A New and Efficient Cyclization Reaction to Construct the Bicyclomycin Ring System: Synthesis of *N,N'*-Dimethyl-4-desmethylenebicyclomycin

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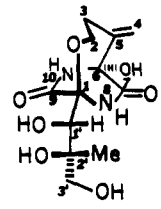
Abstract: Mercury(II) perchlorates effect the rapid and efficient concomitant deprotection/cyclization of 3,6-substituted-(silyloxypropyl)(pyridylthio)piperazinediones **6** to afford the corresponding bridged bicyclic piperazinediones **3**. The pyridyl thioethers **6** are synthesized from the corresponding N-protected piperazinediones by sequential enolate alkylation followed by regio- and stereoselective enolate sulfenylation. This sequence provides an efficient "three-pot" synthesis of the bridged bicyclic derivatives **3** in high yield. Bicyclic piperazinedione **3a** has been converted into *N,N'*-dimethyl-4-desmethylenebicyclomycin (**29**) by regio- and stereocontrolled functionalization of the bridgehead carbanions. The synthesis of **29** from commercially available sarcosine anhydride is accomplished in six steps in good yield.

Bicyclomycin **1**, an antibiotic recently discovered by two Japanese groups, was obtained from cultures of *Streptomyces sapporonensis*[1] and *Streptomyces aizunensis*.[2] Bicyclomycin possesses a unique chemical structure and exhibits a unique mechanism of antibacterial action,[3,4] no relation being noted to any groups of the known antibiotics. The relative[5] and absolute[6] configuration of bicyclomycin has been firmly established by X-ray crystallographic analysis.



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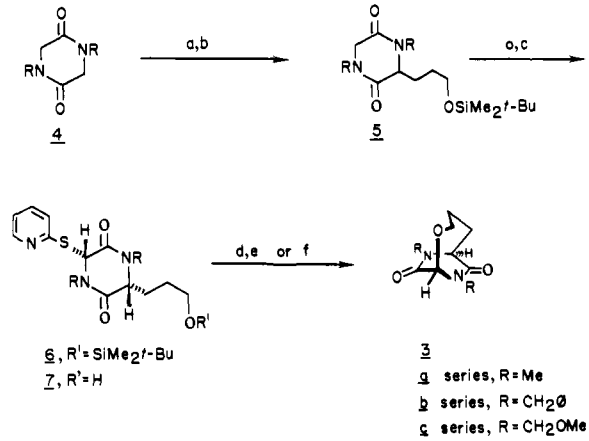
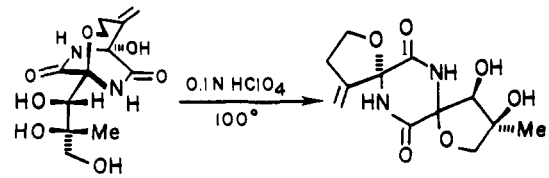
The interesting profile of antibacterial activity and low toxicity of bicyclomycin has prompted intense investigation into the chemistry of this substance.[7] Several synthetic approaches to bicyclomycin have been reported,[6,8] but no successful total synthesis of bicyclomycin has appeared. This unique and biologically important compound offers a challenging synthetic and biomechanistic problem. Of particular synthetic interest is the construction of the novel and delicate oxidized bicyclic piperazinedione nucleus. It seemed to us that the most difficult problem in synthesizing bicyclomycin is the introduction of the C-6 hydroxyl group, since this oxygen atom is readily lost in the acid-catalyzed dehydration[6] of bicyclomycin to the thermodynamically more stable[6,8c] spiropiperazinedione derivative **2**.

Scheme I[a]



[a] Reagents and conditions: a = LDA, THF, −78 °C; b = $I(CH_2)_3OSiMe_2$-*t*-Bu, HMPA; c = 2,2'-dipyridyl disulfide; d = HF·pyridine, THF, 25 °C; e = $AgClO_4$, CH_2Cl_2, 25 °C; f = $PhHgClO_4$, THF, 25 °C.



1 **2**

Results and Discussion

Recently, we reported[9] the synthesis and bridgehead carbanion[8c,10] functionalization of bicyclic derivative **3a**. In this paper, we delineate a generally useful and efficient method for the

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

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

(3) M. Iseki, T. Miyoshi, H. Aoki, and H. Imanaka, *J. Antibiot.*, **29**, 155 (1976).

(4) A. Someya, M. Iseki, and N. Tanaka, *J. Antibiot.*, **31**, 712 (1978).

(5) Y. Tokuma, S. Koda, T. Miyoshi, and Y. Morimoto, *Bull. Chem. Soc. Jpn.*, **47**, 18 (1974).

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

(7) B. W. Müller, O. Zak, W. Kump, W. Tosch, and O. Wacker, *J. Antibiot.*, **32**, 402 (1979).

(8) (a) Maag, H. 2nd Chemical Congress of the North American Continent, Division of Organic Chemistry, Las Vegas, NV, Aug 1980; Abstr. 347; (b) L. V. Dunkerton and R. M. Ahmed, *Tetrahedron Lett.*, **21**, 1803 (1980); (c) S. Nakatsuka, K. Yoshida, and T. Goto, *ibid.*, **22**, 2009 (1981); (d) C. Shin, Y. Sato, and J. Yoshimura, *ibid.*, **22**, 2401 (1981); (e) T. Fukuyama, B. D. Robins, and R. A. Sachleben, *ibid.*, **22**, 4155 (1981); (f) J. H. Hoare and P. Yates, *J. Chem. Soc., Chem. Commun.*, 1126 (1981).

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

(10) For related bicyclic piperazinedione dithioacetal-stabilized (sulfur-stabilized) bridgehead carbanions, see T. Fukuyama, S. Nakatsuka, and Y. Kishi, *Tetrahedron*, **37**, 2045 (1981), and references cited therein.

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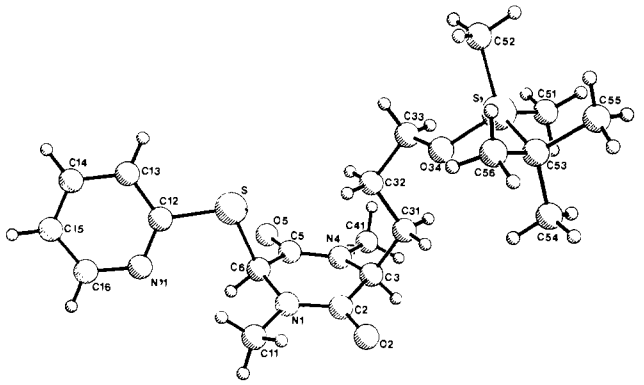
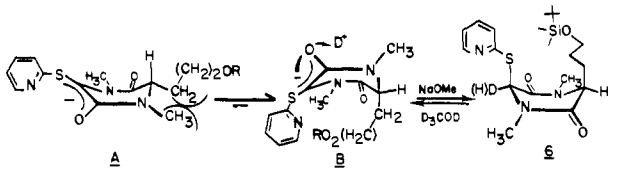


Figure 1. Molecular Structure of **6a**. Atoms are shown as spheres of fixed arbitrary radius.

synthesis of these simple bicyclomycin model compounds (**3a–c**) involving as a key step the metal-mediated intramolecular cyclization of pyridyl thioethers **6** and **7**. In addition, **3a** has been converted into (±)-*N,N'*-dimethyl-4-desmethylenebicyclomycin (**29**) by stereo- and regioselective functionalization of the bridgehead carbons to introduce the required C-6 hydroxyl group and C-1 polyoxo side chain.

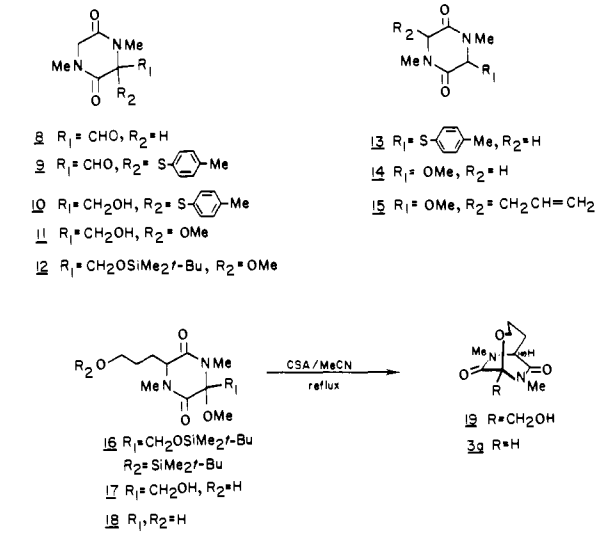
Scheme I summarizes the synthesis of bicyclic piperazinediones **3a–c** from the corresponding N-protected piperazinediones **4a–c**. Alkylation of the enolates derived from **4** with *tert*-butyldimethylsiloxy-3-iodopropane[11] in the presence of HMPA afforded the monoalkylated derivatives **5** in 41–79% yield. Generation of the enolate of **5** with LDA in THF at −78 °C followed by addition of the enolate to a solution of 2,2'-dipyridyl disulfide afforded the sulfenylated derivatives **6** as single regio- and stereoisomers in 80–95% isolated yield. The stereochemistry of the pyridyl thioethers (**6**) was expected to be of the anti configuration from a consideration of related literature precedent[12] and experimental data on the attempted epimerization of **6**.[13] X-ray crystallographic analysis of **6a**, however, unambiguously revealed that the stereochemistry of **6a** was of the syn configuration (see Figure 1).

Treatment of **6** with a catalytic amount of $NaOCH_3$ in CD_3OD rapidly exchanged the methine proton adjacent to sulfur (^1H NMR analysis). However, absolutely no evidence for the formation of any of the anti epimer was obtained under these conditions. Clean, sharp signals in the ^1H NMR spectrum of the C-6 deuterated **6a** produced during the attempted epimerization clearly indicate that the enolate anion deuterates (or protonates) from the face opposite the bulky silyloxypropyl residue (rotamer B) producing exclusively

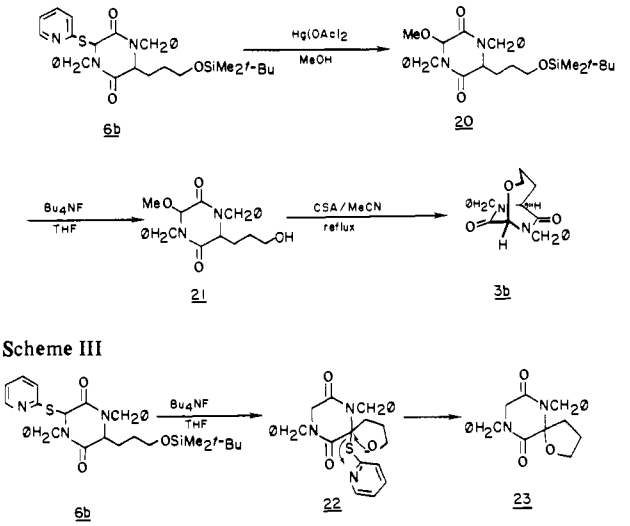


the syn stereoisomer. As the X-ray structure of **6a** indicates, the piperazinedione adopts a boat conformation in which both the silyloxypropyl and pyridylthio groups are held pseudoaxially. Inspection of CPK models clearly show significant steric compression between the *N*-methyl group and the C-1 CH_2 in the alternative boat conformer (cf. rotamers A and B) where both groups are pseudoequatorial. Thus, the stereoselectivity of the sulfenylation reactions (**5** → **6**) may be explained by the intermediacy of the C-6 enolate anion (formed subsequent to sulfenylation), which protonates on the convex face of the more stable rotamer B.

Chart I



Scheme II



Scheme III

Our initial efforts to bring about the direct cyclization of **6** to the bicyclic derivatives **3** were uniformly unsuccessful under a variety of conditions (e.g., AgF/HMPA, etc). Thus, the silyl protecting group was first removed very cleanly by treatment with excess HF·pyridine complex[14] to afford the alcohols **7** in virtually quantitative yield. Without further purification, treatment of **7** with 1.0 equiv of silver perchlorate[15,16] in CH_2Cl_2 at room temperatue for 2–3 h cleanly effected intramolecular cyclization affording the desired bicyclic compounds **3a–c** in 60–93% yield. The silver(I)-mediated cyclization is extremely mild compared to the acid-mediated cyclizations of methoxy alcohols[9] **17** and **18** (Chart I) and the related acid-mediated cyclizations of Maag[8a] and Nakatsuka.[8c] Both alcohols **17** and **18** have been prepared from aldehyde **9** (**9** → **10** → **11** → **12** → **16** for **17**, 39%; **9** → **13** → **14** → **15** for **18**, 29%). The alcohols **7** could be induced to cyclize in the presence of camphorsulfonic acid but required prolonged reflux temperatures (80 °C), and the yield of bicyclic

(11) A procedure for the preparation of this reagent was kindly furnished by Professor A. I. Meyers (unpublished results); prepared from 3-bromopropanol by silylation followed by Finklestein reaction and distillation; bp 41–44 °C 00.04mmHg).

(12) For related observations see (a) S. Nakatsuka, K. Sasaki, K. Yamaguchi, and T. Goto, *Chem. Lett.*, 695 (1981); (b) R. M. Williams and W. H. Rastetter, *J. Org. Chem.*, **45**, 2625 (1980); and also ref 10.

(13) Compound **6** is treated with potassium *tert*-butoxide in *tert*-butanyl alcohol/THF at room temperature and followed by ^1H NMR while warming to 40 °C; no epimerization occurs under these conditions.

(14) K. C. Nicolaou, S. P. Seitz, and M. R. Pavia, *J. Am. Chem. Soc.*, **103**, 1222 (1981); tetra-*n*-butylammonium fluoride in THF causes significant destruction of the substrate.

(15) Silver(I) triflate was found to work equally well in this application.

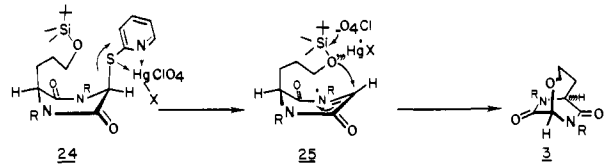
(16) This reaction is analogous to the metal-mediated glycosidation reactions (modified Koenigs–Knorr reaction); see R. J. Ferrier, R. W. Hay, and N. Vethavlyasar, *Carbohydr. Res.*, **27**, 55 (1973); T. Mukaiyama, T. Nakatsuka, and S. Shoda, *Chem. Lett.*, 487 (1979); S. Hanessian, C. Bacquet, and N. Lehong, *Carbohydr. Res.*, **80**, C17 (1980).

product was considerably less (48–77%) than that obtained with the metal. In the absence of acid, the alcohols **7** were found to be thermally quite stable in a variety of solvents (toluene, THF, acetonitrile) at reflux temperature for prolonged periods of time; starting material was cleanly recovered, and no detectable cyclized products were formed under these conditions.

Related to the above, the pyridyl thioethers **6** could be efficiently and stereospecifically transformed into the corresponding methoxy derivatives **20**[17] by treatment with mercuric acetate in methanol at room temperature. Removal of the silyl protecting group with tetra-*n*-butylammonium fluoride afforded the alcohol **21**, which could be cleanly cyclized to the bicyclic derivative (demonstrated here for **6b**) **3b** in the presence of 1 equiv of camphorsulfonic acid in acetonitrile at reflux for 12 h (Scheme II).

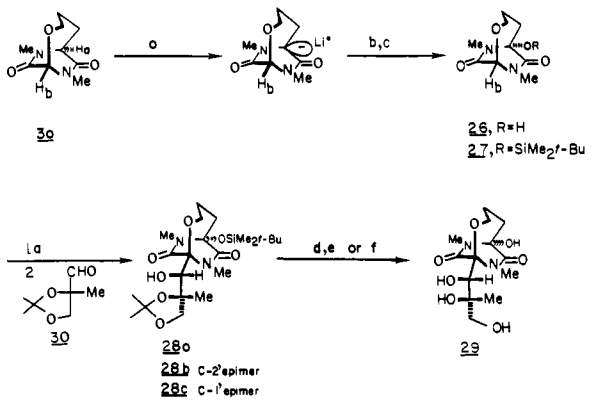
Several comments regarding the removal of the silyl protecting group are relevant. Interestingly, attempted removal of the silyl group from **6b** with tetra-*n*-butylammonium fluoride at room temperature for several hours led to the production of spiropiperazinedione **23** (36% yield, Scheme III) plus smaller amounts of the desired alcohol **7** and other unidentified products. Formation of **23** must arise via an inter- or intramolecular transsulfenylation to afford intermediate **22**, which suffers intramolecular cyclization, furnishing **23**. None of the bridged bicyclic derivative **3** was formed under these conditions. Use of the HF·pyridine complex[18] circumvented this problem, affording the sterically pure alcohols **7** in high yield.

During the course of an investigation of the effect of the metal (Ag^+, Cu^{2+}, Hg^{2+}, Pb^{2+}) and the counterion (ClO_4^-, $CF_3SO_3^-$, BF_4^-, etc.) on the rate of the cyclization reaction, we were pleasantly surprised to find that *addition of 2.0 equiv of phenylmercuric perchlorate to the silyl-protected pyridyl thioethers 6 directly afforded the desired bicyclic compounds 3 in 90–99% isolated yield in 2–3 min at room temperature*! Several features of this remarkable one-pot deprotection/cyclization are noteworthy. Addition of 1.0 equiv of phenylmercuric perchlorate to **6** immediately produced a partially insoluble complex, but no cyclization took place until the second equivalent of the mercury salt[19] was added. Although a detailed mechanism for this reaction is not presently available, it is apparent from analysis of the crude reaction mixture (after aqueous isolation) that the perchlorate ion captures the *tert*-butyldimethylsilyl residue; *tert*-butyldimethylsilyl alcohol is produced in equimolar amounts to the bicyclic piperazinedione (HPLC and ^1H NMR analysis with authentic silanol). From these observations, it seems reasonable that the Hg(II) species complexes with the pyridyl thioether moiety (**24**) and the second equivalent effects the removal of the silyl



residue.[20] However, since the stereochemistry of **6** is syn, simple intramolecular S_N2 displacement is precluded and removal of the pyridylthio residue must *precede* formation of the C-1–O bond. Thus, the intermediacy of iminamide **25** may be invoked from consideration of the available data. The observed stability of **6** in the presence of 1 equiv of $PhHgClO_4$ suggests that the obligate second equivalent of $PhHgClO_4$ facilitates the formation of **25** by "doubly activating" the pyridyl thioether moiety through complexation.

Scheme IV[a]



[a] Reagents and conditions: a = LDA, THF, −78 °C; b = MoOPH; c = *t*-$BuMe_2SiOTf$, CH_2Cl_2, 2,6-lutidine, 25 °C; d = $Bu_4NF·3H_2O$, THF, 0 °C; e = H_2SO_4, MeOH, H_2O; f = HF·pyridine, THF, 25 °C.

Additionally, we have found that the perchlorate anion is obligate in the removal of the silyl residue;[21] other counterions such as triflate, fluoroborate, and chloride totally fail in bringing about cyclization/deprotection.

Regardless of the mechanistic details, this remarkable cyclization/deprotection affords an overall "three-pot" synthesis of bicyclic piperazinediones **3** under extremely mild conditions in high yield.

As previously reported,[9] functionalization of the bridgehead positions of **3a** can be realized via formation of the C-1 and C-6 bridgehead carbanions. So that the versatility of the unsubstituted derivatives **3** can be illustrated, dimethylpiperazinedione **3a** has been stereo- and regioselectively converted into (±)-*N*,*N*′-dimethyl-4-desmethylenebicyclomycin **29** (Scheme IV).

For **3a**, we have observed[9] that the bridgehead methine adjacent to the methylene (Ha) is more acidic than the bridgehead methine adjacent to the bridging oxygen (Hb). Thus, treatment of **3a** with 1.5 equiv of LDA in THF at −78 °C, followed by addition of MoOPH,[22] affords bridgehead alcohol **26** as the only isolable product in 65% yield (Scheme IV). Protection of the hydroxyl group as the corresponding *tert*-butyldimethylsilyl ether was accomplished by treatment of **26** with *tert*-butyldimethylsilyl triflate[23] in methylene chloride in the presence of 2,6-lutidine to afford the silyl derivative **27** (90% yield).

Treatment of **27** with 1.5 equiv of LDA in THF at −78 °C followed by addition of aldehyde **30**[24] resulted in a stereoselective aldol condensation to afford the three diastereomeric aldols[25] **28a–c** in 52%, 14%, and 13% isolated yields; the ratio of the three isomers

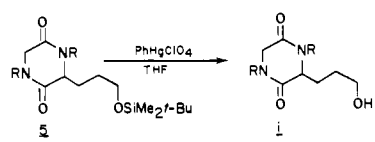
(17) A single diastereoisomer is produced in this transformation, but a stereochemical assignment could not be made based on the available spectral data.

(18) K. C. Nicolaou, S. P. Seitz, M. R. Pavia, and N. A. Petasis, *J. Org. Chem.*, **44**, 4011 (1979).

(19) Silver(I) perchlorate alone or phenylmercuric chloride alone completely fail in effecting this deprotection/cyclization.

(20) We have also found that $Hg(ClO_4)_2$ and $Cu^{I}ClO_4·4MeCN$ cleanly effect the deprotection/cyclication; phenylmercuric perchlorate remains the reagent of choice for both operational and safety considerations.

(21) Treatment of the *tert*-butyldimethylsilyl ethers **5** with 1 equiv of phenylmercuric perchlorate in THF at room temperature rapidly cleaved the silyl ether to furnish the corresponding alcohol **i** in high yield. Application of this methodology to other systems is under investigation.



(22) MoOPH = oxodiperoxymolybdenum–hexamethylphosphorictriamide–pyridine; see E. Vedejs and J. E. Telschow, *J. Org. Chem.*, **41**, 740 (1976).

(23) *tert*-Butyldimethylsilyl triflate was prepared by addition of silver(I) triflate to a CH_2Cl_2 solution of *tert*-butyldimethylsilyl chloride. The freshly prepared silyl triflate was used directly as a 0.1 M solution in CH_2Cl_2; for related uses and preparation see E. J. Corey, H. Cho, C. Rücker, and O. H. Hua, *Tetrahedron Lett.*, **22**, 3455 (1981).

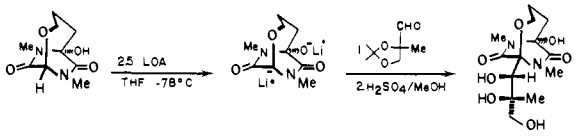
(24) Prepared from the corresponding alcohol by oxidation with Me_2SO, oxalyl chloride, Et_3N (Swern conditions); see ref 6 and P. Calinaud and J. Gelas, *Bull. Soc. Chim. Fr.*, 1228 (1975).

(25) A similar aldol condensation was done independently by Nakatsuka and co-workers and has recently appeared in print: S. Nakatsuka, K. Yoshida, and T. Goto, *Tetrahedron Lett.*, **22**, 4973 (1981); we thank Professor Nakatsuka for sharing their progress with us prior to publication.

being ca. 4:1:1. Although four diastereomers are possible from this condensation, we have only detected three. This aldol condensation clearly exhibits "double stereodifferentiation",[26] since both the aldehyde **30** and bicyclic piperazinedione **27** are racemic.[27] The major aldol **28a** was clearly shown to possess the correct relative configuration as shown by a single-crystal X-ray structural determination (see supplementary section).

The major aldol **28a** was sequentially treated with 1 equiv of tetra-*n*-butylammonium fluoride·trihydrate in THF at 0 °C, followed by hydrolysis[7] with 0.2 N H_2SO_4 in MeOH at 25 °C to afford (±)-*N,N'*-dimethyl-4-desmethylenebicyclomycin **29** (27% overall yield from **28a**). Alternatively, removal of both the acetonide and silyl protection was effected concomitantly by treatment of **28a** with HF·pyridine complex in THF at 25 °C to afford **29** (74%).

While it was instructive to utilize the *tert*-butyldimethylsilyl-protected derivative **27** for manipulation of the C-6 hydroxyl group, we have also found that the C-6 hydroxyl could be effectively protected as the lithium alkoxide during the aldol condensation. Thus, treatment of the bicyclic alcohol **26** with 2.5 equiv of LDA



26 31 29

in THF at −78 °C generated the corresponding dianion **31**, which underwent clean aldol condensation with **30** to afford the diastereomeric[28] acetonide aldols. The major product from this condensation was, as expected, the desired isomer; removal of the acetonide[7,29] furnished **29** in 16% overall yield from **26**. This last dianion condensation reduces the overall number of synthetic transformations required to synthesize **29** to only six steps.

The synthetic methodology developed herein will provide a highly versatile and flexible means for preparing a wide variety of bicyclomycin analogues by appropriate bridgehead functionalization of the common bicyclic derivative of the general structure **3**. Application of this chemistry to a total synthesis of bicyclomycin and analogues is currently in progress.

Experimental Section

1,4-Dimethyl-3-[3′-[(*tert*-butyldimethylsilyl)oxy]propyl]-2,5-piperazinedione (5a). To a stirred solution of sarcosine anhydride (**4a**) (340 mg, 2.39 mmol, 1.0 equiv) in THF (20 mL) at −78 °C was added LDA (3.1 mmol, 1.3 equiv) in THF (5 mL). After the enolate solution was stirred 2 min at −78 °C, HMPA (0.85 mL, 4.78 mmol, 2.0 equiv) was added and the mixture transferred via cannula into a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-1-iodopropane (1.43 g, 4.78 mmol, 2.0 equiv) in THF (5 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C and for **4** h at room temperature, diluted with CH_2Cl_2, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 290 mg (39% or 55% based on recovered sarcosine anhydride) of **5a**, mp 96.5–97 °C (hexanes): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.01 (6 H, s), 0.90 (9 H, s), 1.2–2.3 (4 H, m), 2.98 (6 H, s), 3.4–3.8 (3 H, m), 3.8–4.1 (2 H, m); IR (NaCl, neat) 1650, 1480, 1395, 1325, 1245, 1095 cm^{-1}; mass spectrum, *m/e* 314 (M^+, 0.79), 313 (M^+ − 1, 2.65), 298 (4.22), 265 (100). Anal. ($C_{15}H_{30}N_2O_3Si$) C, H, N.

1,4-Dimethyl-3-[3′-[(*tert*-butyldimethylsilyl)oxy]propyl]-6-(2″-pyridylthio)-2,5-piperazinedione (6a). To a stirred solution of **5a** (324 mg, 1.03 mmol, 1.0 equiv) in THF (20 mL) at −78 °C was added LDA (1.23 mmol, 1.2 equiv) in THF (5 mL). The enolate solution was stirred 2 min at −78 °C and transferred via cannula into a solution of 2,2′-dipyridyl disulfide (295 mg, 1.34 mmol, 1.3 equiv) in THF (5 mL) at −78 °C. The mixture was stirred for 10 min at −78 °C, allowed to warm to room temperature, diluted with CH_2Cl_2, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 400 mg (92%) of pure sulfide **6a**, mp 103–105 °C (Et_2O): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.02 (6 H, s), 0.90 (9 H, s), 1.2–2.3 (4 H, m), 3.02 (6 H, s), 3.3–4.1 (3 H, m), 6.60 (1 H, s), 6.9–7.3 (2 H, m), 7.3–7.7 (1 H, m), 8.5 (1 H, m); IR (NaCl, neat) 1660, 1450, 1405, 1395, 1295 cm^{-1}; mass spectrum, *m/e* 345 (4.74), 313 (9.43), 255 (30.21), 220 (42.52), 28.1 (100). Anal. ($C_{20}H_{33}N_3O_3SiS$) C, N, H, S.

8,10-Dimethyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (3a). Method A. The protected pyridyl thioether **6a** (148 mg, 0.35 mmol, 1.0 equiv) was dissolved in THF (5 mL) in a plastic vessel at room temperature. Excess HF·pyridine complex was added, and the reaction was allowed to stir for 2 h, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 109 mg (quantitative) of sterically pure **7a** (glass), which was used directly for the following cyclization without further purification; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.4–2.6 (4 H, m), 3.1 (6 H, s), 3.65–4.3 (4 H, m), 6.70 (1 H, s), 7.0–7.9 (3 H, m), 8.6 (1 H, m).

The alcohol **7a** was dissolved in CH_2Cl_2 (10 mL), and $AgClO_4$ (73 mg, 0.35 mmol, 1.0 equiv) was added in one portion. The mixture was allowed to stir for 4 h at room temperature, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 89 parts CH_2Cl_2/9 parts of MeOH/1 part of NH_4OH) to afford 65 mg (93%) of pure bicyclic piperazinedione **3a**, mp 160–161 °C (EtOAc/hexanes): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.73 (2 H, m), 2.14 (2 H, m), 2.97 (3 H, s), 3.03 (3 H, s), 3.3–3.9 (2 H, m), 4.04 (1 H, t, *J* = 3 Hz), 5.12 (1 H, s); IR (NaCl, neat) 1660, 1480, 1405, 1390, 1300, 1258, 1245 cm^{-1}; mass spectrum, *m/e* 198 (M^+, 57), 140 ($M^+ - C_3H_6O$, 19.5%), 32 (100). Exact mass calcd for $C_9H_{14}N_2O_3$ (M^+) 198.1005, found *m/e* 198.1024. Anal. ($C_9H_{14}N_2O_3$) C, H, N.

Method B. The protected pyridyl thioether **6a** (80 mg, 0.18 mmol, 1.0 equiv) was dissolved in THF (5 mL) at room temperature. To this solution was added a freshly prepared solution of phenylmercuric perchlorate (0.37 mmol, 2.0 equiv). The mixture was allowed to stir for 2 min at room temperature, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 89 parts of CH_2Cl_2/9 parts of MeOH/1 part of NH_4OH) to afford 34.2 mg (96%) of pure, crystalline bicyclic piperazinedione, which was identical with that obtained from method A in every respect. Under the same conditions, $Hg(ClO_4)_2$ worked equally well for this reaction.

1,4-Dibenzyl-3-[3′-[(*tert*-butyldimethylsilyl)oxy]propyl]-2,5-piperazinedione (5b). To a stirred solution of 1,4-dibenzyl-2,5-piperazinedione (**4b**) (1.47 g, 5.0 mmol, 1.0 equiv) in THF (50 mL) at −78 °C was added LDA (5.5 mmol, 1.1 equiv) in THF (5 mL). The resulting yellow-orange solution was stirred 1 min at −78 °C, HMPA (1.3 mL, 7.5 mmol, 1.5 equiv) was added, and the mixture was stirred 2 min at −78 °C. The mixture was transferred via cannula into a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-1-iodopropane (2.25 g, 7.5 mmol, 1.5 equiv) in THF (5 mL) at −78 °C. The mixture was allowed to stir at −78 °C for 1 h and for 8 h at room temperature. The mixture was diluted with CH_2Cl_2, poured into 0.5 N HCl, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel flash column (eluted with Et_2O) to afford 1.4 g (60%) of **5a** (79% based on recovered starting material), mp 87–88 °C (CH_2Cl_2/Et_2O/hexane): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.05 (6 H, s), 0.95 (9 H, s), 1.15–1.76 (2 H, m), 1.83–2.17 (2 H, m), 3.52 (2 H, t, *J* = 5.8 Hz), 3.85 (3 H, m), 3.94 (1 H, $^1/_2$ABq, *J* = 15 Hz), 4.26 (1 H, $^1/_2$ABq, *J* = 14.4 Hz), 4.79 (1 H, $^1/_2$ABq, *J* = 14.4 Hz), 5.22 (1 H, $^1/_2$Abq, *J* = 15 Hz), 7.24 (10 H, s); IR (NaCl, neat) 1660, 1450, 1250, 1090 cm^{-1}; mass spectrum, *m/e* 466 (M^+, 6.25), 451 (1.93), 409 (77.36), 91 (100). Anal. ($C_{27}H_{38}N_2O_3Si$) C, H, N.

1,4-Dibenzyl-3-[3′-[(*tert*-butyldimethylsilyl)oxy]propyl]-6-(2″-pyridylthio)-2,5-piperazinedione (6b). To a stirred solution of **5b** (295.2 mg, 0.63 mmol, 1.0 equiv) in THF (20 mL) at −78 °C was added LDA (0.82 mmol, 1.3 equiv) in THF (5 mL). After stirring for 1 min at −78 °C, the enolate solution was transferred via cannula into a solution of 2,2′-dipyridyl disulfide (181 mg, 0.82 mmol, 1.0 equiv) in THF (5 mL)

(26) See Clayton H. Heathcock, in "Comprehensive Carbanion Chemistry", Vol II, Chapter 4, T. Durst and E. Buncel, Eds., Elsevier, Amsterdam, 1981.

(27) Use of the optically active aldehyde **30** for coupling and resolution of the racemic bicyclic moiety is currently being investigated.

(28) In contrast to the aldol condensation with **27**, all four possible diastereomers were isolated from this reaction. The stereochemistry of the minor isomers was not determined and the stereochemistry of the major aldol was unambiguously correlated with that of **28a** by removal of the silyl group (see Experimental Section).

(29) Small amounts (5–15%) of the diastereomeric bis-spiropiperazinediones were routinely produced during the removal of the acetonide with either HF·py or H_2SO_4/MeOH.

at −78 °C. The mixture was allowed to stir for 15 min at −78 °C and 15 min at room temperature, diluted with CH_2Cl_2, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with Et_2O) to afford 311 mg (85.7%) of pure sulfide **6b**, mp 120–121 °C (CH_2Cl_2/Et_2O): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.00 (6 H, s), 0.85 (9 H, s), 1.1–2.4 (4 H, m), 3.58 (2 H, m), 3.89 (1 H, m), 3.96 (1 H, $^1/_2$ABq, J = 15 Hz), 4.00 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.14 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.17 (1 H, $^1/_2$ABq, J = 15 Hz), 6.55 (1 H, s), 7.19 (13 H, m), 8.39 (1 H, m); IR (NaCl, neat) 1650, 1440, 1080 cm^{-1}; mass spectrum, m/e 256 (1.29), 171 (100), 115 (1.98), 110 (2.61), 91 (4.76). Anal. ($C_{32}H_{41}N_3O_3SiS$) C, H, N, S.

8,10-Dibenzyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (3b). Method A. The protected pyridyl thioether **6b** (216.7 mg, 0.37 mmol, 1.0 equiv) was dissolved in 10 mL of THF in a plastic vessel at room temperature. Excess HF·pyridine complex was added, and the reaction was allowed to stir for 1 h at room temperature. The mixture was diluted with CH_2Cl_2, poured into 0.1 N NaOH, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 171 mg (quantitative) of diastereomerically pure **7b**, which was used for the following cyclization without further purification. ^1H NMR ($CDCl_3$, Me_4Si) δ 1.4–2.3 (4 H, m), 3.63 (2 H, t, J = 5 Hz), 3.8–4.3 (4 H, m), 4.9–5.3 (2 H, m), 6.55 (1 H, s), 6.8–7.9 (13 H, m), 8.4 (1 H, m).

The alcohol **7b** was dissolved in CH_2Cl_2 (15 mL), and $AgClO_4$ (100 mg, 0.48 mmol, 1.3 equiv) was added in one portion. The mixture was allowed to stir for 2 h at room temperature, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with Et_2O) to afford 78 mg (60%) of pure bicyclic **3b**, mp 171–172 °C (EtOAc): ^1H NMR ($CDCl_3$, $CHCl_3$) δ 1.34–1.75 (2 H, m), 1.87–1.97 (2 H, m), 3.27–3.50 (1 H, m), 3.71–3.93 (1 H, m), 4.08 (1 H, t, J = 4 Hz), 4.10 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.28 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.85 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.07 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.18 (1 H, s), 7.29 (10 H, s); IR (NaCl, neat) 1655, 1460, 1440, 1420, 1305, 1260, 1090, 1065, 1045, 930 cm^{-1}; mass spectrum, m/e 350 (M^+, 13.13), 289 (14.57), 259 (2.21), 217 (1.83), 91 (100). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

Method B. The same procedure as that described for **6a** was used for **6b**; pure bicyclic **3b** (90%) was obtained from PTLC silica gel (eluted with Et_2O) and was identical with that obtained from method A in every respect.

1,4-Bis(methoxymethyl)-3-[3′-[(*tert*-butyldimethylsilyl)oxy]propyl]-2,5-piperazinedione (5c). To a stirred solution of piperazinedione **4c** (1.428 g, 7.07 mmol, 1.0 equiv) in THF (10 mL) at −78 °C was added a solution of LDA (8.48 mmol, 1.2 equiv) in THF (5 mL). HMPA (2.21 mL, 12.7 mmol, 1.8 equiv) was added and the dark enolate solution stirred for 20 min at −78 °C. This solution was transferred via cannula into a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-1-iodopropane (3.8 g, 12.7 mmol, 1.8 equiv) in THF (10 mL) at −78 °C. The mixture was allowed to stir for 20 min at −78 °C and 2 h at room temperature. The mixture was diluted with CH_2Cl_2, poured into H_2O, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel flash column (eluted sequentially with hexane, 75% hexane/EtOAc, 50% hexane/EtOAc, 25% hexane/EtOAc) to afford 0.740 g (28% or 41% based on recovered **4c**) of **5c** (oil): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.00 (6 H, s), 0.85 (9 H, s), 1.4–2.1 (4 H, m), 3.25 (6 H, s), 3.56 (2 H, br t), 3.98 (3 H, m), 4.55 (1 H, $^1/_2$ABq, J = 10 Hz), 4.56 (1 H, $^1/_2$ABq, J = 10 Hz), 4.85 (1 H, $^1/_2$ABq, J = 10 Hz), 4.92 (1 H, $^1/_2$ABq, J = 10 Hz); IR (NaCl, neat) 2960, 2855, 1675, 1618, 1460, 1260, 1100, 835 cm^{-1}; mass spectrum, m/e 359 ($M^+ - CH_3$, 3.37), 317 ($M^+ - C_4H_9$, 100), 213 (29.3), 45 (C_2H_5O, 85).

1,4-Bis(methoxymethyl)-3-[3′-[(*tert*-butyldimethylsilyl)oxy]propyl]-6-(2″-pyridylthio)-2,5-piperazinedione (6c). To a stirred solution of **5c** (250 mg, 0.67 mmol, 1.0 equiv) in THF (5 mL) at −78 °C was added LDA (0.87 mmol, 1.3 equiv) in THF (2 mL). After being stirred for 20 min at −78 °C, the dark enolate solution was transferred via cannula into a solution of 2,2′-dipyridyl disulfide (220 mg, 1.0 mmol, 1.4 equiv) in THF (2.5 mL) at −78 °C. The mixture was allowed to stir for 20 min at −78 °C and for 1 h at room temperature, diluted with CH_2Cl_2, poured into H_2O, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel flash column (eluted sequentially with hexane, 25% acetone/hexane, 50% acetone–hexane) to afford 255 mg (79%) of **6c** (oil): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.17 (6 H, s), 0.91 (9 H, s), 1.5–2.4 (4 H, m), 3.36 (6 H, s), 3.71 (2 H, m), 4.1 (1 H, t, J = 7 Hz), 4.59 (1 H, $^1/_2$ABq, J = 10 Hz), 4.59 (1 H, $^1/_2$ABq, J = 11 Hz), 5.09 (1 H, $^1/_2$ABq, J = 10 Hz), 5.05 (1 H, $^1/_2$ABq, J = 11 Hz), 6.87 (1 H, s), 6.85–7.10 (2 H, m), 7.25–7.55 (1 H, m), 8.20–8.39 (1 H, m); IR (NaCl, neat) 2940, 2860, 1690, 1420, 1100, 840, 780 cm^{-1}; mass spectrum, m/e 483 (M^+, 2.59); 316 ($M^+ - C_4H_9$, C_5H_4NS), 213 (31.96), 45 (66.88).

8,10-Bis(methoxymethyl)-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (3c). Method A. The protected pyridyl thioether **6c** was converted into the corresponding alcohol **7c** by treatment with HF·pyridine complex exactly as described above for **6a** and **6b** to afford sterically pure **7c** (quantitative), which was used for the following cyclization without further purification; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.6–2.4 (4 H, m), 3.37 (6 H, s), 3.68–3.80 (2 H, m), 4.26 (1 H, t, J = 6 Hz), 4.63 (1 H, $^1/_2$ABq, J = 10 Hz), 5.11 (1 H, $^1/_2$ABq, J = 10 Hz), 4.78 (1 H, $^1/_2$ABq, J = 10 Hz), 5.27 (1 H, $^1/_2$ABq, J = 10 Hz), 6.87 (1 H, s), 7.04–7.36 (2 H, m), 7.40–7.72 (1 H, m), 7.36–7.60 (1 H, m).

The alcohol **7c** (80 mg, 0.29 mmol, 1 equiv) was dissolved in CH_2Cl_2 (15 mL) at room temperature, and $AgClO_4$ (143 mg, 0.382 mmol, 1.3 equiv) was added in one portion. The mixture was allowed to stir for 2 h at room temperature, diluted with CH_2Cl_2, poured into 0.1 N NaOH, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 89 parts of CH_2Cl_2/9 parts of MeOH/1 parts of NH_4OH) to afford 64 mg (84.3%) of bicyclic piperazinedione **3c** (oil): ^1H NMR ($CDCl_3$, Me_4Si) δ 1.77–1.86 (2 H, m), 2.07–2.21 (2 H, m), 3.32 (3 H, s), 3.34 (3 H, s), 3.59–3.69 (1 H, m), 3.78–3.91 (1 H, m), 4.27 (1 H, t, J = 4 Hz), 4.62 (1 H, $^1/_2$ABq, J = 10 Hz), 4.75 (1 H, $^1/_2$ABq, J = 11 Hz), 4.85 (1 H, $^1/_2$ABq, J = 11 Hz), 5.03 (1 H, $^1/_2$ABq, J = 10 Hz), 5.34 (1 H, s); IR (NaCl, neat) 2940, 1682, 1450, 1110 cm^{-1}; mass spectrum, m/e 258 (M^+, 8.03), 243 ($M^+ - CH_3$, 5.16), 227 ($M^+ - CH_3O$, 6.06), 198 (7.37), 45 (C_2H_5O, 100). Anal. ($C_{11}H_{18}N_2O_5$) C, H, N.

Method B. Direct cyclization of **6c** under the conditions used for **6a,b** were unsuccessful due to the lability of the *N*-methoxymethyl groups under these conditions; thus, prior removal of the silyl group (method A) in this particular case was found to be necessary.

1,4-Dimethyl-3-(*p*-tolylthio)-3-formyl-2,5-piperazinedione (9). To a stirred solution of 1,4-dimethyl-3-formyl-2,5-piperazinedione (**8**)[12b] (4.68 g, 27.5 mmol, 1.0 equiv) in THF (100 mL) at −78 °C was added Et_3N (2.78 g, 27.5 mmol, 1.0 equiv). To this solution was added *p*-toluenesulfenyl chloride (4.56 g, 28.9 mmol, 1.05 equiv) in THF (20 mL) over a 15-min period. After the addition was complete, the resulting white suspension was stirred for 30 min at −78 °C, allowed to warm to 0 °C, and filtered to remove Et_3N·HCl. Evaporation of the solvent under reduced pressure afforded an oily residue from which crystals formed upon addition of 2 mL of Et_2O to afford 7.15 g of pure **9** (89.1%); mp 95–97 °C (CH_2Cl_2/Et_2O): ^1H NMR ($CDCl_3$, Me_4Si) δ 2.26 (1 H, $^1/_2$ABq, J = 18 Hz), 2.43 (3 H, s), 2.73 (3 H, s), 3.10 (3 H, s), 3.47 (1 H, $^1/_2$ABq, J = 18 Hz), 7.35 (4 H, m), 9.65 (1 H, s); IR (NaCl, neat) 1735, 1665, 1375 cm^{-1}; mass spectrum, m/e 263 (M^+ − CHO, 1.68), 170 (21.98), 169 (8.22), 123 (34.46), 39.8 (100).

1,4-Dimethyl-3-(hydroxymethyl)-3-(*p*-tolylthio)-2,5-piperazinedione (10). To a stirred solution of **9** (3.06 g, 10.5 mmol, 1.0 equiv) in THF (60 mL) at −78 °C was added a solution of $LiAl(OBu^t)_3H$ (3.47 g, 13.65 mmol, 1.3 equiv) in THF (30 mL). The mixture was stirred for 1 h at −78 °C, allowed to come to room temperature, and stirred for an additional 2 h. The mixture was diluted with CH_2Cl_2 and acidified with 1 N HCl. The aqueous layer was thoroughly extracted with CH_2Cl_2; the combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 2.79 g of pure alcohol **10** (90%), mp 152–153 °C (CH_2Cl_2/Et_2O): ^1H NMR ($CDCl_3$, Me_4Si) δ 2.35 (1 H, $^1/_2$ABq, J = 18 Hz), 2.42 (3 H, s), 2.78 (3 H, s), 3.27 (3 H, s), 3.49 (1 H, $^1/_2$ABq, J = 18 Hz), 3.92 (1 H, $^1/_2$ABq, J = 12 Hz), 4.56 (1 H, $^1/_2$ABq, J = 12 Hz), 3.2–4.5 (1 H, br, D_2O exch), 7.30 (5 H, m); IR (NaCl, neat) 3360 (br), 1660, 1640, 1630, 1380 cm^{-1}; mass spectrum, m/e 294 (M^+, 2.27), 264 (6.47), 170 (100). Anal. ($C_{14}H_{18}N_2O_3S$) C, H, N, S.

1,4-Dimethyl-3-(hydroxymethyl)-3-methoxy-2,5-piperazinedione (11). To a stirred solution of **10** (2.79 g, 9.5 mmol, 1.0 equiv) in CH_3OH (15 mL) was added $Hg(OAc)_2$ (3.18 g, 9.99 mmol, 1.05 equiv) at room temperature. After being stirred for 6 h at room temperature, the resulting white suspension was diluted with CH_2Cl_2, poured into H_2O, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel flash column (eluted with 10% MeOH in CH_2Cl_2) to afford 1.76 g (92%) of methoxy alcohol **11**, mp 126–128.5 °C (CH_2Cl_2/Et_2O): ^1H NMR ($CDCl_3$, Me_4Si) δ 2.98 (3 H, s), 3.06 (3 H, s), 3.23 (3 H, s), 3.74 (1 H, $^1/_2$ABq, J = 11 Hz), 4.03 (1 H, $^1/_2$ABq, J = 11 Hz), 4.01 (1 H, $^1/_2$ABq, J = 17 Hz), 4.31 (1 H, $^1/_2$ABq, J = 17 Hz), 4.53 (1 H, br, D_2O exch); IR (NaCl, neat) 3360 (br), 1660, 1450, 1390 cm^{-1}; mass spectrum, m/e 171 ($M^+ - OCH_3$, 100), 157 (9.92), 143 (19.74). Anal. ($C_8H_{14}N_2O_4$) C, H, N.

1,4-Dimethyl-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-methoxy-2,5-piperazinedione (12). To a mixture of **11** (0.3773 g, 1.86 mmol, 1.0 equiv), *tert*-butyldimethylsilyl chloride (0.3371 g, 2.24 mmol, 1.2 equiv), and imidazole (0.3039 g, 4.46 mmol, 2.4 equiv) was added DMF (2 mL) at room temperature. After being stirred for 12 h at room temperature, the mixture was diluted with CH_2Cl_2, poured into 0.1 N HCl, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 0.5772 g (99%) of pure silyl ether **12**, mp 64.5–66 °C (hexanes/Et_2O): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.02 (6 H, s), 0.78 (9 H, s), 2.91 (3 H, s), 3.00 (3 H, s), 3.16 (3 H, s), 3.59 (1 H, $^1/_2$ABq, J = 9 Hz), 3.89 (1 H, $^1/_2$ABq, J = 9 Hz), 3.96 (2 H, s); IR (NaCl, neat) 1668, 1450, 1430, 1380, 1110 cm^{-1}; mass spectrum, m/e 316 (M^+, 0.62), 285 ($M^+ - OCH_3$, 3.46), 259 (66.31), 171 (100). Anal. ($C_{14}H_{28}N_2O_4Si$) C, H, N.

1,4-Dimethyl-3-(*p*-tolylthio)-2,5-piperazinedione (13). To a stirred solution of aldehyde **9** (4.0 g, 13.7 mmol) in CH_2Cl_2 (80 mL) was added 0.1 N NaOH (137 mL). The mixture was vigorously stirred for 20 min. The aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford the sulfide **13** (3.3 g, 91%), mp 180–182 °C (EtOAc): ^1H NMR ($CDCl_3$, Me_4Si) δ 2.22 (1 H, $^1/_2$ABq, J = 18 Hz), 2.40 (3 H, s), 2.75 (3 H, s), 3.18 (3 H, s), 3.35 (1 H, $^1/_2$ABq, J = 18 Hz), 4.94 (1 H, s), 7.31 (4 H, m); IR (NaCl, neat) 1655, 1460, 1390, 1305, 1110 cm^{-1}; mass spectrum, m/e 264 (M^+, 1.86), 246 (54.33), 123 (60.64), 32 (100). Anal. ($C_{13}H_{16}N_2O_2S$) C, H, N, S.

1,4-Dimethyl-3-methoxy-2,5-piperazinedione (14). To a stirred solution of the sulfide **13** (3.8 g, 14.4 mmol, 1.0 equiv) in MeOH (200 mL) was added $Hg(OAc)_2$ (4.6 g, 14.4 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 1 h, filtered, evaporated, and triturated with MeOH. Filtration of insoluble salts, evaporation, and trituration with hexane afforded methyl ether **14** as a syrup, which separates cleanly from the hexane. The clear syrup was washed several times with hexane to afford 2.16 g (85%) of pure **14**: ^1H NMR ($CDCl_3$, Me_4Si) δ 3.02 (3 H, s), 3.09 (3 H, s), 3.52 (3 H, s), 3.88 (1 H, $^1/_2$ABq, J = 18 Hz), 4.19 (1 H, $^1/_2$ABq, J = 18 Hz), 4.75 (1 H, s); IR (NaCl, neat) 1665, 1390, 1160 cm^{-1}; mass spectrum, m/e = 172 (M^+, 82), 142 (61.3), 42 (100).

1,4-Dimethyl-3-methoxy-6-allyl-2,5-piperazinedione (15). To a stirred solution of methyl ether **14** (145 mg, 0.84 mmol, 1.0 equiv) in THF (4 mL) at −78 °C was added LDA (1.0 mmol, 1.2 equiv) in THF (2 mL). The enolate solution was stirred for 1 min at −78 °C and transferred via cannula into a solution of allyl bromide (0.3 g, 2.5 mmol, 3.0 equiv) in THF (1 mL) at −78 °C. The dark solution was allowed to stir 1 h at −78 °C, warmed to room temperature, and stirred an aditional 0.5 h at room temperature. The mixture was diluted with CH_2Cl_2, poured into 1 N HCl, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with EtOAc, three elutions) to afford 117 mg (65.5%) of **15** as a glass: ^1H NMR ($CDCl_3$, Me_4Si) δ 2.7–2.9 (2 H, m), 3.10 (6 H, s), 3.43 (3 H, s), 4.18 (1 H, t, J = 4 Hz), 4.91 (1 H, s), 5.0–5.9 (3 H, m); IR (NaCl, neat) 1670, 1650, 1450, 1395, 1320, 1065 cm^{-1}; mass spectrum, m/e 212 (M^+, 12.04), 171 (100).

1,4-Dimethyl-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-methoxy-6-[3'-[(*tert*-butyldimethylsilyl)oxy]propyl]-2,5-piperazinedione (16). To a stirred solution of **12** (316 mg, 1.0 mmol, 1.0 equiv) in THF (8 mL) at −78 °C was added LDA (1.3 mmol, 1.3 equiv) in THF (2 mL). The yellow enolate solution was stirred for 1 min, and HMPA (0.52 mL) was added. After being stirred 1 min at −78 °C, the solution was transferred via cannula to a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-1-iodopropane (0.78 g, 2.6 mmol, 2.6 equiv) in THF (2 mL) at −78 °C. The mixture was allowed to stir 2 h at −78 °C, warmed to room temperature, and stirred an additional 1.5 h. The mixture was diluted with CH_2Cl_2, poured into H_2O, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 203 mg of **16** plus 108 mg of the corresponding diastereoisomer (64% combined), which were recombined for the subsequent transformations. Data for the major isomer: mp 72.5–73.5 °C (Et_2O/hexane): ^1H NMR ($CDCl_3$, Me_4Si) δ 0.01 (6 H, s), 0.02 (6 H, s), 0.86 (9 H, s), 0.92 (9 H, s), 1.05–1.8 (2 H, m), 1.8–2.5 (2 H, m), 2.90 (3 H, s), 3.01 (3 H, s), 3.20 (3 H, s), 3.2–3.9 (4 H, m), 4.01 (1 H, t, J = 4 Hz); IR (NaCl, neat) 1665, 1250, 1115, 830 cm^{-1}; mass spectrum, m/e 488 (M^+ + 1, 0.88), 487 (M^+, 0.44%), 456 ($M^+ - OCH_3$, 2.76), 431 (100). Anal. ($C_{23}H_{48}N_2O_5Si_2$) C, H, N.

1,4-Dimethyl-3-(hydroxymethyl)-3-methoxy-6-(3'-hydroxypropyl)-2,5-piperazinedione (17). To a stirred solution of **16** (0.203 g, 0.41 mmol, 1.0 equiv) in THF (2 mL) was added tetra-*n*-butylammonium fluoride trihydrate (0.33 g, 1.04 mmol, 2.5 equiv) at room temperature. The reaction was allowed to stir for 6 h, neutralized with 1 N HCl in CH_3OH, evaporated, and separated on PTLC silica gel (eluted twice with 10% MeOH in CH_2Cl_2) to afford the polar diol **17** (89 mg, 83%), mp 166–168 °C; ^1H NMR (CD_3OD, Me_4Si) δ 1.3–1.7 (2 H, m), 1.7–2.6 (2 H, m), 2.96 (3 H, s), 3.06 (3 H, s), 3.22 (3 H, s), 3.2–3.8 (4 H, m), 4.22 (1 H, t, J = 4 Hz); IR (NaCl, neat) 3300 (br), 1648, 1415 cm^{-1}; mass spectrum, m/e 260 (M^+, 0.56), 229 ($M^+ - OCH_3$, 100).

1,4-Dimethyl-3-methoxy-6-(3'-hydroxypropyl)-2,5-piperazinedione (18). To a stirred solution of olefin **15** (230 mg, 1.06 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was added B_2H_6 (1.06 mmol, 3.0 equiv) in THF. The mixture was allowed to stir for 15 min at 0 °C and for 4 h at room temperature. The reaction was quenched by sequential addition of 1 N NaOH (1.5 mL) and 30% H_2O_2 (0.42 mL), diluted with CH_2Cl_2, poured into brine, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford 153 mg (61%) of methoxy alcohol **18** as a glass: ^1H NMR ($CDCl_3$, Me_4Si) δ 1.4–2.4 (4 H, m), 2.7 (1 H, br s, D_2O exch), 3.00 (3 H, s), 3.04 (3 H, s), 3.56 (3 H, s), 3.4–3.8 (2 H, m), 4.60 (1 H, s); IR (NaCl, neat) 3400 (br), 1660, 1445, 1395, 1330, 1060 cm^{-1}; mass spectrum, m/e 198 (37.93), 128 (60.7), 74 (100).

8,10-Dimethyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (3a). To a stirred solution of methoxy alcohol **18** (66 mg, 0.3 mmol, 1.0 equiv) in MeCN (5 mL) was added camphorsulfonic acid (80 mg, 0.34 mmol, 1.1 equiv) and the mixture refluxed for 18 h. Evaporation of the solvent and separation of the crude mixture on PTLC silica gel (eluted with 89 parts of CH_2Cl_2/9 parts of MeOH/1 part of NH_4OH) afforded 28.4 mg (48%) of bicyclic piperazinedione **3a**, which was identical with that obtained from **6a** in every respect.

1-(Hydroxymethyl)-8,10-dimethyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (19). To a stirred solution of diol **17** (88 mg, 0.34 mmol, 1.0 equiv) in MeCN (3 mL) was added camphorsulfonic acid (100 mg, 0.4 mmol, 1.2 equiv) and the mixture refluxed for 6 h. The reaction was diluted with CH_2Cl_2, poured into aqueous $NaHCO_3$, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 89 parts of CH_2Cl_2/9 parts of MeOH/1 part of NH_4OH) to afford 57.6 mg (75%) of bicyclic piperazinedione **19**, mp 163–164 °C (EtOAc): ^1H NMR ($CDCl_3$, Me_4Si) δ 1.6–1.85 (2 H, m), 2.08–2.8 (2 H, m), 2.42 (1 H, dd, J_{ax} = 9 Hz, J_{bx} = 6 Hz, D_2O exch), 3.00 (3 H, s), 3.10 (3 H, s), 3.27–3.85 (2 H, m), 3.78 (1 H, dd, J_{ax} = 9 Hz, J_{ab} = 12.5 Hz), 4.10 (1 H, t, J = 4.5 Hz), 4.37 (1 H, dd, J_{bx} = 6 Hz, J_{ab} = 12.5 Hz); IR (NaCl, neat) 3400 (br), 1660, 1455, 1385 cm^{-1}; mass spectrum, m/e 228 (M^+, 37.9), 198 ($M^+ - CH_2O$, 29.8), 170 ($M^+ - C_3H_6O$, 26.7), 113 (100). Anal. ($C_{10}H_{16}N_2O_4$) C, H, N.

1,4-Dibenzyl-3-[3'-[(*tert*-butyldimethylsilyl)oxy]propyl]-6-methoxy-2,5-piperazinedione (20). To a stirred solution of silyl ether **6b** (341 mg, 0.6 mmol, 1.0 equiv) in MeOH (10 mL) plus THF (2 mL) was added $Hg(OAc)_2$ (208 mg, 0.65 mmol, 1.1 equiv) in one portion. The mixture was stirred for 12 h at room temperature, filtered, evaporated, and separated on PTLC silica gel (eluted with 33% Et_2O in Hexane) to afford 297 mg (99%) of diastereomerically pure **20** (oil): ^1H NMR ($CDCl_3$, $CHCl_3$) δ 0.03 (6 H, s), 0.89 (9 H, s), 1.0–1.6 (2 H, m), 1.6–2.3 (2 H, m), 3.38 (3 H, s), 3.36–4.22 (5 H, m), 4.77 (1 H, s), 5.2–5.6 (2 H, m), 7.29 (10 H, s); IR (NaCl, neat) 1660, 1440, 1245, 1090, 1060, 825 cm^{-1}; mass spectrum, m/e 481 ($M^+ - CH_3$, 1.74), 464 (1.6), 439 (22.7), 149 (100), 91 (46.8).

8,10-Dibenzyl-8,10-diaza-2-oxabicyclo[4.2.2]decane-7,9-dione (3b) from 21. Tetra-*n*-butylammonium fluoride trihydrate (227 mg, 0.72 mmol, 1.2 equiv) was added in one portion to a stirred solution of silyl ether **20** (297 mg, 0.6 mmol, 1.0 equiv) in THF (15 mL) at room temperature. The mixture was stirred for 1 h at room temperature, evaporated, and separated on PTLC silica gel (eluted with Et_2O) to afford 177 mg (77%) of diastereomerically pure methoxy alcohol **21** (glass), which was directly used for the following cyclization; ^1H NMR ($CDCl_3$, $CHCl_3$) δ 1.1–2.3 (4 H, m), 3.50 (3 H, s), 3.7–4.3 (5 H, m), 4.60 (1 H, s), 4.8–5.4 (3 H, m), 7.29 (10 H, s).

The methoxy alcohol **21** (177 mg, 0.46 mmol, 1.0 equiv) was dissolved in MeCN (15 mL), camphorsulfonic acid (106 mg, 0.46 mmol, 1.0 equiv) was added in one portion, and the mixture was refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was diluted with CH_2Cl_2 and washed with 0.5 N NaOH. The organic extract was dried over anhydrous sodium sulfate, filtered, evaporated, and crystallized from EtOAc to afford 137 mg (85%) of bicyclic **3b**, which was identical with that obtained from **6b** in every respect.

Spiropiperazinedione 23 from 6b. To a stirred solution of **6b** (311 mg, 0.54 mmol, 1.0 equiv) in THF (15 mL) containing powdered, activated 4-Å sieves at −78 °C was added a solution of tetra-*n*-butylammonium fluoride trihydrate (188 mg, 0.6 mmol, 1.1 equiv) in THF (5 mL) dropwise. The solution was allowed to warm gradually to room temperature and stirred for 10 h at room temperature. The mixture was neutralized with 1 N HCl in MeOH (0.6 mL), filtered, and evaporated. Separation of the residue on PTLC silica gel (eluted with 25% hexanes in Et_2O) afforded 68 mg (36%) of dibenzylspiropiperazinedione **23** (oil):

^{1}H NMR ($CDCl_3$, 360 MHz, Me_4Si) δ 1.8–2.3 (3 H, m), 2.7 (1 H, m), 3.93 (1 H, $^1/_2$ABq, J = 18 Hz), 4.05 (2 H, m), 4.10 (1 H, $^1/_2$ABq, J = 18 Hz), 4.47 (1 H, $^1/_2$ABq, J = 16.5 Hz), 4.63 (2 H, m), 4.90 (1 H, $^1/_2$ABq, J = 16.5 Hz), 7.25 (10 H, m); IR (NaCl, neat) 1670, 1490, 1449, 1430, 1400, 1030 cm^{-1}; mass spectrum, m/e 350 (M^+, 2.91), 245 (4.98), 217 (6.81), 174 (10.28), 91 (100).

8,10-Dimethyl-8,10-diaza-6-hydroxy-2-oxabicyclo[4.2.2]decane-7,9-dione (26). To a stirred solution of bicyclic piperazinedione **3a** (34 mg, 0.17 mmol, 1.0 equiv) in THF (2 mL) at −78 °C was added a solution of LDA (0.26 mmol, 1.5 equiv) in THF (1 mL). Immediately, a deep green solution resulted. After being stirred for 1 min at −78 °C, MoOPH (148 mg, 0.34 mmol, 2.0 equiv) was quickly added in one portion. The mixture was allowed to stir for 30 min at −78 °C, warmed to room temperature, and stirred an additional 30 min. The reaction was diluted with CH_2Cl_2, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 50% acetone in Et_2O) to afford the alcohol **26** (24 mg, 65%) as a glass: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.5–1.65 (1 H, m), 1.75–1.85 (1 H, m), 1.87–1.97 (1 H, m), 2.23–2.33 (1 H, m), 3.02 (3 H, s), 3.07 (3 H, s), 3.47 (1 H, dd, J = 9 Hz, J = 14 Hz), 3.88 (1 H, dd, J = 8 Hz, J = 14 Hz), 4.52 (1 H, s, D_2O exch), 5.14 (1 H, s); IR (NaCl, neat) 3350 (br), 1670, 1640, 1390 cm^{-1}; mass spectrum, m/e 214 (M^+, 2.19), 172 (100), 156 (3.76). Anal. ($C_9H_{14}N_2O_4$) C, H, N.

8,10-Dimethyl-8,10-diaza-6-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[4.2.2]decane-7,9-dione (27). *tert*-Butyldimethylsilyl triflate was freshly prepared in situ by addition of 1.0 equiv of Ag(I) triflate to a dry CH_2Cl_2 solution of *tert*-butyldimethylsilyl chloride and vigorously stirred for 30 min. The AgCl precipitated during this time and was allowed to settle. The supernatant was used directly as a 0.1 M solution.

To a stirred solution of alcohol **26** (54.3 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added 1.5 equiv of a freshly prepared CH_2Cl_2 solution of *tert*-bityldimethylsilyl triflate. To this solution was added 2,6-lutidine (53 mg, 0.5 mmol, 2.0 equiv) in one portion. The mixture was stirred for 4 h at room temperature, diluted with CH_2Cl_2, poured into 0.1 N HCl, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 50% acetone in Et_2O) to afford 74.3 mg (90%) of the silyl-protected derivative **27**, mp 140–141 °C (CH_2Cl_2): ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.03 (3 H, s), 0.17 (3 H, s), 0.92 (9 H, s), 1.55–2.0 (2 H, m), 2.05–2.17 (2 H, m), 3.00 (3 H, s), 3.05 (3 H, s), 3.41 (1 H, m), 3.83 (1 H, m), 5.10 (1 H, s); IR (NaCl, neat) 1670, 1450, 1385, 1240, 1180 cm^{-1}; mass spectrum, m/e 328 (M^+, 0.93), 313 ($M^+ - CH_3$, 0.56), 271 (14.19), 243 (2.25), 184 (13.38), 28 (100). Anal. ($C_{15}H_{28}N_2O_4Si$) C, H, N.

Preparation of Aldol 28 from 27 and 30. To a stirred solution of bicyclic piperazinedione **27** (40 mg, 0.12 mmol, 1.0 equiv) in THF (2 mL) at −78 °C was added to a solution of LDA (0.18 mmol, 1.5 equiv) in THF (1 mL). The mixture was stirred for 1 min at −78 °C, and aldehyde **30** (35 mg, 0.24 mmol, 2.0 equiv) was added dropwise. The mixture was stirred for 4 h at −78 °C, warmed to room temperature, diluted with CH_2Cl_2, poured into brine, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted twice with Et_2O) to afford three diastereomeric aldols **28**: major isomer (30 mg, 52%); minor isomer (7 mg, 13%); minor isomer (8 mg, 14%).

Data for major aldol **28a**: mp 123–124 °C (hexanes); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.15 (3 H, s), 0.30 (3 H, s), 0.94 (9 H, s), 1.17 (3 H, s), 1.34 (3 H, s), 1.39 (3 H, s), 1.89–2.15 (4 H, m), 3.00 (3 H, s), 3.07 (3 H, s), 3.24–3.76 (1 H, m), 3.84–3.98 (3 H, m), 4.10 (1 H, d, J = 10 Hz), 6.45 (1 H, d, J = 10 Hz, D_2O exch); IR (NaCl, neat) 3330 (br), 1685, 1650, 1375, 1250, 1185, 1130, 1070, 1055, 830 cm^{-1}; mass spectrum, m/e 457 ($M^+ - CH_3$, 7.9), 415 ($M^+ - C_4H_9$, 44.3), 357 (27.1), 115 (100). Anal. ($C_{22}H_{40}N_2O_7Si$) C, H, N.

Data for minor isomer **28b**: mp 124–126 °C (hexanes); ^{1}H NMR ($CDCl_3$, $CHCl_3$) δ 0.14 (3 H, s), 0.28 (3 H, s), 0.87 (9 H, s), 1.13 (3 H, s), 1.31 (3 H, s), 1.43 (3 H, s), 1.44–2.13 (4 H, m), 2.97 (3 H, s), 3.01 (3 H, s), 3.23–3.46 (1 H, m), 3.65 (1 H, $^1/_2$ABq, J = 9.0 Hz), 3.83–3.89 (1 H, m), 4.09 (1 H, d, J = 10.5 Hz), 4.23 (1 H, $^1/_2$ABq, J = 9.0 Hz), 5.88 (1 H, d, J = 10.5 Hz, D_2O exch); IR (NaCl, neat) 3360 (br), 1680, 1645, 1380, 1250, 1190, 1130, 1070, 1055, 830 cm^{-1}; mass spectrum, m/e 472 (M^+, 0.3), 457 ($M^+ - CH_3$, 8.7), 415 ($M^+ - C_4H_9$, 47.9), 357 (30.5), 115 (100). Anal. ($C_{22}H_{40}N_2O_7Si$) C, H, N.

Data for minor isomer **28c**: mp 160–161 °C (Et_2O/hexanes); ^{1}H NMR ($CDCl_3$, $CHCl_3$) δ 0.14 (3 H, s), 0.28 (3 H, s), 0.89 (9 H, s), 1.22 (3 H, s), 1.33 (3 H, s), 1.38 (3 H, s), 1.58–2.15 (4 H, m), 2.84 (1 H, d, J = 3.9 Hz), 2.97 (3 H, s), 3.24 (3 H, s), 3.20–3.42 (1 H, m), 3.71 (1 H, $^1/_2$ABq, J = 8.4 Hz), 3.70–4.10 (1 H, m), 4.18 (1 H, $^1/_2$ABq, J = 8.4 Hz), 4.85 (1 H, d, J = 3.9 Hz); IR (NaCl, neat) 3400 (br), 1670, 1370, 1245, 1180 cm^{-1}; mass spectrum, m e 472 (M^+, 0.4), 457 ($M^+ - CH_3$, 10.4), 415 ($M^+ - C_4H_9$, 41.8), 115 (100). Anal. ($C_{22}H_{40}N_2O_7Si$) C, H, N.

***N,N'*-Dimethyl-4-desmethylenebicyclomycin (29).** To a stirred solution of the major aldol **28a** (17 mg, 0.035 mmol, 1.0 equiv) in THF (2 mL) at 0 °C was added a solution of *n*-$Bu_4NF\cdot 3H_2O$ (15 mg, 0.045 mmol, 1.3 equiv) in THF (1 mL) dropwise. The mixture was stirred for 1 h at 0 °C and for 2 h at room temperature, diluted with CH_2Cl_2, poured into saturated NaCl solution, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and filtered through a small plug of silica gel (Et_2O/acetone) to afford the corresponding C-6 hydroxyl derivative, which was used for the subsequent acetonide removal without further purification; ^{1}H NMR ($CDCl_3$, $CHCl_3$) δ 1.12 (3 H, s), 1.32 (3 H, s), 1.37 (3 H, s), 1.6–2.2 (4 H, m), 2.99 (3 H, s), 3.10 (3 H, s), 3.3–3.7 (1 H, m), 3.8–4.1 (5 H, m), 6.33 (1 H, d, J = 10.25 Hz, D_2O exch). The residue was dissolved in MeOH (0.42 mL), and 0.2 N H_2SO_4 (0.34 mL) was added. The mixture was stirred for 3 h at room temperature. A suspension of $Ba(OH)_2\cdot 8H_2O$ (23 mg, 0.07 mmol, 2.0 equiv) in H_2O (0.5 mL) was added, and the mixture was stirred vigorously, evaporated, and separated on PTLC silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 3 mg (27% from **28**) of **29** as a glass: ^{1}H NMR (C_6D_6, 360 MHz, C_6HD_5) δ 1.01 (3 H, s), 1.2–1.5 (1 H, m), 1.68–1.76 (1 H, m), 1.95–2.0 (1 H, m), 2.35–2.55 (3 H, m), 2.65 (3 H, s), 2.70 (3 H, s), 2.96 (1 H, d, J = 10 Hz, D_2O exch), 3.56 (1 H, $^1/_2$ABq, J = 10.2 Hz), 3.70 (1 H, d, J = 10 Hz, D_2O exch), 3.73–3.81 (1 H, m), 4.14 (1 H, $^1/_2$ABq, J = 10.2 Hz), 4.24 (1 H, m), 6.44 (1 H, s, D_2O exch); IR (NaCl, neat) 3370 (br), 1665, 1640, 1380, 1035 cm^{-1}; mass spectrum, m/e 300 (8.2), 214 (23.1), 213 (98.5), 105 (0.5), 28 (100). Anal. ($C_{13}H_{22}N_2O_7$) C, H, N.

29 from HF·Py Deprotection of 28. To a stirred solution of aldol **28a** (28.1 mg, 0.06 mmol) in THF (3 mL) was added excess HF·pyridine complex at room temperature. The mixture was stirred for 3 h at room temperature, diluted with CH_2Cl_2, poured into saturated NaCl, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 89 parts of CH_2Cl_2/9 parts of MeOH/1 part of NH_4OH) to afford 14 mg (74%) of **29**, which was identical in every respect with that obtained as described above for **28a** by the two step deprotection sequence.

29 via the Dianion 31. To a stirred solution of alcohol **26** (11.5 mg, 0.054 mmol, 1.0 equiv) in THF (1 mL) at −78 °C was added a solution of LDA (0.16 mmol, 3.0 equiv) in THF (1 mL). The solution stirred for 1 min at −78 °C, and the aldehyde **30** (23 mg, 0.16 mmol, 3.0 equiv) was added in one portion. The mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature, diluted with CH_2Cl_2, poured into saturated NaCl, and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 89 parts of CH_2Cl_2/9 parts of MeOH/1 part of NH_4OH) to afford four diastereomeric aldols (58% combined) in a ratio of 2:1.5:1.5:1 plus unreacted starting material (17%). The major aldol was identical in every respect with the intermediate formed from Bu_4NF deprotection of **28a** (see experimental above). The acetonide was similarly hydrolyzed with 0.2 N H_2SO_4 in MeOH to afford **29**, which was identical with that obtained from **28a**.

Note, all ^{1}H NMR measurements except those noted at 360 MHz were obtained at 100 MHz.

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Registry No. **3a**, 83135-81-3; **3b**, 83135-85-7; **3c**, 83135-88-0; **4a**, 5076-82-4; **4b**, 42492-87-5; **4c**, 7383-57-5; **5a**, 83135-78-8; **5b**, 83135-82-4; **5c**, 83135-86-8; **6a**, 83135-79-9; **6b**, 83135-83-5; **6c**, 83151-93-3; **7a**, 83135-80-2; **7b**, 83135-84-6; **7c**, 83135-87-9; **8**, 83135-89-1; **9**, 83135-90-4; **10**, 83135-91-5; **11**, 83135-92-6; **12**, 83135-93-7; **13**, 83135-94-8; **14**, 83135-95-9; **15**, 78878-00-9; **16**, isomer 1, 83151-94-4; **16**, isomer 2, 83135-96-0; **17**, 83135-97-1; **18**, 78878-01-0; **19**, 83135-

98-2; **20**, 83135-99-3; **21**, 83136-00-9; **23**, 83152-06-1; **26**, 83136-01-0; **27**, 83136-02-1; **28a**, 83136-03-2; **28b**, 83136-05-4; **28c**, 83198-40-7; **29**, 83136-04-3; **30**, 81600-36-4; 3-[(*tert*-butyldimethylsilyl)oxy]-1-iodopropane, 78878-05-4; 2,2′-dipyridyl sulfide, 4262-06-0; phenylmercuric perchlorate, 19664-02-9; *p*-toluenesulfenyl chloride, 933-00-6.

Supplementary Material Available: X-ray stereostructure for compound **28a** plus Tables 1–10, including fractional atom coordinates, bond lengths, bond angles, hydrogen coordinates, and temperature factors for both structures **6a** and **28a**. Full experimental section for both structure determinations is also included (49 pages). Ordering information is given on any current masthead page.

Effect of 3-Methyl Substituents on the Thermal [1,5]- and [1,7]-Sigmatropic Hydrogen Shifts of Vinylallenes and Other Seco Steroids Related to Vitamin D: Synthesis of 3-Methyl- and 3,3-Dimethyl-Substituted Analogues of 3-Deoxy-1α,25-dihydroxyvitamin D_3[1]

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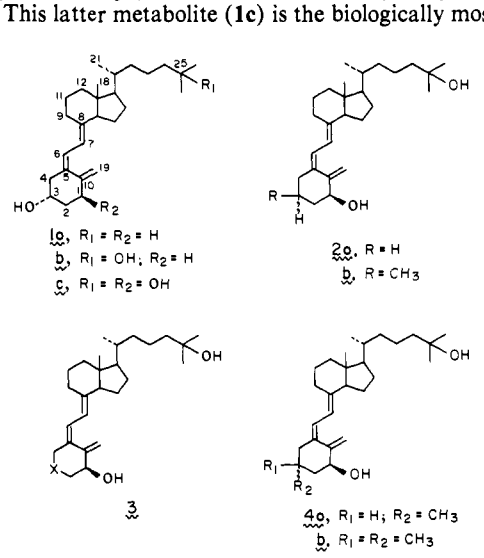
Abstract: The 3-methyl-substituted analogues of 1α,25-dihydroxyvitamin D_3 (**2b**, **4a**, and **4b**), useful for probing structure–function relationships in the vitamin D_3–endocrine system, were synthesized by using vinylallenols **21–26** as key intermediates. The vinylallenols and their rearrangement products were studied to determine the effect of 3-methyl substitutents on their thermal behavior. The thermal rearrangement (100 °C) of vinylallenols of this type involves a [1,5]-sigmatropic hydrogen shift by either of two competing pathways. While one pathway affords a product containing the vitamin D triene, the products in the competing process consist of a triad of seco steroids related by [1,7]-sigmatropic hydrogen shifts. The vinylallenols **21**, **22**, **25**, and **26** were synthesized by coupling the C/D fragment, de-*A*,*B*-8α-ethynyl-25-cholesten-8β-ol benzoate (**16b**), with a heterocuprate derived from silyl ethers of *cis*-2,5-dimethyliodocyclohex-2-en-1-ol (**19b**) or 2,5,5-trimethyliodocylohex-2-en-1-ol (**20**) (followed by deprotection). The epimeric vinylallenols **23** and **24** were obtained by an S_N2 displacement process at C-1 of the corresponding *cis*-vinylallenols **21** and **22**, respectively. The thermolysis products of each vinylallenol rearrangement in the 3-methyl series were separated and characterized. The major products from the 1*R* alcohols **21** and **24** were the corresponding vitamins **27** and **39** whereas vitamins **31** and **35** were minor products of the thermolysis of the 1*S* alcohols **22** and **23**. In each case, the remaining products consisted of a triad of thermally interconvertible isomers of the type **8**, **9**, and **10**. The vitamin isomers possessing the side-chain double bond (**31**, **27**, and **43**) were further elaborated to the desired 1α,25-dihydroxyvitamin analogues **2b**, **4a**, and **4b**.

The principal metabolic pathway of vitamin D_3 (**1a**, cholecalciferol) involves successive hydroxylation to produce 25-hydroxyvitamin D_3 (**1b**) and then 1α,25-dihydroxyvitamin D_3 (**1c**).[2] This latter metabolite (**1c**) is the biologically most active substance known for eliciting the classic vitamin D mediated responses, intestinal calcium absorption (ICA) and bone-calcium mobilization (BCM). It is believed to be the physiologically active form of **1a**, and it should be considered to behave as a steroid hormone both from a functional and a structural point of view. The synthesis of analogues related to this steroid hormone continues to be of considerable interest in order to better understand its mode of action. Although previous studies had established that the hydroxyl functionalities at the C-1 and C-25 positions were most critical for optimum biological activity,[3] modifications at the C-3 position imparted biological properties of unusual interest to this hormone. Unlike the natural metabolite **1c**, which elicits both ICA and BCM, the 3-deoxy analogue **2a** exhibited only ICA activity.[4] Since this selective agonist ability is potentially useful



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