10% Pd/C, 20% Pd/C, 20% Pt(OH)$_2$/C), and hydrolytic (H_3PO_4/PhOH, TFA, HBr) attempts (many solvents, temperatures, etc. examined) to remove the N-benzyl groups on more than a dozen bicyclic compounds resulted in cleavage of the bicyclic system (C-1-O ether linkage) and/or (in the case of hydrogenolysis) saturation of the benzylic aromatic rings. Scheme V illustrates the synthesis of demethylenebicyclomycin 12c and 6-deoxydemethylenebicyclomycin 12b from the same unsubstituted bicyclic precursor 8c. Both systems displayed relatively modest selectivity in the aldol condensation step as compared to that we have achieved[16] in the total synthesis of 1. This was especially true for the deoxy compound 19, which was the intermediate diastereomer (shown) in the condensation.[19] The anomalous behavior[11,12,16] of this aldol condensation may be attributable to the C-6 trimethylsilyl residue, which presumably alters the conformation of the bicyclic carbanion relative to the C-6 alkoxy species.

As expected, removal of the amide blocking groups changes the solubility characteristics of the structure from being generally lipophilic/hydrophobic (N-alkylated) to hydrophilic/lipophobic (-NH-). It is noteworthy that the simplest bicyclomycin analogue 8h is totally devoid of antibacterial activity. Adding functionality to this basic nucleus in order of increasing complexity furnishes the structures shown below. These basic bicyclic nuclei have

all been prepared for the *first* time by cerric ammonium

(18) The excellent procedure of Yoshimura was employed: Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

(19) We thank Dr. Hans Maag for providing a spectrum of compound 12b ($R_1 = R_2 = R_3 = R_4 = H$).

Table II. Minimal Inhibitory Concentration[a] ($\mu g/mL$)

		10c ($R_1 = CH_2Ph$, $R_2 = OH$, $R_3 = H$)	bicyclomycin Ro 21-7023
G- rods	*Pseudomonas aeruginosa* 56	>1000	>1000
	Proteus vulgaris 101N	>1000	>1000
	Escherichia coli 94	>1000	250
	Klebsiella pneumoniae 369	>1000	250
	Serratia marcescens SM	>1000	>1000
	Serratia sp. 101	>1000	>1000
	Acinetobacter calcoaceticus PCI_3	>1000	1000
G+ cocci	*Streptococcus faecium* ATCC 8043	>1000	>1000
	Staphylococcus aureus 82	>1000	>1000
	Micrococcus luteus PCI	500	>1000
G+ rods	*Bacillus megaterium* 164	500	>1000
	Bacillus sp. E	>1000	>1000
	Bacillus subtilis 558	250	>1000
	Bacillus sp. TA	250	>1000
	Mycobacterium phlei 78	>1000	1000
G+ filament molds	*Streptomyces cellulosae* 097	500	500
	Paecilomyces varioti M16	>1000	>1000
	Penicillium digitatum 0184	>1000	>1000
yeasts	*Candida albicans* 155	>1000	>1000
	Saccharomyces cerevisiae 90	>1000	>1000

[a] Lowest concentration still showing zone of inhibition by the agar-diffusion well method (serial dilutions up to 1000 $\mu g/mL$).

nitrate deprotection[18] of the corresponding N,N'-bis(p-methoxybenzyl) derivatives as described in the Experimental Section. Both the 6-hydroxy-5-demethylene derivative 8i and the 6-deoxy-5-methylene derivative 10b lack antimicrobial activity at the maximum levels tested (1 mg/mL). Antimetabolite tests were carried out on minimal agar medium by the agar-diffusion well method. Table II provides the antimicrobial spectrum of the only active analogue, 10c ($R_1 = CH_2Ph$, $R_2 = OH$, $R_3 = H$); all other compounds tested against the 20 microorganism screen (see Table II) were inactive. Although the activity exhibited by the N-benzyl compound 10c was relatively weak, we were surprised to discover that *this material displayed a different spectrum of activity than bicyclomycin*, showing Gram-positive inhibition against *Micrococcus luteus, Bacillus megaterium, Bacillus subtilus, Bacillus* sp. TA, and *Streptomyces cellulosae*. It should also be noted that all of the compounds tested are racemic and (presumably) the activity exhibited by 10c results from a single antipode. The absolute configuration of the active antipode for analogue 10c remains to be determined; the different spectrum of activity suggests that the naturally configured antipode is not necessarily the one displaying antimicrobial activity. The activity displayed by compound 10c when compared to the total lack of antimicrobial activity of the demethylene 8 and deoxy (10a and 10b) analogues would seem to support the hypotheses outlined in Schemes I and II that the partnership of the C5 *exo*-methylene and C-6 hydroxyl group in this unique bicyclic structure are obligate, minimal structural requirements for antimicrobial activity. However, the lack of activity displayed by the corresponding lipophobic derivative 10d indicates that the solubility characteristics of these structures are very important. Compound 10d, which contains the complete structural nucleus of bicyclomycin but lacks the C-1'-C-3' trihydroxyisobutyl side chain, indicates the potential importance of this moiety for binding, chelation, or penetration. The Ciba-Geigy study as well as the diminished activity of the C-1'/C-2' acyl derivatives of bicyclomycin also points to the importance of the C-1'-C-3' functionality. The demethylenebicyclomycin de-

rivative **12c** was also inactive, which again suggests that the complete structure of bicyclomycin is generally obligate for antimicrobial activity. The active analogue **10c**, which displays a different spectrum of activity than bicyclomycin, is indicative of a distinct enzymic target; the mechanism of action in terms of chemical interaction with the bacterial proteins, however, may be similar for both **10c** and **1**. It is expected that demonstration of enzyme inhibitory properties for these compounds will be forthcoming. Preliminary evaluation of totally synthetic (±)-bicyclomycin[16] showed half the antimicrobial activity of the optically pure (+) natural sample against *E. coli 94* and *Klebsiella pneumoniae 369*. This result indicates that the enantiomorph in the racemate is devoid of antimicrobial activity.

The bicyclo[3.2.2] homologues **9a-e**, **17**, and **18** did not exhibit antimicrobial activity, again indicating that this bicyclic nucleus lacks intrinsic activity. Attempts to hydroxylate **18** at the bridgehead position[20] have thus far been unsuccessful in producing testable amounts of material. Thus a direct comparison of the bicyclo[3.2.2] homologue of **10c** is presently not available and will have to await future scrutiny.

These preliminary investigations into the pharmacological potentialities of a unique class of antibiotics first represented by **1** suggest many interesting structural and mechanistic experiments to further test the hypotheses outlined in Schemes I–III as well as fostering more refined notions of the chemical mechanism of action of bicyclomycin. Studies along these lines are in progress and shall be reported on in due course from these laboratories.

Experimental Section

¹H NMR spectra were recorded on JEOL FX-100 (100 MHz), IBM/Bruker WP-270 (270 MHz) and WP-200 (200 MHz), or Nicolet (360 MHz) spectrometers and are reported in δ values. Melting points were recorded on a Mel-Temp instrument in open capillaries and are uncorrected. Microanalyses are within ±0.4% of the calculated values. Infrared spectra were recorded on a Beckman 4240 spectrophotometer and are reported as λ_{max} (cm⁻¹). Low-resolution mass spectra were determined on a VG MM16F-GC mass spectrometer.

Thin-layer chromatography (TLC) was carried out on E. Merck 0.25-mm precoated silica gel glass plates (60F-254) by using 5% phosphomolybdic acid in ethanol–heat and/or UV light as developing agent. Preparative-layer chromatography (PTLC) was carried out on glass-backed TLC plates with a fluorescent indicator on a Harrison Research chromatotron using 1.0-, 2.0-, or 4.0-mm layer thickness silica gel adsorbents. Separations of less than 50 mg were carried out on standard glass-backed E. Merck 0.25-mm silica gel plates; the separated products were eluted from the adsorbent with distilled THF. Flash column chromatography was performed by using Woelm silica gel 32–63.

Solvents and reagents were all purified and dried according to standard protocol. NMR multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; J, coupling constant in hertz. The chemical shifts of protons part of an AB quartet ($^1/_2$AB q) are calculated by using a standard weighting formula.

8,10-Diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (8h, R₁ = R₂ = R₃ = R₄ = H). To a stirred, room temperature suspension of 8,10-bis(*p*-methoxybenzyl)-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (**8c**), prepared as described in ref 14 (68 mg, 0.165 mmol, 1.0 equiv), in 33% aqueous acetonitrile (1.5 mL) was added CAN (318 mg, 0.58 mmol, 3.5 equiv). The mixture was stirred at room temperature for 2 h and absorbed onto PTLC silica gel (eluted with 10% MeOH in CH₂Cl₂) to afford 16 mg (57%) of the debenzylated product **8a** as an amorphous white solid:[21] NMR

(270 MHz) (Me₂SO-*d₆*, Me₄Si) δ 1.729–1.754 (2 H, m), 1.895–1.930 (2 H, m), 3.631–3.724 (2 H, m), 3.816 (1 H, br s), 4.972 (1 H, d, J = 4.73 Hz), 8.405 (1 H, br s), 8.897 (1 H, br s); IR (NaCl, neat) 1685, 1445, 1415, 1105, 1025 cm⁻¹; mass spectrum, m/e 170 (M⁺, 16), 169 (1.9), 155 (2.3), 142 (4.6), 127 (14.4), 111 (13.3), 97 (20), 85 (25.7), 83 (26.2), 77 (100).

Note: Additional, firm evidence for the assigned structure was obtained by treatment of this material with NaH/BrCH₂Ph in Me₂SO to afford in 55% yield 8,10-dibenzyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (**8b**, R₁ = CH₂Ph; R₂ = R₃ = R₄ = H; see ref 11 for spectroscopic and analytical data).

8,10-Bis(*p*-methoxybenzyl)-8,10-diaza-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (8, R₁ = CH₂Ph-*p*-OCH₃; R₂ = OH; R₃ = R₄ = H). To a stirred solution of 8,10-bis(*p*-methoxybenzyl)-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione[14] (**8c**; 163 mg, 0.39 mmol, 1.0 equiv) in THF (7.5 mL) containing HMPA (0.35 mL, 1.987 mmol, 5.0 equiv) at −78 °C was added a solution of LDA (0.51 mmol, 10 equiv) in THF (2.5 mL). While the dark-colored solution was stirred for 34 min at −78 °C, a stream of dry O₂ was bubbled through the solution for 5 min at −78 °C; the cooling bath was removed, and oxygen was bubbled through the mixture until the temperature had reached ambient. Several drops of H₂O was added and the mixture was diluted with ether, poured into H₂O, and extracted thoroughly with ether. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, evaporated, and separated by PTLC silica gel (eluted with 6% acetone in Et₂O) to afford 89 mg (53% or 62.6% based on recovered starting material) of the pure bridgehead alcohol 8: mp 187–187.5 °C (recryst CH₂Cl₂/Et₂O/hexanes); ¹H NMR (270 MHz) (CDCl₃, CHCl₃) δ 1.463–1.533 (2 H, m), 0.778–1.881 (2 H, m), 3.257 (1 H, dd, J_1 = 13.32 Hz, J_2 = 9.23 Hz), 3.714–3.723 (1 H, m), 3.758 (3 H, s), 3.771 (3 H, s), 4.191 (1 H, $^1/_2$AB q, J = 14.26 Hz), 4.503 (1 H, $^1/_2$AB q, J = 13.88 Hz), 4.725 (1 H, s), 4.777 (1 H, $^1/_2$AB q, J = 13.88 Hz), 4.925 (1 H, $^1/_2$AB q, J = 14.26 Hz), 5.158 (1 H, s), 6.776–6.852 (4 H, m), 7.197–7.229 (2 H, m), 7.340–7.428 (2 H, m); IR (NaCl, neat) 3370, 1675, 1610, 1505, 1430, 1240, 1170, 1100, 1025, 920, 800 cm⁻¹; mass spectrum, m/e 426 (M⁺, 3.6), 340 (1.0), 305 (2.1), 241 (11.3), 226 (10.9), 219 (198), 210 (1.4), 192 (10.2), 175 (2.1), 162 (492), 156 (16.9), 149 (7.3), 136 (11.9), 121 (100), 116 (97.9), 101 (39.6). Anal. (C₂₃H₂₆N₂O₆) C, H, N.

8,10-Diaza-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (8i, R₁ = H; R₂ = OH; R₃ = R₄ = H). To a stirred, room temperature solution of 8 (R₁ = CH₂Ph-*p*-OMe, R₂ = OH, R₃ = R₄ = H) (35 mg, 0.082 mmol, 1.0 equiv) in MeCN/H₂O (1.1 mL, 2:1 v/v) was added CAN (202 mg, 0.369 mmol, 4.5 equiv) in one portion. The mixture was stirred for 80 min at room temperature and directly separated on PTLC silica gel (eluted with 12% MeOH in CH₂Cl₂) to afford 5.2 mg (35%) of the deprotected amide **8i** as an amorphous white solid:[21] ¹H NMR (270 MHz) (Me₂SO-*d₆*, Me₄Si) δ 1.550–1.723 (2 H, m), 1.767–2.035 (2 H, m), 3.585–3.760 (2 H, m), 4.802 (1 H, d, J = 4.37 Hz), 6.592 (1 H, s), 8.706 (1 H, br s), 8.983 (1 H, d, J = 4.37 Hz); IR (NaCl, neat) 3260, 3200, 1685, 1440, 1275, 1130, 1070 cm⁻¹.

8,10-Dibenzyl-8,10-diaza-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (8j, R₁ = CH₂Ph; R₂ = OH; R₃ = R₄ = H). To a stirred solution of 8,10-dibenzyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (**8b**, R₁ = CH₂Ph; R² = R³ = H; see ref 11 for preparation) (25 mg, 0.07 mmol, 1.0 equiv) and HMPA (62 μL, 0.35 mmol, 5 equiv) in THF (2 mL) at −78 °C was added LDA (0.107 mmol, 1.5 equiv) in THF (1 mL). After stirring of the dark-colored solution for 50 min at −78 °C, a stream of dry O₂ gas was bubbled through the solution for 70 min at −78 °C, and the mixture was quenched with H₂O (0.1 mL). The reaction was allowed to warm to room temperature, stirred 20 min, diluted with CH₂Cl₂, poured into brine, and thoroughly extracted with CH₂Cl₂. The combined extracts were dried over anhydrous Na₂SO₄, filtered, evaporated and separated on PTLC silica gel (eluted with Et₂O) to afford the tertiary alcohol **8j** (9.3 mg, 35.7% or 53% based on recovered starting material) oil: ¹H NMR (100 MHz) (CDCl₃,

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(20) Compound 18 can be regioselectively elaborated at both bridgehead positions exactly analogous to **10a** via generation and quenching of the corresponding bridgehead carbanions.

(21) Compounds reported as amorphous solids were recalcitrant to recrystallization and were precipitated from MeOH or THF; combustion analytical data were not obtainable on these materials.

CHCl$_3$) δ 1.46–2.06 (4 H, m), 3.19–4.07 (2 H, m), 4.24 (1 H, $^1/_2$AB q, J = 14.4 Hz), 4.62 (1 H, $^1/_2$AB q, J = 13.9 Hz), 4.68 (1 H, s, D$_2$O exch), 4.79 (1 H, $^1/_2$AB q, J = 13.9 Hz), 5.04 (1 H, $^1/_2$AB q, J = 14.4 Hz), 5.18 (1 H, s), 7.30–7.47 (10 H, m); IR (NaCl, neat) 3400, 3060, 3015, 1675, 1600, 1585, 1495, 1435, 1260, 1085, 730, 690 cm^{-1}; mass spectrum, m/e 366 (M$^+$, 0.7), 275 (0.7), 57 (100).

7,9-Bis(*p*-methoxybenzyl)-7,9-diaza-4-vinyl-2-oxabicyclo-[3.2.2]nonane-6,8-dione (9, R$_1$ = CH$_2$Ph-*p*-OCH$_3$; R$_2$ = R$_3$ = H; R$_4$ = CH=CH$_2$) [note: the preparation of 7,9-bis(*p*-methoxybenzyl)-7,9-diaza-4-[2-(phenylselenyl)ethyl]-2-oxabicyclo-[3.2.2]nonane-6,8-dione (9, R$_1$ = CH$_2$Ph-*p*-OMe; R$_2$ = R^3 = H; R$_4$ = CH$_2$CH$_2$SePh) appears in ref 16b]: ^{1}H NMR (CDCl$_3$, Me$_4$Si) δ 1.20–1.40 (2 H, m), 2.20–2.38 (1 H, m), 2.72 (2 H, t, J = 7.80 Hz), 3.51 (1 H, dd, J_{vic} = 10.31 Hz, J_{gem} = 12.59 Hz), 3.75 (1 H, s), 3.78–3.88 (1 H, m), 3.79 (3 H, s), 3.80 (3 H, s), 4.19 (1 H, $^1/_2$AB q, J = 14.61 Hz), 4.29 (1 H, $^1/_2$AB q, J = 14.86 Hz), 4.74 (1 H, $^1/_2$AB q, J = 14.86 Hz), 4.74 (1 H, $^1/_2$AB q, J = 14.61 Hz), 5.02 (1 H, s), 6.83 (2 H, d, J = 8.64 Hz), 6.83 (2 H, d, J = 8.68 Hz), 7.05 (2 H, d, J = 8.68 Hz), 7.10 (2 H, d, J = 8.64 Hz), 7.26–7.30 (3 H, m), 7.45–7.49 (2 H, m); IR (NaCl, neat) 1691, 1612, 1515, 1247, 1030 cm^{-1}; mass spectrum, m/e 580 (M$^+$, 5.2), 459 (3.5), 423 (2.4), 121 (100).

To a stirred solution of 9 (R$_1$ = CH$_2$Ph-*p*-OMe, R$_2$ = R$_3$ = H, R$_4$ = CH$_2$CH$_2$SePh)[16] (80 mg, 0.138 mmol, 1.0 equiv) in THF (4 mL) at room temperature was added 30% H$_2$O$_2$ (0.02 mL, 0.691 mmol, 5.0 equiv), and the mixture was heated to reflux. After 20 min, the mixture was cooled to room temperature, diluted with CH$_2$Cl$_2$, poured into H$_2$O, and exhaustively extracted with CH$_2$Cl$_2$. The combined extracts were dried over anhydrous Na$_2$SO$_4$, filtered, concentrated, and separated by PTLC silica gel to afford 47 mg (81%) of olefin 9 as a solid: mp 115–116 °C (recryst CH$_2$Cl$_2$); ^{1}H NMR (270 MHz) (CDCl$_3$, (CH$_3$)$_4$Si) δ 2.85 (1 H, dd, J_{vic} = 7.52 Hz, J_{vic} = 7.12 Hz, J_{vic} = 7.12 Hz), 3.69–3.89 (2 H, m), 3.79 (6 H, s), 3.88 (1 H, s), 4.10 (1 H, $^1/_2$AB q, J = 14.64 Hz), 4.29 (1 H, $^1/_2$AB q, J = 14.74 Hz), 4.77 (1 H, $^1/_2$AB q, J = 14.64 Hz), 4.96 (1 H, $^1/_2$AB q, J = 14.74 Hz), 5.07 (1 H, s), 5.11 (1 H, d, J_{cis} = 9.55 Hz), 5.15 (1 H, d, J_{trans} = 17.05 Hz), 5.23 (1 H, ddd, J_{cis} = 9.55 Hz, J_{trans} ≈ 17.05 Hz, J_{vic} = 7.52 Hz), 6.85 (4 H, d, J = 8.47 Hz), 7.12 (4 H, d, J = 8.47 Hz); IR (NaCl, neat) 1690, 1612, 1513, 1240, 1030 cm^{-1}; mass spectrum, m/e 422 (M$^+$, 7.1), 301 (11.2), 217 (2.5), 121 (100). Anal. (C$_{24}$H$_{26}$N$_2$O$_5$) C, H, N.

7,9-Diaza-4-vinyl-2-oxabicyclo[3.2.2]nonane-6,8-dione (9c, R$_1$ = R$_2$ = R$_3$ = H; R$_4$ = CH=CH$_2$). To a stirred solution of 7,9-bis(*p*-methoxybenzyl)-7,9-diaza-4-vinyl-2-oxabicyclo[3.2.2]-nonane-6,8-dione (9, R$_1$ = CH$_2$Ph-*p*-OCH$_3$; R$_2$ = R$_3$ = H; R$_4$ = CH=CH$_2$) (100 mg, 0.237 mmol, 1.0 equiv) in CH$_3$CN (0.48 mL) and H$_2$O (0.24 mL) was added ceric ammonium nitrate (324.7 mg, 0.592 mmol, 2.5 equiv). The mixture was allowed to stir for 15 min at ambient temperature, diluted with CH$_2$Cl$_2$, and immediately separated on chromatotron (PTLC) silica gel (eluted with 10% MeOH in CH$_2$Cl$_2$, then 20% MeOH in CH$_2$Cl$_2$) to afford unreacted starting material (49 mg), a mixture of mono-N-deprotected olefins (21 mg), and the desired N,N-deblocked olefin 9c (5 mg, 12% or 22% by conversion) as an amorphous solid.[21] 9c: ^{1}H NMR (270 MHz) (CD$_3$OD, Me$_4$Si) δ 2.75 (1 H, m), 3.54 (1 H, s), 3.60 (1 H, dd, J = 9.76, J = 12.76 Hz), 3.85 (1 H, dd, J = 5.44, J = 12.76 Hz), 4.70 (1 H, s), 5.13 (1 H, dd, J = 10.43, J = 1.13 Hz), 5.20 (1 H, dd, J = 17.51, J = 1.13 Hz), 5.65 (1 H, dd, J = 10.43, J = 17.51, J = 7.23); IR (NaCl, neat) 3250, 1690, 1615, 1518, 1245, 1050 cm^{-1}. The mixture of mono-N-deprotected olefins upon treatment with CAN (6 equiv) exactly as described above led to ca. 50% yield of the desired compound 9c.

7,9-Dibenzyl-7,9-diaza-4-(2-hydroxyethyl)-2-oxabicyclo-[3.2.2]nonane-6,8-dione (16, Bn = CH$_2$Ph). To a stirred solution of diol 15[16] (670 mg, 1.36 mmol, 1.0 equiv) in THF (20 mL) was added silver perchlorate (566 mg, 2.73 mmol, 2.0 equiv) at 25 °C. The mixture was allowed to stir 40 min, diluted with CH$_2$Cl$_2$, poured into 0.1 N NaOH, and thoroughly extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, concentrated, and purified by PTLC silica gel (eluted with 4% MeOH in CH$_2$Cl$_2$) to afford 510 mg (99%) of the bicyclic alcohol 16 (oil): ^{1}H NMR (100 MHz) (CDCl$_3$, Me$_4$Si) δ 1.26–1.92 (3 H, m), 3.18–3.97 (5 H, m), 4.36–4.89 (4 H, m), 5.12 (1 H, s), 7.30 (10 H, m); IR (NaCl, neat) 3480, 1680, 1455, 1270, 1220, 1065, 750 cm^{-1}; mass spectrum, m/e 380 (M$^+$, 1.0), 292 (3.0), 252 (1.1), 91 (49.5).

7,9-Dibenzyl-7,9-diaza-4-vinyl-2-oxabicyclo[3.2.2]nonane-6,8-dione (9d, R$_1$ = CH$_2$Ph; R$_2$ = R$_3$ = H; R$_4$ = CH=CH$_2$). To a stirred solution of 16 (Bn = CH$_2$Ph) (110 mg, 0.289 mmol, 1.0 equiv) in THF (3 mL) at 0 °C were added Et$_3$N (81 μL, 0.58 mmol, 2.0 equiv) and methanesulfonyl chloride (25 μL, 0.31 mmol, 1.1 equiv). The mixture was stirred for 30 min, diluted with Et$_2$O, filtered, evaporated, and purified by PTLC silica gel (eluted with 33% hexanes in EtOAc) to afford 130 mg (98.7%) of the corresponding mesylate 9 (R$_1$ = CH$_2$Ph, R$_2$ = R$_3$ = H, R$_4$ = CH$_2$CH$_2$OSO$_2$CH$_3$): ^{1}H NMR (100 MHz) (CDCl$_3$, Me$_4$Si) δ 1.33–1.92 (3 H, m), 2.96 (3 H, s), 3.24–4.18 (5 H, m), 4.36–4.87 (4 H, m), 5.11 (1 H, s), 7.27–7.33 (10 H, m); IR (NaCl, neat) 1695, 1450, 1355, 1170, 950, 915, 725 cm^{-1}.

To a stirred suspension of diphenyl diselenide (182 mg, 0.58 mmol, 1.1 equiv) in EtOH (4 mL) at 0 °C was added NaBH$_4$ (46 mg, 1.22 mmol, 2.3 equiv). After the mixture was stirred for 10 min at 0 °C, a solution of the mesylate obtained as above (240 mg, 0.53 mmol, 1.0 equiv) in EtOH (2 mL) was added dropwise. The mixture was stirred for 1.5 h, diluted with CH$_2$Cl$_2$, poured into brine, and thoroughly extracted with CH$_2$Cl$_2$. The combined extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated to afford the crude selenide (310 mg), which was directly used for the next step without further purification. Treatment of this material in THF (5 mL) with 30% H$_2$O$_2$ (0.16 mL, 5.3 mmol, 10 equiv) at 0 °C (1 min addition) was followed by warming the reaction to ambient temperature. The mixture was stirred 29 h at room temperature, refluxed for 1.5 h, cooled, diluted with CH$_2$Cl$_2$, poured into 0.1 N HCl, and thoroughly extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, evaporated, and purified by PTLC silica gel (eluted with 33% EtOAc in hexanes) to afford 71 mg (37.2%) of the olefin 9d as colorless needles: mp 127.5–128.5 °C (recryst CH$_2$Cl$_2$/hexanes); ^{1}H NMR (360 MHz) (CDCl$_3$, CHCl$_3$) δ 2.42–2.50 (1 H, m), 3.67 (1 H, dd, J = 12.87 Hz, J = 12.87 Hz), 4.02 (1 H, dd, J = 12.87 Hz, J = 12.87 Hz), 4.10 (1 H, d, J = 2.77 Hz), 4.70 (1 H, $^1/_2$AB q, J = 14.50 Hz), 4.73 (1 H, $^1/_2$AB q, J = 14.75 Hz), 5.02 (1 H, $^1/_2$AB q, J = 14.50 Hz), 5.07 (1 H, $^1/_2$AB q, J = 14.75 Hz), 5.16 (1 H, dd, J = 0.82 Hz, J = 17.54 Hz), 5.33 (1 H, d, J = 9.94 Hz), 5.38 (1 H, s), 5.76 (1 H, ddd, J = 7.55 Hz, J = 9.94 Hz, J = 17.54 Hz), 7.02–7.40 (10 H, m); IR (NaCl, neat) 1690, 1500, 1450, 1215, 1075, 750 cm^{-1}; mass spectrum, m/e 362 (M$^+$, 8.2), 332 (2.2), 292 (2.3), 271 (2.3), 264 (2.2), 91 (100).

7,9-Dibenzyl-7,9-diaza-4-(hydroxymethyl)-2-oxabicyclo-[3.2.2]nonane-6,8-dione (17, Bn = CH$_2$Ph). A stream of ozone was bubbled through a CH$_2$Cl$_2$ (3 mL) solution of 9d (R$_1$ = CH$_2$Ph, R$_2$ = R$_3$ = H, R$_4$ = CH=CH$_2$), (47 mg, 0.13 mmol, 1.0 equiv) for 100 min. The mixture was allowed to come to room temperature, evaporated, THF (3 mL) was added, and the mixture was cooled to 0 °C. To this cold, stirred solution was added LAH (4 mg, 0.1 mmol, 0.75 equiv). The mixture was stirred for 2 h, diluted with CH$_2$Cl$_2$, poured into 0.1 N HCl, and thoroughly extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, evaporated, and purified by PTLC silica gel (eluted with 9% hexanes in EtOAc) to afford 11 mg (23%) of alcohol 17: mp 161–162 °C (recryst CH$_2$Cl$_2$/hexanes). ^{1}H NMR (100 MHz) (CDCl$_3$, Me$_4$Si) δ 1.74–2.00 (1 H, m), 3.33–4.11 (5 H, m), 4.35–4.89 (4 H, m), 5.10 (1 H, s), 7.31 (10 H, s); IR (NaCl, neat) 3440, 1695, 1500, 1455, 1285, 1265, 1070, 905, 730 cm^{-1}; mass spectrum, m/e 366 (M$^+$, 7.1), 336 (1.1), 292 (12.4), 275 (2.4), 91 (100).

The diastereomer 17 (epimeric at C-4) was obtained from the diastereomeric bicyclic alcohol 16 (epimeric at C-4) in 53% overall yield following the same procedures described above. Spectroscopic and analytical data is as follows for this series.

4-*epi*-17: mp 128–128.5 °C (recryst CH$_2$Cl$_2$/Et$_2$O/hexanes); ^{1}H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 1.665–1.695 (1 H, m), 2.298–2.425 (1 H, m), 3.209 (1 H, dd, J_1 = 10.751 Hz, J_2 = 7.951 Hz), 3.397 (1 H, dd, J_1 = 10.751 Hz, J_2 = 5.843 Hz), 3.665 (1 H, dd, J_1 = 12.743 Hz, J_2 = 9.122 Hz), 3.853 (1 H, dd, J_1 = 12.743 Hz, J_2 = 5.205 Hz), 4.110 (1 H, d, J= 1.512 Hz), 4.344 (1 H, $^1/_2$AB q, J = 15.042 Hz), 4.370 (1 H, $^1/_2$AB q, J = 14.726 Hz), 4.871 (1 H, $^1/_2$AB q, J= 15.042 Hz), 4.993 (1 H, $^1/_2$AB q, J = 14.726 Hz), 5.091 (1 H, s), 7.138–7.474 (10 H, m); IR (NaCl, neat) 3430, 3030, 1685, 1495, 1450, 1355, 1260, 1160, 1060, 945, 725, 690 cm^{-1}. Anal. (C$_{21}$H$_{22}$N$_2$O$_4$) C, H, N.

4-*epi*-7,9-Dibenzyl-7,9-diaza-4-vinyl-2-oxabicyclo[3.2.2]-nonane-6,8-dione (9, R_1 = CH_2Ph; R_2 = R_3 = H; R_4 = CH=CH_2): mp 120–120.5 °C (recryst CH_2Cl_2/Et_2O/hexane); ^1H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 2.869–2.902 (1 H, m), 3.465–3.899 (2 H, m), 3.918 (1 H, d, J = 1.416 Hz), 4.217 (1 H, $^1/_2$AB q, J = 14.889 Hz), 4.336 (1 H, $^1/_2$AB q, J = 14.990 Hz), 4.891 (1 H, $^1/_2$AB q, J = 14.889 Hz), 5.074 (1 H, $^1/_2$AB q, J = 14.990 Hz), 5.090 (1 H, s), 5.133–5.408 (3 H, m), 7.184–7.346 (10 H, m); IR (NaCl, neat) 3060, 3030, 1680, 1495, 1450, 1425, 1270, 1165, 1075, 1060, 910, 725, 690 cm^{-1}. Anal. ($C_{22}H_{22}N_2O_3$) C, H, N.

8,10-Diaza-5-methylene-2-oxabicyclo[4.2.2]decane-7,9-dione (10b, R_1 = R_2 = R_3 = H). To a stirred solution of 10^{16} (R_1 = CH_2Ph-p-OCH$_3$, R_2 = R_3 = H) (14 mg, 0.03 mmol, 1.0 equiv) in MeCN (0.1 mL) was added CAN (72.75 mg, 0.133 mmol, 4.0 equiv). The mixture was stirred for 1.2 h, diluted with MeOH (1 mL), and separated by PTLC silica gel (eluted with 20% MeOH in CHCl$_3$) to afford 5.5 mg (91%) of the fully deprotected bicyclic piperazinedione 10b as an amorphous solid plus 1 mg (ca. 8%) of a mixture of mono-*N*-(p-methoxybenzyl)piperazinediones (10): ^1H NMR (270 MHz) (Me$_2$SO-d_6, Me$_2$SO) δ 2.35–2.60 (2 H, m), 3.78 (1 H, dd, J = 1.46 Hz, J = 6.84 Hz), 3.83 (1 H, dd, J = 1.46 Hz, J = 6.84 Hz), 4.26 (1 H, s), 4.87 (1 H, s), 5.00 (1 H, s), 5.06 (1 H, s), 8.68 (1 H, D$_2$O exch), 9.02 (1 H, D$_2$O exch); IR (NaCl, neat) 3300–3200, 1680, 1620, 1250 cm^{-1}.

8,10-Diaza-5-methylene-6-hydroxy-2-oxabicyclo[4.2.2]de-cane-7,9-dione (10d, R_1 = H; R_2 = OH; R_3 = H). To a MeCN (0.1 mL) solution of 10^{16} (R_1 = CH_2Ph-p-OCH$_3$, R_2 = OH, R_3 = H) (4.0 mg, 0.009 mmol, 1.0 equiv) was added H$_2$O (0.01 mL) followed by CAN (22.53 mg, 0.041 mmol, 4.5 equiv). The reaction was stirred for 1.2 h at room temperature, diluted with MeOH (1 mL), and separated by PTLC silica gel (eluted with 5:1 CHCl$_3$/MeOH) to afford 1.2 mg (66.4%) of the fully deprotected amide 10d plus trace amounts of the monodeprotected mixture: mp 168–169 °C (recryst acetone/THF); ^1H NMR (270 MHz) (Me$_2$SO-d_6, Me$_2$SO) δ 2.50–2.70 (2 H, m), 3.56 (1 H, dd, J_{gem} = 9.10 Hz, J_{vic} = 2.5 Hz), 3.78 (1 H, dd, J_{vic} = 2.5 Hz, J_{gem} = 11.1 Hz), 6.95 (1 H, s, D$_2$O exch), 8.89 (1 H, br s, D$_2$O exch), 9.14 (1 H, br s, D$_2$O exch); IR (NaCl, neat) 3600–3200, 1690, 1620, 1250 cm^{-1}.

7,9-Dibenzyl-7,9-diaza-4-methylene-2-oxabicyclo[3.2.2]-nonane-6,8-dione (18, Bn = CH_2Ph). A stirred solution of 17 (18.6 mg, 0.019 mmol, 1.0 equiv) was treated with methanesulfonyl chloride (12 μL) and Et$_3$N (29 μL) in THF (1 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was filtered and evaporated, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (6 μL, 0.38 mmol, 2.0 equiv) in toluene (1 mL) was added, and the mixture was heated at reflux for 17 h. After cooling to room temperature, the mixture was diluted with CH$_2$Cl$_2$, poured into 0.1 N HCl solution, and thoroughly extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, evaporated, and separated on PTLC silica gel (eluted with 50% EtOAc in hexanes) to afford 2.5 mg (38.5%) of olefin 18: mp 185–185.5 °C (recryst CH_2Cl_2/Et_2O/hexanes); ^1H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 4.163 (1 H, $^1/_2$AB q, J = 14.062 Hz), 4.335 (1 H, $^1/_2$AB q, J = 14.062 Hz), 4.363 (1 H, s), 4.385 (1 H, $^1/_2$AB q, J = 15.036 Hz), 4.486 (1 H, $^1/_2$AB q, J = 14.741 Hz), 4.778 (1 H, $^1/_2$AB q, J = 14.741 Hz), 4.483 (1 H, $^1/_2$AB q, J = 15.036 Hz), 5.069 (1 H, s), 5.106 (1 H, s), 5.117 (1 H, s), 7.200–7.361 (10 H, m); IR (NaCl, neat) 1695, 1450, 1215, 1055, 755 cm^{-1}; mass spectrum, m/e 348 (M$^+$, 2.5), 261 (1.1), 243 (1.8), 91 (100). Anal. ($C_{21}H_{20}N_2O_3$) C, H, N.

An improved procedure for the preparation of 18 was found by converting the mesylate derived from 17 to the selenide followed by H$_2$O$_2$ oxidation and elimination (THF, reflux, 12 h) exactly as described above for preparation of the vinyl derivative from 16 (77.4% overall yield from 17).

8,10-Dibenzyl-8,10-diaza-6-hydroxy-1-[2′-methyl-1′-hydroxy-2′,3′-(isopropylidenedioxy)propyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (12a, R_1 = CH_2Ph; R_2 = OH; R_3, R_4 = $C(CH_3)_2$). To a stirred solution of alcohol 8j (R_1 = CH_2Ph, R_2 = OH, R_3 = R_4 = H) (135 mg, 0.368 mmol, 1.0 equiv) in THF (5 mL) at −100 °C was added n-BuLi (0.88 mmol, 2.4 equiv) dropwise. After the mixture was stirred for 15 min at −100 °C, 2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (212 mg, 1.47 mmol, 4 equiv) was added. The mixture was allowed to stir 15 min at −100 °C and 30 min at room temperature, diluted with CH$_2$Cl$_2$, poured

into saturated NaCl (aqueous), and thoroughly extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated, and the residue was separated on PTLC silica gel (eluted with 50% ether in hexanes) to afford the diol 12a (60.3 mg, 32.3% major diastereomer or 46.5% based on recovered 8j; plus 15.3 mg of a diastereomer, 8.2% or 12% based on recovered 8j plus unreacted 8j (41.3 mg, 30.6%)).

Major diastereomer 12a: mp 168–169 °C (recryst Et$_2$O/hexanes); ^1H NMR (360 MHz) (CDCl$_3$, CHCl$_3$) δ 0.738 (3 H, s), 1.140–1.367 (2 H, m), 1.330 (3 H, s), 1.337 (3 H, s), 1.683–1.767 (1 H, m), 2.033–2.133 (1 H, m), 2.721–2.786 (1 H, m), 3.449–3.518 (1 H, m), 3.748 (1 H, $^1/_2$AB q, J = 9.16 Hz), 4.097 (1 H, $^1/_2$AB q, J = 9.16 Hz), 4.603 (1 H, d, J = 9.97 Hz), 4.611 (2 H, s), 4.693 (1 H, $^1/_2$AB q, J = 15.19 Hz), 4.915 (1 H, s, D$_2$O exch), 5.145 (1 H, $^1/_2$AB q, J = 15.19 Hz), 6.505 (1 H, d, J = 9.97 Hz, D$_2$O exch), 7.20–7.60 (10 H, m); IR (NaCl, neat) 3400, 3060, 3030, 1665, 1605, 1500, 1435, 1405, 1380, 1250, 1205, 1075, 905, 850, 730, 700 cm^{-1}. Anal. ($C_{28}H_{34}N_2O_7$) C, H, N.

Minor diastereomer 12a: ^1H NMR (100 MHz) (CDCl$_3$, CHCl$_3$) δ 1.19–2.16 (13 H, m), 2.78–3.53 (2 H, m), 3.14 (1 H, d, J = 4.39 Hz), 3.65 (1 H, $^1/_2$AB q, J = 8.54 Hz), 4.15 (1 H, $^1/_2$AB q, J = 8.54 Hz), 4.65 (2 H, s), 4.79 (1 H, d, J = 4.39 Hz, D$_2$O exch), 4.91 (1 H, s, D$_2$O exch), 4.94 (1 H, $^1/_2$AB q, J = 15.13 Hz), 5.42 (1 H, $^1/_2$AB q, J = 15.13 Hz), 7.20–7.59 (10 H, m); IR (NaCl, neat) 3420, 3060, 3030, 1660, 1605, 1495, 1455, 1400, 1375, 1325, 1255, 1100, 1055, 905, 725 cm^{-1}. (Note: The minor diastereomer was not submitted for bioassay.)

8,10-Bis(p-methoxybenzyl)-8,10-diaza-1-[2′-methyl-1′-hydroxy-2′,3′-(isopropylidenedioxy)propyl]-2-oxabicyclo-[4.2.2]decane-7,9-dione (19, R_1 = CH_2Ph-p-OCH$_3$; R_2 = H; R_3, R_4 = $C(CH_3)_2$). To a stirred, −78 °C solution of 8c (R_1 = CH_2Ph-p-OCH$_3$, R_2 = R_3 = R_4 = H) (101 mg, 0.246 mmol, 1.0 equiv) containing HMPA (0.21 mL, 1.23 mmol, 5.0 equiv) in THF (4 mL) was added a solution of LDA (0.27 mmol, 1.1 equiv) in THF (2 mL). The mixture stirred for 42 min at −78 °C and chlorotrimethylsilane (47 μL, 0.369 mmol, 1.5 equiv) was added. The mixture was allowed to come to room temperature over a 45-min period and was recooled to −78 °C. A solution of LDA (0.61 mmol, 2.5 equiv) in THF (2 mL) was added and the solution stirred for 20 min at −78 °C and (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (177 mg, 1.23 mmol, 5 equiv) was added dropwise. The mixture was allowed to come to room temperature. After stirring 35 min at room temperature, tetra-n-butyl-ammonium fluoride trihydrate (466 mg, 1.47 mmol, 6 equiv) was added in one portion. After stirring 30 min at room temperature, the mixture was diluted with CH$_2$Cl$_2$, poured into brine, and thoroughly extracted with CH$_2$Cl$_2$. The combined extracts were dried over anhydrous Na$_2$SO$_4$, filtered, evaporated, and separated on a silica gel column (50 g of silica gel, eluted with 5% MeOH in CH$_2$Cl$_2$) to afford alcohol 19 (13 mg, 10% or 12% based on recovered starting material); other isomers (26.5 mg, 19.5% or 24.2% based on recovered starting material) and starting material (19.5 mg, 19.3%) were also obtained. ^1H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 1.199 (3 H, s), 1.370 (3 H, s), 1.409 (3 H, s), 1.748–1.886 (2 H, m), 1.966–2.071 (2 H, m), 2.778–2.869 (1 H, m), 3.483–3.574 (1 H, m), 3.781 (3 H, s), 3.807 (3 H, s), 3.875–4.999 (5 H, m), 4.689 (1 H, $^1/_2$AB q, J = 15.756 Hz), 6.655 (1 H, d, J = 9.571 Hz), 4.998 (1 H, $^1/_2$AB q, J = 15.756 Hz), 6.655 (1 H, d, J = 9.571 Hz), 6.753–6.889 (4 H, m), 7.179–7.266 (2 H, m), 7.486–7.538 (2 H, m); IR (NaCl, neat) 3320, 3050, 1670, 1610, 1515, 1435, 1405, 1300, 1245, 1175, 1105, 1070, 1030, 905, 730 cm^{-1}; mass spectrum, m/e 544 (M$^+$, 1.4), 539 (1.1), 497 (4.4), 441 (5.1), 121 (68.4), 59 (100).

8,10-Diaza-(2′-methyl-1′,2′,3′-trihydroxypropyl)-2-oxabi-cyclo[4.2.2]decane-7,9-dione (12b, R_1 = R_2 = R_3 = R_4 = H). To a stirred, room-temperature solution of alcohol 19 obtained above (10 mg, 0.018 mmol, 1 equiv) in CH$_2$Cl$_2$ (1 mL) was added DMAP (24 mg, 0.2 mmol, 11 equiv). After the mixture was stirred for 10 min, trifluoroacetic anhydride (25 μL, 0.18 mmol, 10 equiv) was added. The mixture was allowed to stir 2 h and directly separated on PTLC silica gel (eluted with 45% hexanes in EtOAc) to afford the 1′-O-trifluoroacetate (oil) (8.4 mg, 72% or 90% based on recovered starting material) and starting material (2 mg, 20%): ^1H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 0.599 (3 H, s), 1.184 (3 H, s), 1.211 (3 H, s), 1.603–2.206 (4 H, m), 3.186–3.288 (1 H, m), 3.524 (1 H, $^1/_2$AB q, J = 9.633 Hz), 3.791 (3 H, s), 3.804 (3 H, s), 3.810–5.051 (6 H, m), 4.396 (1 H, $^1/_2$AB q, J = 9.633 Hz), 6.145

(1 H, s), 6.775–7.595 (8 H, m); IR (NaCl, neat) 1785, 1680, 1610, 1510, 1360, 1300, 1245, 1210, 1170, 1145, 1025, 725 cm^{-1}.

To a stirred, room-temperature suspension of the trifluoroacetate (8.2 mg, 0.012 mmol, 1 equiv) in MeCN/H$_2$O (0.25 mL, 2:1 v/v) was added CAN (41 mg, 0.072 mmol, 6 equiv) in one portion. The mixture was stirred for 2 h at room temperature and directly separated on PTLC silica gel (eluted with 20% MeOH in CH$_2$Cl$_2$) to afford triol **12b** (1.5 mg, 45.5%) as an amorphous solid: mp 264 °C dec; ^{1}H NMR (270 MHz) (Me$_2$SO-d_6, Me$_4$Si) δ 1.155 (3H, s), 1.643–1.783 (2 H, m), 1.860–1.968 (2 H, m), 3.231–3.814 (5 H, m), 3.843 (1 H, d, J = 7.714 Hz), 4.474 (1 H, br s, D$_2$O exch), 5.166 (1 H, d, J = 7.714 Hz, D$_2$O exch), 5.176 (1 H, s, D$_2$O exch), 8.214 (1 H, d, J = 3.466 Hz, D$_2$O exch), 8.765 (1 H, s, D$_2$O exch); IR (NaCl, neat) 3340, 1670, 1600, 1555, 1540, 1415, 1055, 1020 cm^{-1}.

8,10-Bis(p-methoxybenzyl)-8,10-diaza-6-hydroxy-1-[2'-methyl-1'-hydroxy-2',3'-(isopropylidenedioxy)propyl]-2-oxabicyclo[4.2.2]decane-7,9-dione (20, R$_1$ = CH$_2$Ph-p-OCH$_3$; R$_2$ = OH; R$_3$, R$_4$ = C(CH$_3$)$_2$). To a stirred solution of alcohol 8 (R$_1$ = CH$_2$Ph-p-OCH$_3$, R$_2$ = OH, R$_3$ = R$_4$ = H) (41 mg, 0.096 mmol, 1 equiv) in THF (2 mL) at –100 °C was added n-BuLi (0.14 mL, 0.288 mmol, 3.0 equiv). After stirring of the mixture for 17 min at –100 °C, 2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde (28 μL, 0.192 mmol, 2.0 equiv) was added and the mixture continued to stir at –100 °C for 42 min. The cooling bath was removed, allowing the temperature to reach ambient over a 40-min period. The mixture was diluted with CH$_2$Cl$_2$, poured into saturated NaCl solution, and thoroughly extracted with CH$_2$Cl$_2$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, evaporated, and separated on PTLC silica gel (eluted with 10% hexanes in Et$_2$O) to afford 22 mg (41%) of diol **20** and 12.2 mg (22.6%) of a diastereomer.

Major diastereomer 20: ^{1}H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 0.806 (3 H, s), 1.352 (3 H, s), 1.364 (3 H, s), 1.640–1.767 (2 H, m), 1.850–2.105 (2 H, m), 2.755–2.835 (1 H, m), 3.490–3.585 (1 H, m), 3.733 (1 H, ^{1}/$_2$AB q, J = 8.37 Hz), 3.783 (6 H, s), 4.126 (1 H, ^{1}/$_2$AB q, J = 8.37 Hz), 4.586 (2 H, s), 4.606 (1 H, d, J = 10 Hz), 4.642 (1 H, ^{1}/$_2$AB q, J = 15.31 Hz), 4.969 (1 H, s), 5.091 (1 H, ^{1}/$_2$AB q, J = 15.31 Hz), 6.621 (1 H, d, J = 10 Hz), 6.810 (4 H, d, J = 8.6 Hz), 7.430 (2 H, d, J = 8.6 Hz), 7.507 (2 H, d, J = 8.6 Hz); IR (NaCl, neat) 3370, 3300, 3060, 1655, 1615, 1515, 1380, 1250, 1175, 1105, 1070, 1035, 910, 740 cm^{-1}; mass spectrum, m/e 570 (M$^+$, 0.4), 451 (1.7), 426 (1.1), 408 (4.6), 392 (0.6), 340 (3.4), 287 (1.5), 272 (3.6), 233 (3), 219 (4.9), 207 (2.1), 192 (2.6), 162 (8.4), 148 (3.3), 136 (14.), 121 (100), 115 (23.4).

Minor diastereomer 20: ^{1}H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 1.310 (3 H, s), 1.391 (3 H, s), 1.405 (3 H, s), 1.608–1.775 (2 H, m), 1.880–2.085 (2 H, s), 2.810–2.915 (1 H, m), 3.182 (1 H, d, J = 4.26), 3.41–3.375 (2 H, m), 3.675 (1 H, ^{1}/$_2$AB q, J = 8.86 Hz), 3.708 (1 H, ^{1}/$_2$AB q, J = 8.58 Hz), 3.753 (3 H, s), 3.761 (3 H, s), 3.957 (1 H, ^{1}/$_2$AB q, J = 8.58 Hz), 4.170 (1 H, ^{1}/$_2$AB q, J = 8.86 Hz), 4.604 (1 H, ^{1}/$_2$AB q, J = 13.2 Hz), 4.948 (1 H, s), 5.405 (1 H, ^{1}/$_2$AB q, J = 13.2 Hz), 6.75–6.821 (4 H, m), 7.365–7.486 (4 H, m), IR (NaCl, neat) 3430, 3070, 1665, 1615, 1520, 1380, 1245, 1175, 1110, 1055, 1035, 910, 730 cm^{-1}.

8,10-Diaza-6-hydroxy-(2'-methyl-1',2',3'-trihydroxypropyl)-2-oxabicyclo[4.2.2]decane-7,9-dione (12c, R$_1$ = R$_3$ = R$_4$ = H; R$_2$ = OH). To a stirred, room-temperature solution of diol 20 (R$_1$ = CH$_2$Ph-p-OCH$_3$, R$_2$ = OH, R$_3$, R$_4$ = C(CH$_3$)$_2$) (87 mg, 0.15 mmol, 1 equiv) in CH$_2$Cl$_2$ (6 mL) was added 4-(dimethylamino)pyridine (205 mg, 1.67 mmol, 11 equiv). After 15 min, trifluoroacetic anhydride (0.22 mL, 1.5 mmol, 10 equiv) was added. The reaction mixture was stirred at room temperature

for 35 min, evaporated, and separated on PTLC silica gel (eluted with 25% hexane in Et$_2$O) to afford the 1'-O-trifluoroacetate (25 mg, 25%) and 1',6-bis(O-trifluoroacetate) (57 mg, 50%).

1'-O-Trifluoroacetate: ^{1}H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 0.359 (3 H, s), 1.127 (3 H, s), 1.146 (3 H, s), 1.506–1.726 (2 H, m), 1.829–2.028 (1 H, m), 2.157–2.258 (1 H, m), 3.047 (1 H, ^{1}/$_2$AB q, J = 9.433 Hz), 3.154–3.234 (1 H, m), 3.709–3.885 (1 H, m), 3.772 (3 H, s), 3.791 (3 H, s), 4.221 (1 H, ^{1}/$_2$AB q, J = 9.433 Hz), 4.516 (1 H, ^{1}/$_2$AB q, J = 13.237 Hz), 4.582 (1 H, ^{1}/$_2$AB q, J = 14.804 Hz), 4.597 (1 H, ^{1}/$_2$AB q, J = 13.327 Hz), 4.712 (1 H, s, D$_2$O exch), 5.024 (1 H, ^{1}/$_2$AB q, J = 14.804 Hz), 6.074 (1 H, s), 6.784–6.884 (4 H, m), 7.381–7.645 (4 H, m); IR (NaCl, neat) 3350, 1785, 1655, 1610, 1510, 1365, 1245, 1210, 1165, 1145, 1030 cm^{-1}.

Exhaustive reacetylation of this compound produced the 1',6-bis(O-trifluoroacetate).

1',6-Bis(O-trifluoroacetate): ^{1}H NMR (270 MHz) (CDCl$_3$, Me$_4$Si) δ 0.360 (3 H, s), 1.125 (3 H, s), 1.144 (3 H, s), 1.497–1.703 (2 H, m), 1.937–2.071 (1 H, m), 2.163–2.251 (1 H, m), 3.047 (1 H, ^{1}/$_2$AB q, J = 9.533 Hz), 3.134–3.243 (1 H, m), 3.529–3.614 (1 H, m), 3.769 (3 H, s), 3.788 (3 H, s), 4.221 (1 H, ^{1}/$_2$AB q, J = 9.533 Hz), 4.497–5.050 (4 H, m), 6.073 (1 H, s), 6.691 (4 H, m), 7.362–7.643 (4 H, m); IR (NaCl, neat) 1785, 1655, 1605, 1505, 1455, 1310, 1240, 1205, 1160, 1100, 1025 cm^{-1}.

To a stirred, room-temperature suspension of the 1',6-bis(O-trifluoroacetate) obtained above (18 mg, 0.027 mmol, 1 equiv) in 0.5 mL of CH$_3$CN/H$_2$O (2/1, v/v) was added ceric ammonium nitrate (89 mg, 0.162 mmol, 6 equiv). The reaction mixture was stirred at room temperature for 2 h, evaporated, and separated twice on PTLC silica gel (1 eluted with 25% EtOAc in Et$_2$O; 2 eluted with 20% MeOH in CH$_2$Cl$_2$) to afford the tetrol **12c** (3.7 mg., 47.4%) as a waxy solid. The same tetrol could also be obtained from the bis(O-trifluoroacetate) as described below.

To a stirred, room temperature suspension of the bisacetate (19.5 mg, 0.025 mmol, 1 equiv) in 0.5 mL of CH$_3$CN/H$_2$O (2/1, v/v) was added ceric ammonium nitrate (84 mg, 0.15 mmol, 6 equiv). The reaction mixture was stirred at room temperature for 2 h, evaporated, and separated twice on PTLC silica gel (1 eluted with 25% EtOAc in Et$_2$O; 2 eluted with 20% MeOH in CH$_2$Cl$_2$) to afford 3 mg (41.4%) of tetrol **12c**: ^{1}H NMR (270 MHz) Me$_2$SO-d_6, Me$_4$Si) δ 1.151 (3 H, s), 1.617–1.757 (2 H, m), 1.803–2.029 (2 H, m), 3.343–3.531 (2 H, m), 3.671–3.777 (2 H, m), 3.850 (1 H, d, J = 7.045 Hz), 4.430–4.452 (1 H, m, D$_2$O exch), 5.182 (1 H, d, J = 7.045 Hz, D$_2$O exch), 5.199 (1 H, s, D$_2$O exch), 6.534 (1 H, br s, D$_2$O exch), 8.542 (1 H, s, D$_2$O exch), 8.839 (1 H, s, D$_2$O exch); IR (NaCl, neat) 3320, 1670, 1390, 1115, 1065, 1015 cm^{-1}.