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# Novel Ring Transformations for 5,5a-Dibromobicyclomycin and Derivatives

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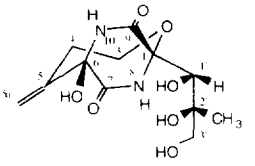
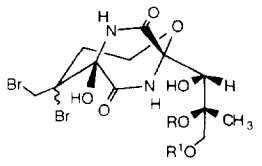
**Abstract**. Both 5,5a-dibromobicyclomycin (**2**) and 5,5a-dibromobicyclomycin-2',3'-acetonide (**3**) were observed to undergo unique ring fragmentation processes under basic conditions. Treatment of **2** and **3** with DBU gave (3*S*, 4*S*, 5*S*)-3-(3-bromobutoxy-3-ene)-4-hydroxy-5-hydroxymethyl-5-methyl-3-oxamido-γ-lactone (**4**) and (1'*S*, 2'*S*, 6*S*)-6-(3-bromobutoxy-3-ene)-6-(1-hydroxy-2,3-*O*,*O*-isopropylidene-2-methyl-2,3-dioxapropyl)-piperazine-2,3,4-trione (**5**) in moderate yields. Dissolution of **3** with KF and 18-crown-6 in DMF yielded **5** and (1*S*, 5*R*, 1'*S*, 2'*S*)-1-bromomethyl)-8,10-diaza-1-(1-hydroxy-2,3-*O*,*O*-isopropylidene-2-methyl-2,3-dioxapropyl)-2-oxabicyclo[3.3.2]decan-6,7,9-trione (**6**). The facility of these ring cleavage transformations has been attributed to the favorable stereoelectronic arrangement of the C(6) hydroxy and C(5a) bromo groups in **2** and **3** for elimination.

Bicyclomycin (**1**) is a structurally rich antibiotic possessing a [4.2.2] bicyclic ring system that contains a piperazinedione unit, a hemiaminal linkage at C(6), an exomethylene group at C(5), and a triol unit appended at the C(1) bridgehead position.[1] Since its discovery in 1972,[2] various mechanistic proposals have been advanced for the mode of action of **1**.[3-5] Most of these hypotheses have suggested that bicyclomycin reacts with a nucleophilic residue within a protein, and that bonding occurs at the C(5)-C(5a) exomethylene group in the antibiotic. Indeed, we have shown that **1** reacted with select thiols and amines at near neutral "pH" values to give C(5a)-substituted products.[5] We have further demonstrated that the primary drug target in *Escherichia coli* is the rho dependent transcription termination factor[6] and that bicyclomycin inhibits rho poly(C)-stimulated hydrolysis of ATP by a noncompetitive, reversible pathway with respect to ATP.[7] In an effort to provide additional information concerning bicyclomycin function we recently prepared 5,5a-dibromo-bicyclomycin[8] (**2**) and the corresponding acetonide **3**. In this paper, we report a series of novel, base-initiated ring rearrangements for **2** and **3**. These reactions add to a series of interesting ring transformations that have been reported for bicyclomycin and analogues proceeding under basic,[9,10] near neutral pH,[5a] and acidic[11,12] conditions.



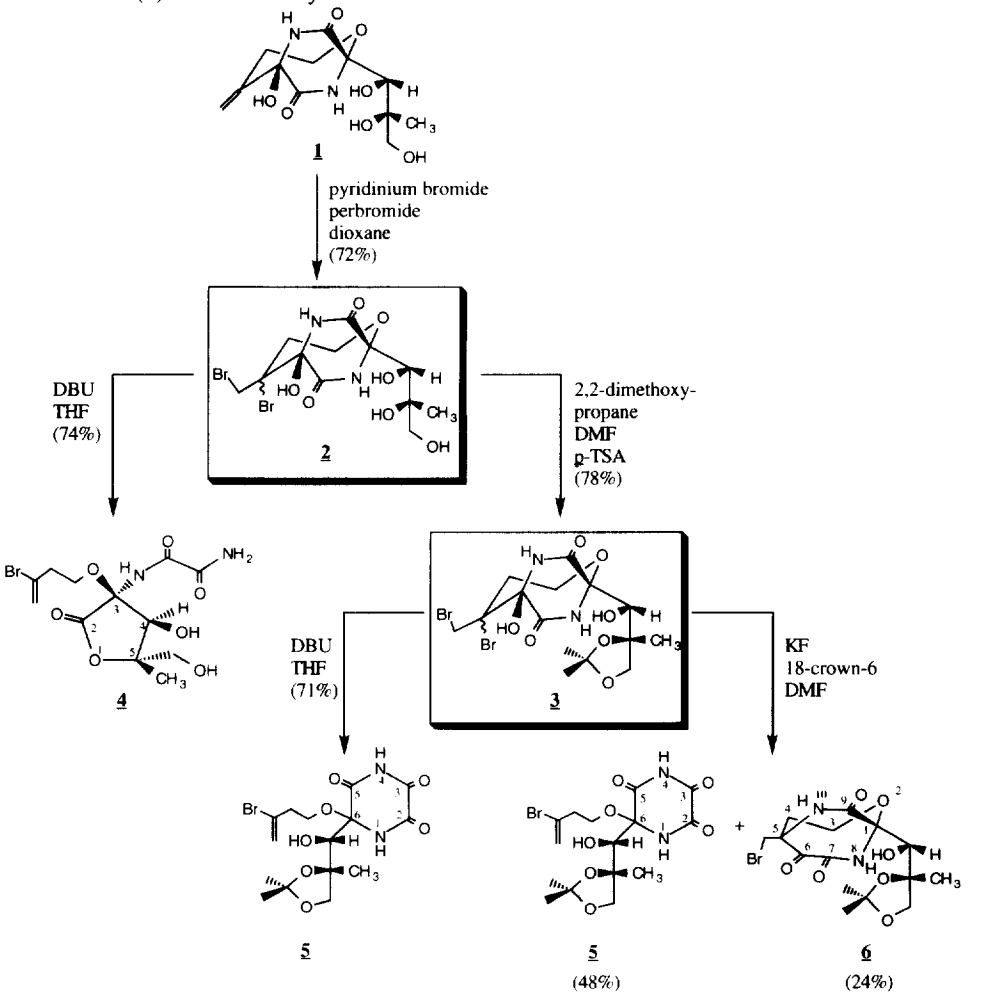
**1**



**2** R, R$^1$ = H
**3** R, R$^1$ = C(CH$_3$)$_2$

## RESULTS AND DISCUSSION

Synthesis of 5,5a-dibromobicyclomycin (**2**) was accomplished in 72% yield by treatment of **1** with pyridinium bromide perbromide in dioxane.[8] $^{13}C$ NMR analysis of **2** indicated that it consisted of a 9:1 mixture of diastereomers. Addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to a tetrahydrofuran (THF) solution of **2** (room temperature, 45 min) generated the rearranged adduct **4** in 74% yield (Scheme 1). Product verification was accomplished using IR, $^1H$ NMR, $^{13}C$ NMR, COSY, HMQC, HMBC, MS, and X-ray spectroscopy (Figure 1). A distinctive feature in the $^1H$ NMR spectrum for **4** was the broad triplet at $\delta$ 2.72, the multiplet centered at $\delta$ 3.86, and the two vinylic signals at $\delta$ 5.47 and $\delta$ 5.74. These resonances have been attributed to the C(3) 3-bromobutoxy-3-ene side chain.




Scheme 1. Base-initiated Products from 5,5a-Dibromobicyclomycins **2** and **3**.

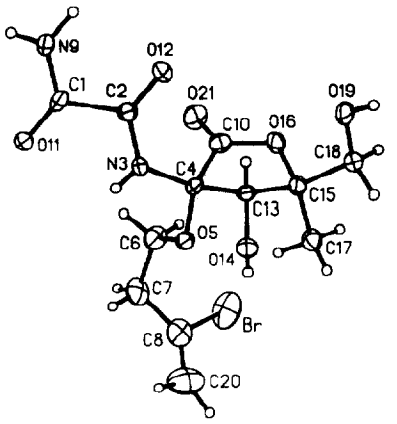
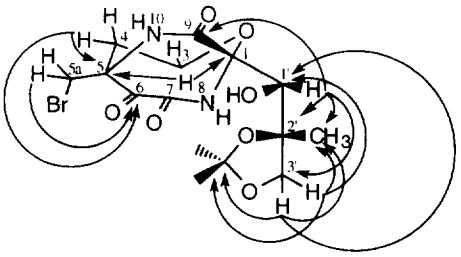



Figure 1. ORTEP drawing for **4** showing the atom numbering scheme. The thermal ellipsoids are 50% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter. Selected bond distances (Å) are as follows: C(4)-C(10), 1.562 (6); C(10)-O(16), 1.340 (5); C(15)-O(16), 1.485 (5); C(13)-C(15), 1.522 (6); C(4)-C(13), 1.535 (6). Selected angles (deg) are as follows: C(10)-C(4)-C(13), 100.3 (3); C(4)-C(10)-O(16), 109.2 (4); C(10)-O(16)-C(15), 111.1 (3); C(13)-C(15)-O(16), 102.0 (3); C(4)-C(13)-C(15), 103.0 (4).

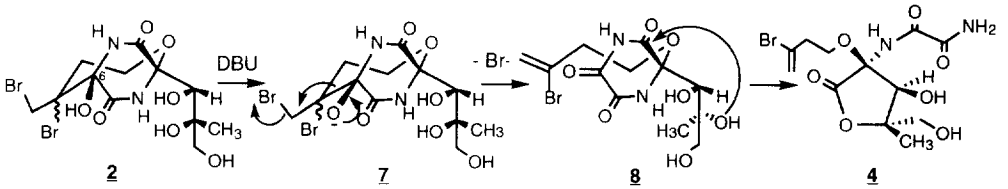
The spectral data for **4** demonstrated that dehydrobromination of **2** proceeded with scission of the C(5)-C(6) bond and lactonization of the C(2') hydroxy group. This finding led us to convert **2** to the C(2'),C(3')-protected acetonide **3**. Treatment of **3** with DBU in THF (room temperature, 40 min) gave only the ring-cleaved piperazinetrione **5** in 71% yield. The $^{1}H$ NMR spectrum for **5** contained the characteristic resonances for the 3-bromobutoxy-3-ene side chain, while three downfield signals (155.4, 156.8, 168.4 ppm) were detected in the $^{13}C$ NMR spectrum for the piperazinetrione ring system. These $^{13}C$ NMR signals were similar to previously observed resonances for piperazinetriones.[13,14] The IR and MS spectra and the HMQC and HMBC experiments were consistent with the proposed structure. Use of KF and 18-crown-6 in place of DBU led to a binary mixture of **5** (48%) and **6** (24%). The $^{13}C$ NMR spectrum for **6** showed three carbonyl resonances located at 165.1, 172.8, and 198.7 ppm for the diazepinetrione ring. In the HMBC experiment, three-bond connectivities were observed for the C(6) carbonyl resonance (198.7 ppm) and the C(4) proton signal at $\delta$ 2.06, and for the C(6) carbonyl peak and the C(5a) proton peak located at $\delta$ 3.55 (Figure 2).



6

Figure 2. Key HMBC responses observed for compound **6**.

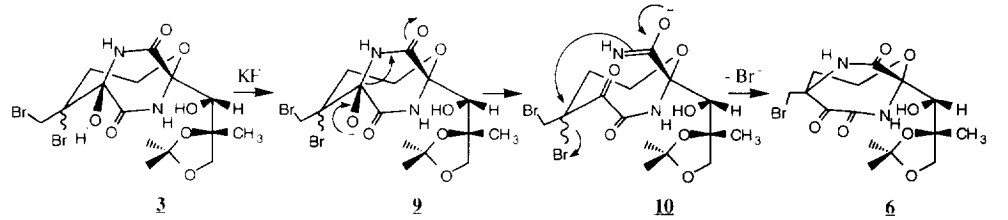
Our findings that the piperazinedione ring in **2** and **3** rapidly underwent rearrangement upon treatment with base in aprotic solvents suggested that both reactions were initiated by ionization of the C(6) hydroxy group. The DBU-mediated conversion of **2** to **4** is believed to proceed by abstraction of the C(6) hydroxy proton followed by C(5)-C(6) bond cleavage and halide elimination to give piperazinetrione **8** (Scheme 2). Lactonization of the C(2') hydroxy group in **8** then produces **4**. This pathway is in agreement with the isolation of piperazinetrione **5** upon treatment of C(2'),C(3')-acetonide **3** with DBU. A similar lactonization process has recently been observed for the oxidative fragmentation of bicyclomycin-5-norketone.[14]



2 7 8 4

Scheme 2. Proposed Pathway for Conversion of **2** to **4**.

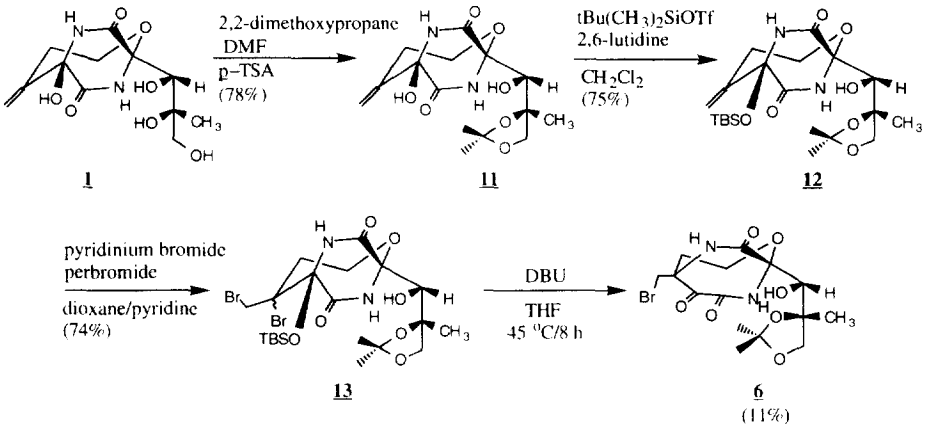
The isolation of both **5** and **6** in the KF-mediated reaction of **3** indicated that a second pathway was competitive with piperazinetrione ring formation. We suspect that **6** is produced by initial generation of the anion **9**, cleavage of the C(6)-N(10) bond to give amide anion **10**, and then displacement of the C(5) bromo group (Scheme 3).[15] Other mechanisms for this transformation are conceivable.



3 9 10 6

Scheme 3. Proposed Pathway for Conversion of **3** to **6**.

Consistent with the proposed involvement of the C(6) hydroxy group in these novel ring rearrangements there was no reaction for the C(6) protected *tert*-butyldimethylsilyl ether **13** upon treatment with DBU in THF (room temperature, 24 h) (Scheme 4). Elevation of the reaction temperature to 45 °C (8 h), however, led to a complex mixture in which **6** was isolated in 11% yield. We have attributed the production of **6** to the deprotection of the C(6) silyl ether under the reaction conditions.




Scheme 4. Synthesis and Reactivity of 5,5a-Dibromobicyclomycin (**13**).

The observed reactivity of 5,5a-dibromobicyclomycins **2** and **3** with base demonstrate the facility with which these compounds undergo ring cleavage and dehydrobromination. The ease of these transformations has been attributed to the favorable stereoelectronic arrangement of the C(6) hydroxy and C(5a) bromo groups in **2** and **3** for elimination.

## EXPERIMENTAL SECTION

*General Methods:* FT-IR spectra were run on an ATI Mattson Genesis Series FT-IR infrared spectrophotometer. Absorption values are expressed in wave numbers ($cm^{-1}$). Proton ($^1H$ NMR) and carbon ($^{13}C$ NMR) nuclear magnetic resonance spectra were taken on General Electric QE 300 NMR instruments. HMBC and HMQC experiments were performed using a Bruker AMX 600 MHz instrument. Chemical shifts ($\delta$) are in parts per million (ppm) relative to $Me_4Si$, and coupling constants ($J$ values) are in Hertz. All chemical ionization and FAB mass spectral investigations were conducted at The University of Texas at Austin by Dr. M. Moini on a Finnegan MAT TSQ-70 instrument.

The solvents and reagents were of the best commercial grade available and were used without further purification unless noted. Tetrahydrofuran was distilled from Na metal and benzophenone, and methylene chloride was distilled from $P_2O_5$. Thin-layer chromatography were run on precoated silica gel GHLF slides (20 X 20 cm; Analtech No. 21251).

*Preparation of 5,5a-Dibromobicyclomycin*[8] *(2).* To an anhydrous dioxane solution (10 mL) of **1** (20 mg, 0.066 mmol) was added pyridinium bromide perbromide (42 mg, 0.132 mmol) over a 45 min period. The solution was stirred at room temperature (90 min), filtered and the solvent evaporated *in vacuo*. The residue was dissolved in methanol and purified by preparative TLC (20% methanol-chloroform) to provide **2** as a white solid: 22 mg (72%); mp 133-135 °C (lit.[8] mp 128-133 °C); $R_f$ 0.44 (20% $CH_3OH$-$CHCl_3$); IR (KBr)

3414, 3256, 2941, 1693, 1396, 1085, 1056 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 1.33 (s, 3 H, C(2')$CH_3$), 2.29-2.38 (m, 1 H, C(4)*H*H'), 2.60-2.68 (m, 1 H, C(4)H*H'*), 3.50 (d, *J* = 11.4 Hz, 1 H, C(3')*H*H'), 3.64 (d, *J* = 11.4 Hz, 1 H, C(3')H*H'*), 3.90-3.98 (m, 1 H, C(3)*H*H'), 4.04 (s, 1 H, C(1')H), 4.05 (d, *J* = 11.4 Hz, 1 H, C(5a)*H*H'), 4.14-4.22 (m, 1 H, C(3)H*H'*), 4.20 (d, *J* = 11.4 Hz, 1 H, C(5a)H*H'*); $^{13}C$ NMR ($CD_3OD$) major diastereomer: 22.4 (C(2')*C*$H_3$), 38.5 (C(4)), 40.3 (C(5a)), 59.5 (C(3)), 66.6 (C(3')), 70.4 (C(5)), 72.5 (C(1')), 76.4 (C(2')), 83.0 (C(6)), 87.4 (C(1)), 167.9 and 168.1 (C(7), C(9)) ppm; $^{13}C$ NMR ($CD_3OD$) minor diastereomer: 40.3 (C(5a)), 70.4 (C(5)), 83.0 (C(6)) ppm, the other signals were not detected; MS (-FAB) $[M-1]^-$: 463 (55%, $C_{12}H_{17}{}^{81}Br_2N_2O_7$), 461 (100%, $C_{12}H_{17}{}^{79}Br^{81}BrN_2O_7$), 459 (64%, $C_{12}H_{17}{}^{79}Br_2N_2O_7$); $M_r$ (-CI) 460.941 47 $[M-1]^-$ (calcd for $C_{12}H_{17}{}^{79}Br^{81}BrN_2O_7$ 460.938 20).

*Preparation of (3S, 4S, 5S)-3-(3-Bromobutoxy-3-ene)-4-hydroxy-5-hydroxymethyl-5-methyl-3-oxamido-γ-lactone (4).* To an anhydrous THF solution (5 mL) of **2** (10 mg, 0.022 mmol) was added DBU (3.3 mg, 0.022 mmol). The solution was stirred at room temperature (45 min), filtered, and the solvent was removed *in vacuo*. The residue was dissolved in methanol and purified by preparative TLC (20% methanol-chloroform) to provide **4** as a white solid: 6 mg (74%); mp 132-134°C; $R_f$ 0.54 (20% $CH_3OH$-$CHCl_3$); IR (KBr) 3401, 3313, 2959, 1785, 1684, 1526, 1398, 1232, 1079 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 1.39 (s, 3 H, C(5)$CH_3$), 2.70-2.74 (br t, 2 H, C(3)OC$H_2$C$H_2$), 3.53 (d, *J* = 12.6 Hz, 1 H, C(5)C*H*H'), 3.66 (d, *J* = 12.6 Hz, 1 H, C(5)CH*H'*), 3.78-3.94 (m, 2 H, C(3)OC$H_2$C$H_2$), 4.60 (s, 1 H, C(4)H), 5.47 (d, *J* = 1.1 Hz, 1 H, C(3)O$(CH_2)_2$C(Br)C*H*H'), 5.74 (d, *J* = 1.1 Hz, 1 H, C(3)O$(CH_2)_2$C(Br)CH*H'*); $^{13}C$ NMR ($CD_3OD$) 17.5 (C(5)*C*$H_3$), 42.2 (C(3)OC$H_2$C$H_2$), 63.3 (C(3)O*C*$H_2$C$H_2$), 66.1 (C(5)*C*$H_2$), 73.1 (C(4)), 85.6 (C(3)), 88.9 (C(5)), 120.0 (C(3)O$(CH_2)_2$C(Br)*C*$H_2$), 131.4 (C(3)O$(CH_2)_2$*C*(Br)C$H_2$), 162.4 and 162.6 (C(3)N(H)*C*(O)*C*(O)$NH_2$), 169.5 (C(2)) ppm; the spectral assignments were in agreement with the COSY, HMQC and HMBC NMR data; MS (+CI) $[M+1]^+$: 383 (100%, $C_{12}H_{18}{}^{81}BrN_2O_7$), 381 (96%, $C_{12}H_{18}{}^{79}BrN_2O_7$); $M_r$ (+CI) 381.030 70 $[M+1]^+$ (calcd for $C_{12}H_{18}{}^{79}BrN_2O_7$ 381.029 74). The proposed structure was confirmed by X-ray crystallographic analysis (Figure 1).

*Preparation of 5,5a-Dibromobicyclomycin-2',3'-acetonide (3).* A dimethylformamide solution (1 mL) containing **2** (20 mg, 0.043 mmol), 2,2-dimethoxypropane (1.5 mL), and a few crystals of *p*-toluenesulfonic acid monohydrate was heated at 55 °C (2 h) under Ar. The solvent was removed *in vacuo* and the residue was dissolved in methanol and purified by preparative TLC (10% methanol-chloroform) to provide **3** as a white solid: 17 mg (78%); mp 145-146 °C; $R_f$ 0.43 (10% $CH_3OH$-$CHCl_3$); IR (KBr) 3407, 3275, 2936, 1694, 1391, 1089, 1052 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 1.37 (s, 3 H, C(2')$CH_3$), 1.45 (s, 6 H, C$(CH_3)_2$), 2.38-2.47 (m, 1 H, C(4)*H*H'), 2.53-2.61 (m, 1 H, C(4)H*H'*), 3.71 (d, *J* = 8.7 Hz, 1 H, C(3')*H*H'), 3.90-4.05 (m, 1 H, C(3)*H*H'), 3.99 (d, *J* = 11.4 Hz, 1 H, C(5a)*H*H'), 4.11 (s, 1 H, C(1')H), 4.11-4.20 (m, 1 H, C(3)H*H'*), 4.21 (d, *J* = 11.4 Hz, 1 H, C(5a)H*H'*), 4.43 (d, *J* = 8.7 Hz, 1 H, C(3')H*H'*); $^{13}C$ NMR ($CD_3OD$) major diastereomer: 25.3 (C(2')*C*$H_3$), 26.8 (C(*C*$H_3$)$_2$), 27.9 (C(*C*$H_3$)$_2$), 40.3 (C(4)), 41.9 (C(5a)), 62.3 (C(3)), 73.0 (C(3') or C(5)), 73.3 (C(3') or C(5)), 74.3 (C(1')), 84.8 (C(6)), 86.5 (C(2')), 88.8 (C(1)), 111.6 (*C*$(CH_3)_2$), 169.5 and 169.6 (C(7), C(9)) ppm; $^{13}C$ NMR ($CD_3OD$) minor diastereomer: 42.1 (C(5a)), 73.1 (C(3') or C(5)) ppm, the other signals were not detected; MS (+CI) $[M+1]^+$: 505 (44%, $C_{15}H_{23}{}^{81}Br_2N_2O_7$), 503 (100%, $C_{15}H_{23}{}^{79}Br^{81}BrN_2O_7$), 501 (69%, $C_{15}H_{23}{}^{79}Br_2N_2O_7$); $M_r$ (+CI) 502.983 57 $[M+1]^+$ (calcd for $C_{15}H_{23}{}^{79}Br^{81}BrN_2O_7$ 502.985 15); $M_r$ (+CI) 500.984 86 $[M+1]^+$ (calcd for $C_{15}H_{23}{}^{79}Br_2N_2O_7$ 500.987 20).

*Preparation of (1'S, 2'S, 6S)-6-(3-Bromobutoxy-3-ene)-6-(1-hydroxy-2,3-O,O-isopropylidene-2-methyl-2,3-dioxapropyl)-piperazine-2,3,5-trione (5).* To an anhydrous THF solution (5 mL) of **3** (10 mg, 0.020 mmol) was added DBU (3.6 mg, 0.024 mmol), and the solution was stirred at room temperature (45 min). The mixture was filtered and the solvent was removed *in vacuo*. The residue was dissolved in methanol and purified by preparative TLC (10% methanol-chloroform) to provide **5** as a white solid: 6 mg (71%); mp 175-178 °C; $R_f$ 0.43 (10% $CH_3OH$-$CHCl_3$); IR (KBr) 3402, 3275, 2925, 2851, 1698, 1669, 1376, 1143, 1051, 881

$cm^{-1}$; $^1H$ NMR ($CDCl_3$:$CD_3OD$, 4:1) δ 1.31 (s, 3 H, C(2')$CH_3$), 1.38 (s, 3 H, C($CH_3$)$_2$), 1.39 (s, 3 H, C($CH_3$)$_2$), 2.68 (t, $J$ = 6.3 Hz, 2 H, C(6)OC$H_2$C$H_2$), 3.44-3.50 (m, 1 H, C(6)OC*H*H'C$H_2$), 3.69 (d, $J$ = 8.6 Hz, 1 H, C(3')*H*H'), 3.74-3.78 (m, 1 H, C(6)OCH*H'*C$H_2$), 3.87 (s, 1 H, C(1')H), 4.30 (d, $J$ = 8.6 Hz, 1 H, C(3')H*H'*), 5.46 (d, $J$ = 1.2 Hz, 1 H, C(6)O(C$H_2$)$_2$C(Br)C*H*H'), 5.67 (d, $J$ = 1.2 Hz, 1 H, C(6)O(C$H_2$)$_2$C(Br)CH*H'*); $^{13}C$ NMR ($CDCl_3$:$CD_3OD$, 4:1) 24.0 (C(2')*C*H$_3$), 26.5 (C(*C*H$_3$)$_2$), 27.6 (C(*C*H$_3$)$_2$), 41.4 (C(6)OC$H_2$C$H_2$), 63.2 (C(6)O*C*H$_2$CH$_2$), 71.8 (C(3')), 75.5 (C(1')), 84.1 (C(2')), 91.6 (C(6)), 110.4 (*C*(CH$_3$)$_2$), 119.5 (C(6)O(C$H_2$)$_2$C(Br)*C*H$_2$), 129.6 (C(6)O(C$H_2$)$_2$*C*(Br)CH$_2$), 155.4 and 156.8 (C(2), C(3)), 168.4 (C(5)) ppm; the spectral assignments were in agreement with the COSY, HMQC and HMBC NMR data; MS (+CI) $[M+1]^+$: 423 (100%, $C_{15}H_{22}{}^{81}BrN_2O_7$), 421(91%, $C_{15}H_{22}{}^{79}BrN_2O_7$); $M_r$ (+CI) 421.060 04 $[M+1]^+$ (calcd for $C_{15}H_{22}{}^{79}BrN_2O_7$ 421.061 04).

*Treatment of* ***3*** *with KF. Preparation of* ***5*** *and (1S, 5R, 1'S, 2'S)-5-(Bromomethyl)-8,10-diaza-1-(1-hydroxy-2,3-O,O-isopropylidene-2-methyl-2,3-dioxapropyl)-2-oxabicyclo[3.3.2]decan-6,7,9-trione* ***(6)*****.** To an anhydrous dimethylformamide solution (1 mL) of **3** (10 mg, 0.020 mmol) and a few crystals of 18-crown-6 was added KF (1.2 mg, 0.020 mmol). The solution was stirred at room temperature (90 min), filtered and the solvent removed *in vacuo*. The residue was then dissolved in methanol and purified by preparative TLC (10% methanol-chloroform) to provide **5** (4 mg, 48%) as an oily solid and **6** (2 mg, 24%) as a white solid.

Compound **5**: $R_f$ 0.43 (10% $CH_3OH$-$CHCl_3$); $^1H$ NMR ($CD_3OD$) δ 1.32 (s, 3 H, C(2')$CH_3$), 1.37 (s, 3 H, C($CH_3$)$_2$), 1.39 (s, 3 H, C($CH_3$)$_2$), 2.73 (t, $J$ = 6.3 Hz, 2 H, C(6)OC$H_2$C$H_2$), 3.46-3.51 (m, 1 H, C(6)OC*H*H'C$H_2$), 3.67-3.72 (m, 1 H, C(6)OCH*H'*C$H_2$), 3.74 (d, $J$ = 8.1 Hz, 1 H, C(3')*H*H'), 3.90 (s, 1 H, C(1')H), 4.26 (d, $J$ = 8.1 Hz, 1 H, C(3')H*H'*), 5.47 (s, 1 H, C(6)O(C$H_2$)$_2$C(Br)C*H*H'), 5.78 (s, 1 H, C(6)O(C$H_2$)$_2$C(Br)CH*H'*), an additional peak at δ 3.61 was observed for 18-crown-6.

Compound **6**: mp 146-150 °C; $R_f$ 0.53 (10% $CH_3OH$-$CHCl_3$); IR (KBr) 3438, 2987, 2933, 1731, 1687, 1540, 1419, 1381, 1257, 881 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 1.32 (s, 3 H, C(2')$CH_3$), 1.35 (s, 6 H, C($CH_3$)$_2$), 2.06 (dd, $J$ = 5.4, 8.0 Hz, 1 H, C(4)*H*H'), 2.86-2.92 (m, 1 H, C(4)H*H'*), 3.55 (d, $J$ = 10.8 Hz, 1 H, C(5a)*H*H'), 3.56-3.68 (m, 1 H, C(3)*H*H'), 3.69 (d, $J$ = 8.9 Hz, 1 H, C(3')*H*H'), 3.79 (d, $J$ = 10.8 Hz, 1 H, C(5a)H*H'*), 4.04 (dd, $J$ = 5.4, 8.0 Hz, 1 H, C(3)H*H'*), 4.18 (d, $J$ = 8.9 Hz, 1 H, C(3')H*H'*), 4.29 (s, 1 H, C(1')H); $^{13}C$ NMR ($CD_3OD$) 20.7 (C(2')*C*H$_3$), 27.4 (C(*C*H$_3$)$_2$), 27.3 (C(*C*H$_3$)$_2$), 35.3 (C(5a)), 44.3 (C(4)), 64.4 (C(3)), 66.8 (C(5)), 72.3 (C(1')), 75.6 (C(3')), 83.8 (C(2')), 91.1 (C(1)), 111.5 (*C*(CH$_3$)$_2$), 165.1 (C(7)), 172.8 (C(9)), 198.7 (C(6)) ppm; the spectral assignments were in agreement with the COSY, HMQC, and HMBC NMR data; MS (+CI) $[M+1]^+$: 423 (96%, $C_{15}H_{21}{}^{81}BrN_2O_7$), 421 (100%, $C_{15}H_{21}{}^{79}BrN_2O_7$); $M_r$ (+CI) 423.05928 $[M+1]^+$ (calcd for $C_{15}H_{21}{}^{81}BrN_2O_7$ 423.05899).

*Preparation of 6-(1,1-Dimethylethyl)dimethylsilylbicyclomycin-2',3'-acetonide* ***(12)*****.** To an anhydrous methylene chloride solution (5 mL) of 2,6-lutidine (37 mg, 0.352 mmol) and **11**[16] (20 mg, 0.058 mmol) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (65 mg, 0.244 mmol) at -10 °C. The solution was stirred (150 min) during which time the temperature was slowly warmed to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in methanol (5 mL) and stirred (90 min) at room temperature. The solution was concentrated *in vacuo* and the residue dissolved in methanol and purified by preparative TLC (3X, 35% ethyl acetate-hexanes) to provide **12** as a white solid: 20 mg (75%); mp 85-87 °C; $R_f$ 0.34 (40% ethyl acetate-hexanes); IR (KBr) 3422, 2932, 2858, 1699, 1386, 1258, 1212, 1171, 1074, 1044, 865, 840, 784 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 0.15 (s, 3 H, Si(C$H_3$)$_2$), 0.22 (s, 3 H, Si(C$H_3$)$_2$), 0.96 (s, 9 H, SiC(C$H_3$)$_3$), 1.39 (s, 3 H, C(2')C$H_3$), 1.42 (s, 3 H, C(C$H_3$)$_2$), 1.45 (s, 3 H, C(C$H_3$)$_2$), 2.60-2.64 (m, 2 H, C(4)H$_2$), 3.72 (d, $J$ = 8.4 Hz, 1 H, C(3')*H*H'), 3.84-3.91 (m, 2 H, C(3)H$_2$), 4.15 (s, 1 H, C(1')H), 4.45 (d, $J$ = 8.4 Hz, 1 H, C(3')H*H'*), 5.12 (s, 1 H, C(5a)*H*H'), 5.54 (s, 1 H, C(5a)H*H'*); $^{13}C$ NMR ($CD_3OD$) -3.3 (Si(C$H_3$)$_2$), -3.0 (Si(C$H_3$)$_2$), 19.2 (Si*C*(CH$_3$)$_3$), 25.0 (C(2')*C*H$_3$), 26.4 (SiC(*C*H$_3$)$_3$), 26.9 (C(*C*H$_3$)$_2$), 28.2 (C(*C*H$_3$)$_2$), 36.3 (C(4)), 66.3 (C(3)), 72.9 (C(3')), 73.3 (C(1')), 85.0 (C(6)), 86.5 (C(2')), 89.0 (C(1)), 111.7

($C(CH_3)_2$), 116.7 (C(5a)), 150.2 (C(5)), 168.6 (C(9)), 170.9 (C(7)) ppm; MS (+CI) 457 $[M+1]^+$; $M_r$ (+CI) 457.236 63 $[M+1]^+$ (calcd for $C_{21}H_{37}N_2O_7Si$ 457.237 01).

*Preparation of 5,5a-Dibromo-6-(1,1-dimethylethyl)dimethylsilylbicyclomycin-2',3'-acetonide (13).* To an anhydrous binary dioxane-pyridine solution (4 mL) containing **12** (20 mg, 0.044 mmol) was added pyridinium bromide perbromide (42 mg, 0.132 mmol). The solution was stirred at room temperature (24 h) and then the solvent was removed *in vacuo*. The residue was dissolved in methanol and purified by preparative TLC (35% ethyl acetate-hexanes) to provide **13** as a white solid: 20 mg (74%); mp 95-97 °C; $R_f$ 0.46 (40% ethyl acetate-hexanes); IR (KBr) 3447, 3365, 2984, 2932, 2858, 1704, 1385, 1254, 1194, 1137, 1084, 1049, 873, 841, 787, 672, 601 $cm^{-1}$; $^1H$ NMR ($CD_3OD$) δ 0.14 (s, 3 H, $Si(CH_3)_2$), 0.30 (s, 3 H, $Si(CH_3)_2$), 0.97 (s, 9 H, $SiC(CH_3)_3$), 1.39 (s, 3 H, $C(2')CH_3$), 1.46 (s, 6 H, $C(CH_3)_2$), 2.40-2.49 (m, 1 H, C(4)*H*H'), 2.55-2.63 (m, 1 H, C(4)H*H'*), 3.73 (d, $J$ = 8.4 Hz, 1 H, C(3')*H*H'), 3.96-4.05 (m, 1 H, C(3)*H*H'), 3.98 (d, $J$ = 11.1 Hz, 1 H, C(5a)*H*H'), 4.09-4.19 (m, 1 H, C(3)H*H'*), 4.13 (s, 1 H, C(1')H), 4.32 (d, $J$ = 11.1 Hz, 1 H, C(5a)H*H'*), 4.44 (d, $J$ = 8.4 Hz, 1 H, C(3')H*H'*); $^{13}C$ NMR ($CD_3OD$) -3.2 ($Si(CH_3)_2$), -3.0 ($Si(CH_3)_2$), 19.5 ($SiC(CH_3)_3$), 25.3 ($C(2')CH_3$), 26.4 ($SiC(CH_3)_3$), 26.5 ($C(CH_3)_2$), 27.9 ($C(CH_3)_2$), 40.0 (C(4)), 41.6 (C(5a)), 62.3 (C(3)), 72.5 (C(3')), 73.1 (C(5)), 74.4 (C(1')), 86.5 (C(2')), 87.4 (C(6)), 88.6 (C(1)), 111.6 ($C(CH_3)_2$), 168.1 (C(7), C(9)) ppm; MS (+CI) $[M+1]^+$: 619 (56%, $C_{21}H_{36}{}^{81}Br_2N_2O_7Si$), 617 (100%, $C_{21}H_{36}{}^{79}Br{}^{81}BrN_2O_7Si$), 615 (48%, $C_{21}H_{36}{}^{79}Br_2N_2O_7Si$); $M_r$ (+CI) 615.073 30 $[M+1]^+$ (calcd for $C_{21}H_{36}{}^{79}Br_2N_2O_7Si$ 615.073 68).

*Treatment of 13 with DBU.* To an anhydrous THF solution (2 mL) of **13** (13 mg, 0.021 mmol) was added DBU (3 mg, 0.021 mmol). The solution was stirred at room temperature under Ar (24 h). TLC analysis indicated no reaction. The solution was then heated at 45 °C (8 h), filtered and the solvent was removed *in vacuo*. TLC analysis of the residue indicated the presence of **6** and **13** along with several other unidentified products. The residue was then dissolved in methanol and purified by preparative TLC (10% methanol-chloroform) to provide **6** (1 mg, 11% yield) and **13** (1 mg, 8% recovery) as white solids.

Compound **6**: $R_f$ 0.53 (10% $CH_3OH$-$CHCl_3$); $^1H$ NMR ($CD_3OD$) δ 1.33 (s, 3 H, $C(2')CH_3$), 1.35 (s, 6 H, $C(CH_3)_2$), 2.06 (dd, $J$ = 5.3, 8.3 Hz, 1 H, C(4)*H*H'), 2.64-2.89 (m, 1 H, C(4)H*H'*), 3.55 (d, $J$ = 11.0 Hz, 1 H, C(5a)*H*H'), 3.61-3.64 (m, 1 H, C(3)*H*H'), 3.69 (d, $J$ = 8.7 Hz, 1 H, C(3')*H*H'), 3.79 (d, $J$ = 11.0 Hz, 1 H, C(5a)H*H'*), 4.06 (dd, $J$ = 5.3, 8.3 Hz, 1 H, C(3)H*H'*), 4.18 (d, $J$ = 8.7 Hz, 1 H, C(3')H*H'*), 4.29 (s, 1 H, C(1')H).

Compound **13**: $R_f$ 0.90 (10% $CH_3OH$-$CHCl_3$); $R_f$ 0.46 (40% ethyl acetate-hexanes); $^1H$ NMR ($CD_3OD$) δ 0.14 (s, 3 H, $Si(CH_3)_2$), 0.30 (s, 3 H, $Si(CH_3)_2$), 0.97 (s, 9 H, $SiC(CH_3)_3$), 1.39 (s, 3 H, $C(2')CH_3$), 1.46 (s, 6 H, $C(CH_3)_2$), 2.40-2.49 (m, 1 H, C(4)*H*H'), 2.55-2.63 (m, 1 H, C(4)H*H'*), 3.73 (d, $J$ = 8.6 Hz, 1 H, C(3')*H*H'), 3.94-4.00 (m, 1 H, C(3)*H*H'), 3.98 (d, $J$ = 11.1 Hz, 1 H, C(5a)*H*H'), 4.10-4.17 (m, 1 H, C(3)H*H'*), 4.12 (s, 1 H, C(1')H), 4.32 (d, $J$ = 11.1 Hz, 1 H, C(5a)H*H'*), 4.44 (d, $J$ = 8.6 Hz, 1 H, C(3')H*H'*).

*Crystallographic Procedure for (3S, 4S, 5S)-3-(3-Bromobutoxy-3-ene)-4-hydroxy-5-hydroxymethyl-5-methyl-3-oxamido-γ-lactone (4).* A colorless fragment having approximate dimensions 0.20 x 0.30 x 0.60 mm was cut from a long thick slab and mounted in a random orientation on a Nicolet R3m/V automatic diffractometer. The sample was placed in a stream of dry $N_2$ gas at –50 °C. Final cell constants, as well as other information pertinent to data collection and refinement, are listed below. The Laue symmetry was determined to be 2/m, and from the systematic absences noted the space group was shown to be either $P2_1$ or $P2_1/m$. Intensities were measured using the θ:2θ scan technique, with the scan rate depending on the count obtained in rapid pre-scans of each reflection. Two standard reflections were monitored after every two hours or every 100 data collected, and these showed no significant change. During data reduction Lorentz and polarization corrections were applied, as well as a semi-empirical absorption correction based on psi scans of 10 reflections having chi angles between 70 and 90°.

Since the unitary structure factors displayed acentric statistics, space group $P2_1$ was assumed from the outset. The structure was solved by the SHELXTL Patterson interpretation program, which revealed the positions of most of the nonhydrogen atoms in the molecule. Remaining atoms were located in subsequent difference Fourier syntheses. The usual sequence of isotropic and anisotropic refinement was followed, after which all hydrogens attached to carbon were entered in ideal calculated positions and constrained to riding motion, with a single variable isotropic temperature factor for all of them. The remaining hydrogens were located in difference maps and allowed to refine independently. The absolute configuration was determined by refinement of a coefficient which multiplies $\Delta f''$, and supported the configuration shown in Figure 1. After all shift/esd ratios were less than 0.1 convergence was reached at the agreement factors listed below. No unusually high correlations were noted between any of the variables in the last cycle of full-matrix least squares refinement, and the final difference density map showed a maximum peak of about 0.5 e/Å$^3$. All calculations were made using Nicolet's SHELXTL PLUS (1987) series of crystallographic programs.

Data Collection and Processing Parameters for Compound **4**. $C_{12}H_{17}BrN_2O_7$; MW=381.22; Space group $P2_1$ (monoclinic); a = 9.138 (1) Å, b = 9.885 (1) Å, c = 9.845 (1) Å, $\beta$ = 116.21 (1) °, V = 798 Å$^3$; Z = 2; $\rho$ = 1.59 g-cm$^{-3}$; $\mu$ (Mo K$\alpha$) = 25.81 cm$^{-1}$; T = –50 °C; scan range: $4° \leq 2\theta \leq 55°$; 1451 independent data ($I>3\sigma$) from 1921 total data collected; R = 0.031; $R_w$ = 0.019, $w = \sigma (F)^{-2}$.

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