mg, 25% from **25**) as a yellow-orange solid: mp 138–140 °C; IR ($CHCl_3$) 1670, 1595 cm^{-1}; NMR ($CDCl_3$) δ 8.32–7.53 (m, 4 H), 7.43–7.13 (m, 2 H), 4.04 (s, 3 H), 3.96 (s, 3 H).

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Registry No. 1, 73453-53-9; 2, 73453-54-0; 3, 73453-55-1; 4, 73453-56-2; 5, 21418-08-6; 6, 66617-31-0; 7, 73453-57-3; 8, 73453-58-4; 9, 73453-59-5; 10, 73453-60-8; 12, 54125-02-9; 13, 73453-61-9; 14, 767-00-0; 18, 73453-62-0; 19, 73453-63-1; 20, 73453-64-2; 21, 73453-65-3; 22, 73453-66-4; 23, 73453-67-5; 24, 73453-68-6; 25, 73453-69-7; 26, 73453-70-0; 27, 73453-71-1; acrylonitrile, 75-05-8.

Syntheses of the Fungal Metabolites (±)-Gliovictin and (±)-Hyalodendrin

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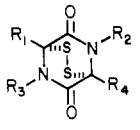
The syntheses of (±)-gliovictin (**9**) and (±)-hyalodendrin (**20**) are described. Factors which control the stereochemistry of alkylation or sulfenylation of piperazinedione-derived enolates are discussed. An improved technique for introducing a mercapto group by enolate sulfenylation is presented.

The epidithiapiperazinedione moiety **1** is common to the



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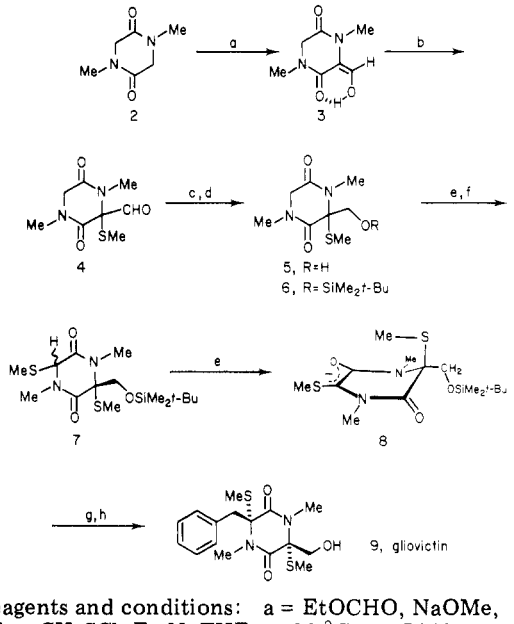
class of fungal metabolites which includes the gliotoxins, sporidesmins, aranotins, verticillins, hyalodendrins, melinacidins, and others.[1a-d] This unique ring system is responsible for the potent antiviral, antifungal, antibiotic, antitumor, and cytotoxic properties which the class displays.

The most successful strategies for the synthesis of epidithiapiperazinediones involve introduction of sulfur into a preformed 2,5-piperazinedione ring. Both nucleophilic and electrophilic sources of sulfur have been utilized.[1a-d] Any approach to epidithiapiperazinediones must address the problem of stereochemistry; both sulfur atoms must be oriented on the same face of the 2,5-piperazinedione ring. Recently, we communicated[2] a stereoselective synthesis of (±)-gliovictin (**9**, Scheme I). Herein, we detail our syntheses of (±)-gliovictin (**9**) and (±)-hyalodendrin (**20**, Scheme III) and discuss factors which control stereochemistry during the assembly of these and other related systems.

Results

Synthesis of (±)-Gliovictin. As outlined in Scheme I, monoformylation of 1,4-dimethyl-2,5-piperazinedione (**2**, sarcosine anhydride) with ethyl formate and sodium methoxide provides enolic aldehyde **3** in 96% yield. Enol **3** can be sulfenylated cleanly at low temperature with a variety of sulfenyl chlorides in the presence of base,[3] typically triethylamine. For example, addition of a slight excess of methylsulfenyl chloride[4] to **3** and 1.0 equiv of triethylamine in tetrahydrofuran at −100 °C provides, after filtration of insoluble $Et_3N{\cdot}HCl$, analytically pure, crystalline (methylthio)carboxaldehyde **4**, in nearly quantitative yield. The high yield and purity of the sulfenylation reactions obviates the need for purification of the derived α-mercapto aldehydes which deformylate upon contact with silica gel or dilute aqueous acid.

Scheme I[a]



[a] Reagents and conditions: a = EtOCHO, NaOMe, THF; b = CH_3SCl, Et_3N, THF, −100 °C; c = LiAl-(t-BuO)$_3$H, THF; d = t-$BuMe_2SiCl$, imidazole, DMF; e = LDA, THF, −78 °C; f = MeSSMe, THF, −78 °C; g = benzyl bromide; h = HCl, MeOH, H_2O.

(1) Reviews: (a) Taylor, A. In "Microbial Toxins"; Academic Press: New York, 1971; Vol. 7, Chapter 10, p 337. (b) Sammes, P. G. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51; (c) Leigh, C.; Taylor, A. *Adv. Chem. Ser.* **1976**, *No. 149*, 228; (d) Ganem, B. *Tetrahedron* **1978**, *34*, 3353.

(2) Williams, R. M.; Rastetter, W. H. *Tetrahedron Lett.* **1979**, 1187.

(3) Somewhat surprisingly, **3** was found to be unreactive toward sulfenyl chlorides (Ph_3CSSCl, CH_3SCl) in the absence of base.

(4) (a) Brintzinger, H.; Pfonnstiel, K.; Koddebusch, H.; Kling, K. E. *Chem. Ber.* **1950**, *83*, 87. (b) Seebach, D.; Teschner, M. *Ibid.* **1976**, *109*, 1601.

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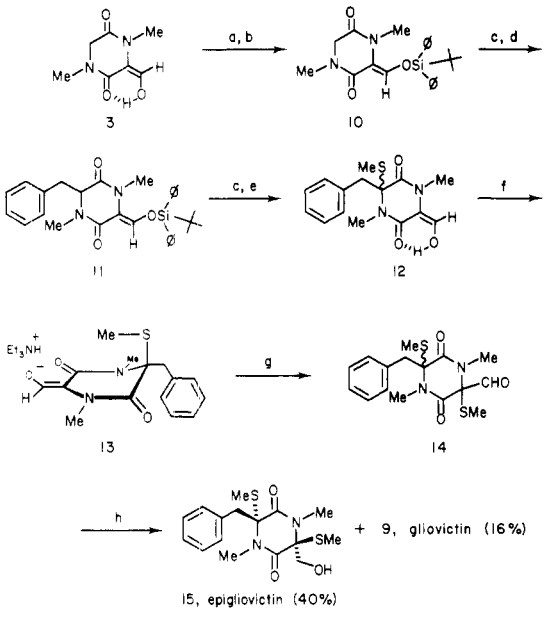
Scheme II[a]

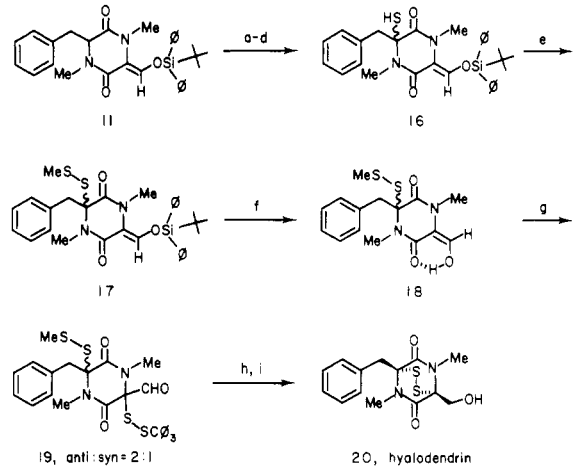


[a] Reagents and conditions: a = *t*-BuOK, THF, EtOH; b = *t*-BuPh$_2$SiCl, DMF; c = LDA, THF, −78 °C; d = benzyl bromide; e = MeSSMe, THF, −78 °C; f = Et$_3$N; g = CH$_3$SCl, THF, −100 °C; h = LiAl(*t*-BuO)$_3$H, THF.

Reduction of **4** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran affords crystalline alcohol **5** (92% yield), thereby introducing the geminal hydroxymethyl and methylthio groups found in (±)-gliovictin (**9**). Stereoselective conversion of **5** into (±)-gliovictin (**9**) is achieved via *tert*-butyldimethylsilyl ether[5] **6** by introduction of the remaining methylthio and benzyl groups. Thus, sulfenylation of the enolate of **6** with dimethyl disulfide gives, after chromatography, a mixture of diastereomers **7** in 51% yield (66% based on recovered **6**).[6] Benzylation of the enolate of diastereomers **7**, followed by acid hydrolysis of the silyl protecting group and chromatography, affords (±)-gliovictin (**9**) in 85% yield (38% overall from sarcosine anhydride or 50% overall based on recovered **6**). Synthetic (±)-gliovictin is indistinguishable from natural material[7] by ^{1}H NMR, IR, mass spectrum, TLC, and combustion analysis. Analysis of crude synthetic (±)-gliovictin by LC reveals that less than 10% of diastereomeric material (see **15**, Scheme II) is formed in the benzylation step (**8** → **9**).

In an alternative, but less stereoselective, approach (Scheme II), silyl enol ether **10** is prepared cleanly from the potassium salt of **3** and *tert*-butyldiphenylsilyl chloride[8] in *N*,*N*-dimethylformamide. Benzylation of the enolate of **10** with benzyl bromide in tetrahydrofuran affords **11** in 80–97% yield (yield varies with scale of reaction, see Experimental Section). Sulfenylation of the enolate of **11** with dimethyl disulfide *directly* affords methylthio enol **12** in 82% yield. An unexpected in situ deprotection of the silyl enol ether by the lithium thiomethoxide generated during sulfenylation occurs in this reaction.[9] As evidence, chromatographic purification of **12** also affords 85% of *tert*-butyldiphenylsilyl methyl thioether.

Scheme III[a]



[a] Reagents and conditions: a = LDA, THF, −78 °C; b = monoclinic sulfur, THF, −78 °C; c = HCl, MeOH; d = NaBH$_4$, EtOH; e = CH$_3$SCl, Et$_3$N, THF, −78 °C; f = HCl, THF, MeOH, H$_2$O; g = Ph$_3$CSSCl, Et$_3$N, THF, −78 °C; h = NaBH$_4$, THF, isopropyl alcohol; i = KI$_3$, pyridine.

The conversion of **12** into (±)-gliovictin (**9**) requires the introduction of geminal hydroxymethyl and methylthio groups as was achieved in the conversions **3** → **4** → **5** of Scheme I. Sulfenylation, however, of the triethylammonium enolate of **12** (see **13**) with methylsulfenyl chloride in tetrahydrofuran at −100 °C affords a 3:1 mixture of diastereomers **14**, favoring the *undesired* anti isomer. Without purification, the mixture of diastereomers **14** is reduced with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran to afford, after chromatography, 16% of (±)-gliovictin (**9**) and 40% of the diastereomer **15** (epigliovictin).

Synthesis of (±)-Hyalodendrin. For the preparation of hyalodendrin (**20**, Scheme III), mercapto instead of methylthio groups must be introduced into the piperazinedione nucleus. Thus, a means was sought to convert **11** into its α-mercapto derivative via the enolate (compare **11** → **12**, Scheme II). Sulfenylation of the enolate of **11** with elemental sulfur in liquid ammonia, according to Schmidt et al.,[10] is precluded, however, by the lability of the silyl enol ether to ammonia. Orthorhombic sulfur (S$_8$) is relatively insoluble in solvents commonly used for enolate chemistry, e.g., tetrahydrofuran. Attempts to sulfenylate the enolate of **11** with orthorhombic sulfur (S$_8$) in this solvent led to dark, complex mixtures of products.

The *tert*-butyldiphenylsilyl enol ether remained, nonetheless, a desirable protecting group. It is stable under reductive conditions, mildly acidic conditions, and the strongly basic conditions required for enolate formation

(5) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(6) Starting material (**6**) is probably regenerated by reaction of the starting enolate with the acidic proton (α to sulfur) in product **7**. The mixture of diastereomers in product **7** thus may be formed, in part, upon quenching of the reaction with HCl(aq) (see Experimental Section). Because of this ambiguity the degree of stereoselectivity during the actual sulfenylation step cannot be determined.

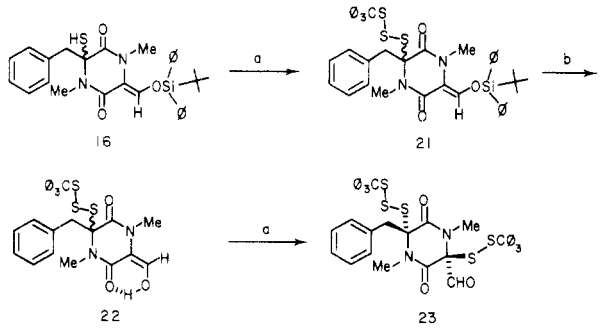
(7) Authentic samples of bis[dethio(methylthio)hyalodendrin] (antipode of gliovictin) and hyalodendrin were kindly furnished by Dr. George M. Strunz of the Canadian Forestry Service. Hyalodendrin and its antipode (No. A26771A) were also kindly provided to us by Eli Lilly and Co. For details of isolation and structure determination of the natural products, see: (a) Dorn, F.; Arigoni, D. *Experientia* **1974**, *30*, 134; (b) DeVault, R. L.; Rosenbrook, W., Jr. *J. Antibiot.* **1973**, *26*, 532; (c) Michel, K. H.; Chaney, M. O.; Jones, N. D.; Hoehn, M. M.; Nagarajan, R. *J. Antibiot.* **1974**, *27*, 57; (d) Strunz, G. M.; Heissner, G. J.; Kakushima, M.; Stillwell, M. A. *Can. J. Chem.* **1974**, *52*, 325; (e) Strunz, G. M.; Kakushima, M.; Stillwell, M. A.; Heissner, C. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2600; (f) Strunz, G. M.; Kakushima, M.; Stillwell, M. A. *Can. J. Chem.* **1975**, *53*, 295; (g) Stillwell, M. A.; Magasi, L. P.; Strunz, G. M. *Can. J. Microbiol.* **1974**, *20*, 579.

(8) Hanessian, S.; Lavalle, P. *Can. J. Chem.* **1975**, *53*, 2975.

(9) A similar, base-promoted desilylation was noted by Danishefsky et al. in their total synthesis of *dl*-pentalenolactone: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1979**, *101*, 7020.

(10) (a) Poisel, H.; Schmidt, U. *Chem. Ber.* **1972**, *105*, 625. (b) Öhler, E.; Poisel, H.; Tataruch, F.; Schmidt, U. *Ibid.* **1972**, *105*, 635.

Scheme IV[a]



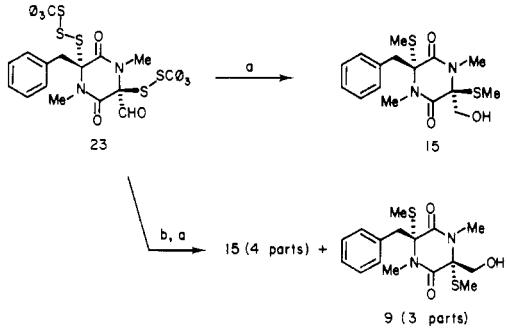
[a] Reagents and conditions: a = Ph_3CSSCl, Et_3N, THF, −78 °C; b = HCl, THF, MeOH, H_2O.

(e.g., lithium diisopropylamide/tetrahydrofuran). Piperazinediones bearing the *tert*-butyldiphenylsilyl group are often crystalline yet are soluble in most organic solvents. Further, deprotection of the silyl enol ether can be achieved under a variety of conditions, i.e., 1.0 equiv of potassium fluoride in methanol at 0 °C, 1.0 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran at 25 °C, liquid ammonia/tetrahydrofuran at −78 °C, 5% HCl in methanol at 25 °C, or LiSMe in tetrahydrofuran (vide supra).

A very simple solution was realized for achieving clean sulfenylation of the enolate of **11** (Scheme III). Warming of orthorhombic sulfur (S_8) to ca. 100 °C in vacuo causes the material to darken slightly, owing to the formation of the allotropic modification, monoclinic sulfur (S_8).[11] Up to 1.0 g of elemental sulfur, treated in this fashion, dissolves in 60 mL of tetrahydrofuran. Rapid cooling of this solution to −78 °C followed immediately by addition of the enolate of **11** provides, upon reductive workup ($NaBH_4$), clean mercaptan **16** in nearly quantitative yield.

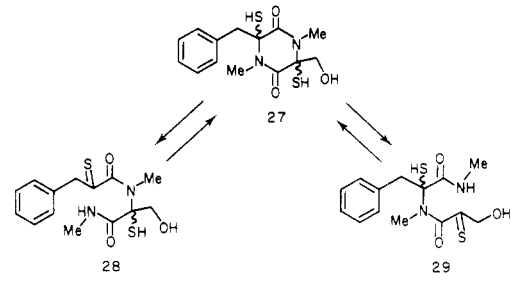
Unfortunately, no highly stereoselective method was readily found[12] for conversion of **16** into (±)-hyalodendrin (**20**). The remainder of Scheme III, nonetheless, depicts a successful conversion. Mercaptan **16** is converted into the corresponding enolic methyl disulfide **18** in 51% yield by reaction with methylsulfenyl chloride[4]/triethylamine followed by removal of the silyl protection by acid hydrolysis. Sulfenylation of **18** with triphenylmethyl chlorodisulfide[13]/triethylamine, in tetrahydrofuran at −78 °C, affords a 2:1 mixture of diastereomers **19**, favoring the *undesired* anti isomer.[14] Reduction of **19** with sodium borohydride followed by oxidation with KI_3 in pyridine[15,16] and chromatography on silica gel affords a 29.4% yield of (±)-hyalodendrin (**20**) as pale yellow crystals. Synthetic

Scheme V[a]

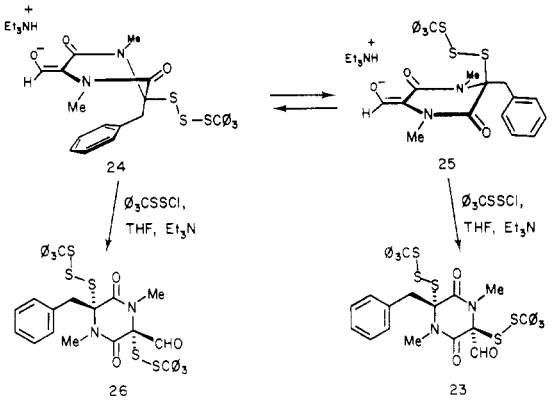


[a] Reagents and conditions: a = $NaBH_4$, MeOH, MeI, pyridine, 0 °C to room temperature; b = $NaBH_4$, THF, isopropyl alcohol, reflux.

Scheme VI



Scheme VII



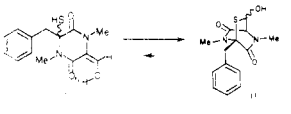
(±)-hyalodendrin,[17] so produced, is indistinguishable from natural material[7] by ^1H NMR, IR, and mass spectra and TLC.

The sulfenylation of the triethylammonium enolate of **18** (Scheme III) can proceed from either face of the piperazinedione, though some preference (i.e., 2:1) is seen for entry of the sulfenylating agent from the side bearing the benzyl group. To assess the influence of the bulk of the group attached to sulfur (e.g., the MeS group in **18**), we prepared the trityl trisulfide **22** (Scheme IV). Thus, mercaptan **16** can be sulfenylated with triphenylmethyl chlorodisulfide[13]/triethylamine (**16** → **21**) and the silyl protection removed by acid hydrolysis, affording **22**. Sulfenylation of the triethylammonium enolate of **22**, as described for **18** (vide supra), produces carboxaldehyde **23** virtually uncontaminated by epimeric material (^1H NMR).

The stereochemistry of **23** is confirmed by its correlation with (±)-epigliovictin (Scheme II). Thus, reductive methylation of **23** (Scheme V) according to Strunz et al.[7d] (CH_3I, $NaBH_4$, pyridine) produces (±)-epigliovictin (**15**)

(11) See entry No. 8764 (sulfur) in: "The Merck Index", 9th ed.; Windholz, M., Ed.; Merck and Co., Inc.: Rahway, NJ 1976.

(12) Deprotection of the silyl group of **16** produced the bicyclic hemimercaptal isomer ii. The equilibration and sulfenylation of i ⇌ ii are currently under investigation in these laboratories.



(13) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 211.

(14) The aldehyde ^1H NMR absorption of the anti isomer appears further downfield than the corresponding absorption for the syn isomer in which the aldehyde proton is shielded by the benzyl group. (see Experimental Section). A similar effect is seen with diastereomers **14** (Scheme II).

(15) Ottenheijm, H. C. J.; Herscheid, J. D. M.; Kerkhoff, G. P. C.; Spande, T. F. *J. Org. Chem.* **1976**, *41*, 3433.

(16) The undesired anti isomer is probably polymerized by KI_3 in pyridine. An origin band on the preparative TLC plate used for purification of **20** may be due to this polymeric material.

(17) For other syntheses of hyalodendrin, see: (a) Strunz, G. M.; Kakushima, M. *Experientia* **1974**, *30*, 719; (b) Fukuyama, T.; Nakatsuka, S.; Kishi, Y. *Tetrahedron Lett.* **1976**, 3393.

plus a trace of (±)-gliovictin (**9**) (LC analysis, ratio of **15** to **9** >10:1). Interestingly, when **23** is first reduced with $NaBH_4$ in refluxing isopropyl alcohol/tetrahydrofuran and then methylated (Scheme V), a 4:3 ratio of (±)-epigliovictin (**15**) to (±)-gliovictin (**9**) is obtained. This result suggests that dithiol **27** (Scheme VI), produced by reduction of **23**, epimerizes in refluxing isopropyl alcohol/tetrahydrofuran. Such an epimerization probably involves formation of thiocarbonyl compounds **28** and **29**, as was recently proposed by Ottenheijm et al. for a related system.[18]

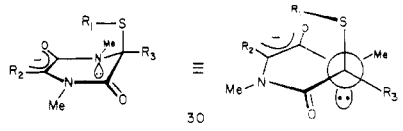
Discussion

Schemes I through IV offer four examples of electrophilic attack on piperazinedione enolates where electrophiles enter 1,4 to sulfur atoms already bound to the piperazinedione rings (viz., **8** → **9**, **13** → **14**, **18** → **19**, and **22** → **23**, respectively). In each case, reaction with a carbon or a sulfur electrophile occurs preferentially, albeit to varying degrees, on the face opposite the existing sulfur functionality. Several factors seem to control the degree of stereoselectivity. Highly stereoselective entries of alkylating agents are noted with the sulfur-stabilized enolate **8** (Scheme I) and with the sulfur-stabilized enolates studied by Kishi et al.[19] The formyl-stabilized enolates (**13**, Scheme II) and those derived from **18** (Scheme III) and **22** (Scheme IV) react with lower stereoselectivity except when the existing group bound to sulfur is large (see **22**, Scheme IV, and the derived enolate **25**, Scheme VII).

The enolate of **18** as well as enolates **8**, **13**, and **25** and those reported by Kishi et al.[19] appear to react via conformations in which the existing *sulfur atom* bound to the piperazinedione *is held in a pseudoaxial orientation.* Thus, for example, the enolate derived from **22** (Scheme IV) appears to react from conformation **25** (Scheme VII). The trityl trisulfide as depicted in **25** effectively blocks entry of the sulfenyl chloride from the top face of the molecule. Reaction from conformation **24** (Scheme VII) would lead predominantly to the unobserved diastereomer **26**.

Enolates **8** and **13** appear to react predominantly via the conformations depicted in Schemes I and II, respectively. We originally[2] attributed this to a *steric preference* of the silyl ether of **8** and the benzyl group of **13** to adopt pseudoequatorial positions. Factors other than steric bulk, however, may actually be more important in determining the conformation of enolates such as **8** and **13**. These enolates lack significant 1,3-diaxial interactions which would tend to force the bulkier substituent into the pseudoequatorial position. The steric relief afforded by holding the methylenes of **8** and **13** away from the relatively planar piperazinedione ring and positioning the geminal sulfur atom in the pseudoaxial position thus may be small.[20]

Stereoelectronic factors may govern the conformation and hence the stereoselectivity of electrophilic attack on sulfur-substituted diketopiperazine enolates. It is possible that a generalized anomeric effect[21] is responsible for holding the sulfur atom in pseudoaxial positions in the enolates. As shown in projection **30**, enolate resonance



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delocalization with the amide carbonyl imparts stability to the carbanion. Undoubtedly, upon enolate formation, amide resonance becomes much less important for the nitrogen atom bound to the enolate carbonyl. This nitrogen atom may actually become pyramidal,[22] thereby lowering electron/electron repulsion with the enolate. With the lone pair highly localized on nitrogen, a nitrogen/sulfur anomeric effect might hold the adjacent sulfur atom in the depicted (see **30**) pseudoaxial position.

Experimental Section

^1H NMR spectra were obtained on a Perkin-Elmer R-24B (60 MHz) or R-22 (90 MHz) spectrometer. High-resolution ^1H NMR spectra were determined on a Bruker HFX-270 spectrometer (Francis Bitter National Magnet Laboratory, Massachusetts Institute of Technology). Chemical shifts from tetramethylsilane are reported on the δ scale. Mass spectra were determined on a Varian MAT 44 system, and high-resolution mass spectra were determined on a CEC 110B Mattauch-Herzog (Du Pont Instruments) high-resolution mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer 567 grating infrared spectrophotometer. Melting points are uncorrected and were obtained in open capillaries (Mel-Temp instrument). Flash chromatography was performed by using E. Merck silica gel 60 (230–400 mesh) according to Still, et al.[23]

The following abbreviations are used throughout this section: THF ≡ tetrahydrofuran, DMF ≡ *N,N*-dimethylformamide, LDA ≡ lithium diisopropylamide, Me_4Si ≡ tetramethylsilane, MeOH ≡ methanol, EtOH ≡ ethanol, EtOAc ≡ ethyl acetate, Et_2O ≡ diethyl ether, Et_3N ≡ triethylamine.

1,4-Dimethyl-3-formyl-2,5-piperazinedione (3). Freshly dried, powdered 1,4-dimethyl-2,5-piperazinedione (16.0 g, 112.5 mmol, 1.0 equiv) and powdered sodium methoxide (13.0 g, 241.4 mmol, 2.14 equiv) were placed in a reaction vessel under a nitrogen atmosphere. Dry THF (150 mL) was added. After the mixture was stirred for 5 min at 0 °C, freshly distilled ethyl formate 45.5 mL, 562.7 mmol, 5.0 equiv) was added dropwise. After the addition was complete, the thick, white suspension was allowed to come to room temperature. THF (50 mL) was added, and the mixture was vigorously stirred 1 h at room temperature, 1 h at reflux, and an additional 3 h at room temperature. The resulting thick, white suspension was cooled to 0 °C, filtered, and washed thoroughly with dry THF. After the white cake was dried in vacuo for 12 h, the product was dissolved in H_2O (500 mL) (the resulting pH was 10), and 1 N HCl was added until the pH was 3–3.5. The water was evaporated under reduced pressure, and the resulting white solid was dried in vacuo, ground to a fine powder, and washed with $CHCl_3$. The filtrate was evaporated under reduced pressure, affording 18.3 g of **3** (95.5%) as white crystals: mp 143–145 °C (recrystallized from $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) 2.99 (3 H, s), 3.09 (3 H, s), 4.02 (2 H, s), 7.00 (1 H, d, J = 11 Hz), 12.47 (1 H, d, J = 11 Hz, D_2O exchangeable); IR (KBr) 3400, 1660, 1615, 1525, 1480, 1435, 1422, 1407, 1360, 1270, 1210, 1150, 930, 870, 470 cm^{-1}; exact mass calcd for $C_7H_{10}N_2O_3$ m/e 170.0691, found 170.0690. Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.30; H, 5.97; N, 16.30.

(18) Herscheid, J. D. M.; Tijhuis, M. W.; Noordik, J. H.; Ottenheijm, H. C. J. *J. Am. Chem. Soc.* **1979**, *101*, 1159.

(19) Reference 17b. Also: Fukuyama, T. Ph.D. Thesis, Harvard University, Department of Chemistry, 1977.

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1,4-Dimethyl-3-(methylthio)-3-formyl-2,5-piperazinedione (4). To a stirred solution of **3** (3.1762 g, 8.66 mmol, 1.0 equiv) in THF (100 mL) at −100 °C was added Et_3N (2.74 mL, 19.6 mmol, 1.05 equiv). To this solution was added freshly prepared CH_3SCl[4] (2.0027 g, 24.26 mmol, 1.3 equiv) in THF (20 mL) over a 10-min period. After the addition was complete, the resulting white suspension was stirred at −100 °C for 30 min, allowed to warm to 0 °C, and filtered cold to remove Et_3N·HCl. Evaporation of the solvent under reduced pressure afforded 4.233 g of pure **4** (100%): mp 98–100 °C (recrystallized from CH_2Cl_2/Et_2O); ^1H NMR (60 MHz, $CDCl_3$) 2.17 (3 H, s), 2.92 (3 H, s), 3.04 (3 H, s), 4.03 (1 H, half an AB q, J = 17 Hz), 4.21 (1 H, half an AB q, J = 17 Hz), 9.43 (1 H, s); IR (KBr) 1740, 1660, 1395, 1008, 735 cm^{-1}; exact mass calcd for $C_7H_9N_2O_3$ ($M^+ - SCH_3$) m/e 169.06131, found 169.06117, calcd for $C_7H_{11}N_2O_2S$ ($M^+ - CHO$) m/e 187.05412, found 187.05449. Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95; S, 14.82. Found: C, 44.41; H, 5.76; N, 12.82; S, 15.02.

1,4-Dimethyl-3-(hydroxymethyl)-3-(methylthio)-2,5-piperazinedione (5). To a stirred solution of **4** (1.6969 g, 7.85 mmol, 1.0 equiv) in THF (20 mL) at −78 °C was added a suspension of $LiAl(t\text{-}BuO)_3H$ (2.992 g, 11.77 mmol, 1.5 equiv) in THF (30 mL). The mixture was stirred at −78 °C for 1 h, allowed to come to room temperature, and stirred an additional 3 h. The reaction was quenched with 1 N HCl, poured into saturated NaCl(aq) and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was taken up in a small volume of CH_2Cl_2 and passed through a plug of silica gel, affording, after removal of the solvent, 1.5709 g of pure alcohol **5** (92%): mp 104–106 °C (recrystallized from CH_2Cl_2/Et_2O/EtOAc); ^1H NMR (90 MHz, $CDCl_3$) 2.04 (3 H, s), 3.03 (3 H, s), 3.13 (3 H, s), 3.7–4.1 (1 H, br s, D_2O exchangeable), 3.84 (1 H, half an AB q, J = 12 Hz), 4.01 (1 H, half an AB q, J = 17 Hz), 4.12 (1 H, half an AB q, J = 17 Hz), 4.33 (1 H, half an AB q, J = 12 Hz); IR (KBr) 3420, 3330, 1660, 1640, 1450, 1395 cm^{-1}; mass spectrum, m/e (relative intensity) 187 (1.05), 171 (25.6), 142 (30), 42 (100). Anal. Calcd for $C_8H_{14}N_2O_3S$: C, 44.02; H, 6.46; N, 12.83; S, 14.69. Found: C, 43.89; H, 6.56; N, 12.71; S, 14.75.

1,4-Dimethyl-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-(methylthio)-2,5-piperazinedione (6). *tert*-Butyldimethylsilyl chloride[5] (1.7151 g, 11.38 mmol, 1.2 equiv), imidazole (1.5522 g, 22.8 mmol, 2.4 equiv), and alcohol **5** (3.07 g, 9.25 mmol, 1.0 equiv) were stirred in DMF (9 mL) at room temperature for 12 h. The solution was diluted with CH_2Cl_2, poured into 0.25 N HCl, and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated, affording 3.19 g of pure, oily silyl ether **6**: yield 100%; ^1H NMR (60 MHz, $CDCl_3$; Me_4Si as external reference) 0.07 (3 H, s), 0.10 (3 H, s), 0.88 (9 H, s), 2.05 (3 H, s), 3.05 (3 H, s), 3.14 (3 H, s), 3.80 (1 H, half an AB q, J = 10 Hz), 4.07 (2 H, s), 4.32 (1 H, half an AB q, J = 10 Hz); IR (neat, NaCl) 1670, 1395, 1260, 1210 cm^{-1}; mass spectrum, m/e (relative intensity) 332 (M^+, 0.14), 317 (0.68), 285 (25.6), 275 (23.9), 228 (55.8), 73 (100).

1,4-Dimethyl-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-(methylthio)-6-(methylthio)-2,5-piperazinedione (7). A solution of **6** (0.7615 g, 2.29 mmol, 1.0 equiv) in THF (22 mL) was cooled to −78 °C. To this stirred solution was added LDA (2.75 mmol, 1.2 equiv) in THF (3 mL) dropwise via a cannula. After the dark-colored solution was stirred for 1 min at −78 °C, the mixture was added to a stirred solution of dimethyl disulfide in THF (5 mL) at −78 °C via a cannula. After being stirred 5 min at −78 °C, the mixture was allowed to come to 0 °C and was quenched with 1 N HCl (3 mL). The mixture was then poured into 0.1 N HCl, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and chromatographed on a preparative silica gel plate (eluted with ethyl acetate) to afford the separated diastereomers of **7** as oils (combined yield 0.4338 g or 50%; 66% yield based on recovered **6**). The *recombined* diastereomers were used in the subsequent step. Data for **7** (major diastereomer): ^1H NMR (90 MHz, $CDCl_3$; Me_4Si external) 0.05 (3 H, s), 0.08 (3 H, s), 0.85 (9 H, s), 2.20 (3 H, s), 2.43 (3 H, s), 3.13 (3 H, s), 3.15 (3 H, s), 3.85 (1 H, half an AB q, J = 10 Hz), 4.35 (1 H, half an AB q, J = 10 Hz), 4.70 (1 H, s); IR (neat, NaCl) 1660, 1260, 1120, 1105, 830 cm^{-1}; exact mass calcd for $C_{14}H_{27}N_2O_3SSi$ ($M^+ - SCH_3$) m/e 331.15117, found 331.14860, calcd for $C_{11}H_{21}N_2O_3S_2Si$ ($M^+ - C_4H_9$) m/e 321.07630, found 321.07697. Data for **7** (minor diastereomer): ^1H NMR (90 MHz, $CDCl_3$; Me_4Si external) 0.09 (3 H, s), 0.13 (3 H, s), 0.93 (9 H, s), 2.04 (3 H, s), 2.23 (3 H, s), 3.20 (6 H, s), 3.85 (1 H, half an AB q, J = 10 Hz), 4.43 (1 H, half an AB q, J = 10 Hz), 4.92 (1 H, s).

(±)-Gliovictin (9). To a stirred solution of diastereomers **7** (1.0051 g, 2.65 mmol, 1.0 equiv) in THF (25 mL) at −78 °C was added a solution of LDA (3.3 mmol, 1.25 equiv) in THF (3.5 mL). After the dark enolate solution was stirred for 2 min at −78 °C, benzyl bromide (1.57 mL, 13.25 mmol, 5.0 equiv) was added. The mixture was allowed to come to room temperature, stirred an additional 15 min, and quenched with enough 1 N HCl to turn the dark solution clear and colorless. The mixture was poured into 0.1 N HCl and extracted thoroughly with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was dissolved in 2 N HCl in MeOH (50 mL) plus a few drops of water and stirred for 6 h at room temperature. The solution was poured into saturated NaCl(aq) and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel flash chromatographic column (eluted with EtOAc) to afford 0.7918 g of (±)-gliovictin (**9**, 85%) as white crystals: mp 118–120 °C; ^1H NMR (270 MHz, $CDCl_3$) 1.54 (1 H, exchangeable, br unsym t, J_{ax} = 7 Hz, J_{bx} = 7.5 Hz), 2.14 (3 H, s), 2.31 (3 H, s), 3.04 (3 H, s), 3.29 (3 H, s), 3.15 (1 H, half an AB q, J = 14 Hz), 3.75 (1 H, half an AB q, J = 14 Hz), 3.14 (1 H, dd, J_{ax} = 7 Hz, J_{ab} = 12 Hz), 3.85 (1 H, dd, J_{bx} = 7.5 Hz, J_{ab} = 12 Hz), 7.08–7.40 (5 H, m); IR (KBr) 3380, 1660, 1636, 1499, 1373, 735, 700 cm^{-1}; exact mass calcd for $C_{15}H_{19}N_2O_2S_2$ ($M^+ - CH_2OH$) m/e 323.08880, found 323.08629, calcd for $C_{15}H_{19}N_2O_3S$ $M^+ - SCH_3$) m/e 307.11164, found 307.11066. Anal. Calcd for $C_{16}H_{22}N_2O_3S_2$: C, 54.21; H, 6.25; N, 7.90; S, 18.09. Found: C, 54.28; H, 6.31; N, 7.69; S, 18.31.

LC analysis (Porasil; CH_2Cl_2/EtOAc, 1:1) of crude **9**, after hydrolysis of the silyl protecting group, revealed that less than 10% of diastereomeric material (epigliovictin, **15**) was present.

1,4-Dimethyl-3-[[(*tert*-butyldiphenylsilyl)oxy]methylene]-2,5-piperazinedione (10). To a stirred suspension of **3** (17.02 g, 100 mmol, 1.0 equiv) in THF (50 mL) and absolute ethanol (200 mL) at 0 °C was added dropwise a THF solution (50 mL) of potassium *tert*-butoxide (14.0 g, 125 mmol, 1.25 equiv) over a 20-min period. After the clear, yellow solution was stirred 15 min at 0 °C, the solvents were evaporated, and the solid, yellow residue was dried in vacuo for 12 h. The yellow, powdery solid was suspended in dry DMF (90 mL), and *tert*-butyldiphenylsilyl chloride[6] (30.0 mL, 115 mmol, 1.15 equiv) was added dropwise at room temperature. A mildly exothermic reaction ensued, leaving a clear yellow-orange solution. Stirring was continued an additional 48 h at room temperature. The solvent was evaporated in vacuo and the residue partitioned between 0.1 N HCl and CH_2Cl_2. The aqueous layer was thoroughly extracted with CH_2Cl_2, and the combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and triturated with pentane, affording 34.7 g of **10** (85%) as white crystals, mp 127–129 °C (recrystallized from CH_2Cl_2). An additional 0.76 g of **10** was obtained from the mother liquors by distilling off residual silyl compounds (total yield 87%). Data for **10**: ^1H NMR (90 MHz, $CDCl_3$) 1.15 (9 H, s), 2.93 (3 H, s), 3.53 (3 H, s), 3.97 (2 H, s), 7.09 (1 H, s), 7.3–7.8 (10 H, m); IR (KBr) 1680, 1630, 1590, 1200, 1165, 800, 712, 700 cm^{-1}; exact mass calcd for $C_{23}H_{28}N_2O_3Si$ m/e 408.18692, found 408.18496.

1,4-Dimethyl-3-[[(*tert*-butyldiphenylsilyl)oxy]methylene]-6-benzyl-2,5-piperazinedione (11). A solution of **10** (24.25 g, 59.4 mmol, 1.0 equiv) in THF (200 mL) was cooled in a CO_2(s)/Et_2O bath. A solution of LDA (62.37 mmol, 1.05 equiv) in THF (40 mL) was added dropwise with stirring. After the mixture was stirred 5 min at −78 °C, the orange enolate solution was transferred via a cannula to a solution of benzyl bromide (35 mL, 297 mmol, 5.0 equiv) in THF (50 mL) at −78 °C. The resulting bright yellow solution was stirred 20 min at −78 °C and allowed to warm to room temperature. The solvent was evaporated, and the oily residue was triturated with pentane until a powdery precipitate formed. The solid was filtered, washed with pentane, and partitioned between pH 7.0 buffer and CH_2Cl_2. The aqueous layer was thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate,

filtered, and evaporated, affording 23.75 g of **11** (80.2%) as white crystals, mp 148.5–150 °C (recrystallized from EtOAc).

Higher yields of **11** (up to 97%) were realized when the reaction was run on smaller scales and the product was separated by chromatography and/or retrieved from the mother liquors of the pentane trituration (vide supra). Data for **11**: ^{1}H NMR (90 MHz, $CDCl_3$) 1.13 (9 H, s), 2.80 (3 H, s), 3.12 (2 H, d, J = 6 Hz), 3.43 (3 H, s), 4.20 (1 H, t, J = 6 Hz), 6.83 (1 H, s), 7.20 (5 H, m), 7.35–7.75 (10 H, m); IR (KBr) 1745, 1670, 1625, 1585, 1210, 1200, 1150, 1110, 780, 750, 715, 700 cm^{-1}; exact mass calcd for $C_{30}H_{34}N_2O_3Si$ m/e 498.23387, found 498.23284. Anal. Calcd for $C_{30}H_{34}N_2O_3Si$: C, 72.25; H, 6.87; N, 5.62. Found: C, 72.12; H, 7.14; N, 5.58.

1,4-Dimethyl-3-(hydroxymethylene)-6-(methylthio)-6-benzyl-2,5-piperazinedione (12). To a stirred solution of **11** (4.00 g, 8.0 mmol, 1.0 equiv) in THF (60 mL) at −78 °C was added a solution of LDA (9.23 mmol, 1.15 equiv) in THF (10 mL). The resulting dark-colored enolate solution was allowed to stir at −78 °C for 3 min and was then transferred, via a cannula, into a solution of dimethyl disulfide (3.6 mL, 40 mmol, 5.0 equiv) in THF (40 mL) at −100 °C. The resulting pale orange solution was stirred 1 h at −100 °C and was then allowed to warm to room temperature. The reaction was quenched with 0.65 N HCl in MeOH (10 mL). The mixture was poured into pH 7.0 buffer and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel column (eluted with 2% methanol in methylene chloride) to give 2.0058 g of **12** (82%) as an air-sensitive oil (must be used immediately after preparation): ^{1}H NMR (60 MHz, $CDCl_3$) 1.97 (3 H, s), 2.98 (3 H, s), 3.18 (3 H, s), 3.04 (1 H, half an AB q, J = 14 Hz), 3.63 (1 H, half an AB q, J = 14 Hz), 6.68 (1 H, d, J = 11 Hz), 7.10 (5 H, m), 12.18 (1 H, d, J = 11 Hz, D_2O exchangeable); IR (neat, NaCl) 3650–3200 (br), 1650, 1595, 1385, 1250, 1185, 1135, 850, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 306 (M^+, 0.55), 275 (6.79), 259 (4.66), 91 (100).

(±)-Epigliovictin (15). To a stirred solution of **12** (0.4602 g, 1.5 mmol, 1.0 equiv) in THF (5 mL) at −100 °C was added Et_3N (0.26 mL, 1.87 mmol, 1.25 equiv). To this solution was added CH_3SCl[4] (0.154 g, 1.87 mmol, 1.25 equiv) in THF (3 mL). After the mixture was stirred 30 min at −100 °C, the white suspension was warmed to 0 °C and filtered to remove Et_3N·HCl. Evaporation of the solvent afforded oily **14**, which by ^{1}H NMR analysis was a 3:1 (anti/syn) mixture of diastereomers. The oily residue was dissolved in THF (5 mL) and cooled to −78 °C. To this solution was added LiAl(t-BuO)$_3$H (0.7628 g, 3.0 mmol, 2.0 equiv) in THF (10 mL). After being stirred 30 min at −78 °C, the mixture was allowed to come to room temperature and was stirred an additional 2 h. The reaction was quenched with 1 N HCl in MeOH, poured into 5% HCl(aq) and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated by preparative silica gel TLC (eluted with 27:3:1 CH_2Cl_2/EtOAc/MeOH) to afford 0.0831 g of (±)-gliovictin (**9**, 15.6%) and 0.2161 g of (±)-epigliovictin (**15**, 40.6%) as white crystals: mp 163–165.5 °C (recrystallized from CH_2Cl_2/Et_2O); ^{1}H NMR (90 MHz, $CDCl_3$) 1.13 (3 H, s), 2.14 (3 H, s), 3.06 (3 H, s), 3.15 (1 H, br s, D_2O exchangeable), 3.29 (3 H, s), 3.20 (1 H, half an AB q, J = 15 Hz), 3.74 (1 H, half an AB q, J = 12 Hz), 3.83 (1 H, half an AB q, J = 15 Hz), 4.16 (1 H, half an AB q, J = 12 Hz), 7.17 (5 H, s); IR (KBr) 3465, 3400, 1665, 1635, 1499, 1380, 755, 700 cm^{-1}; exact mass calcd for $C_{15}H_{19}N_2O_2S_2$ (M^+ − CH_2OH) m/e 323.08880, found 323.08844, calcd for $C_{15}H_{19}N_2O_3S$ (M^+ − SCH_3) m/e 307.11164, found 307.11344. Anal. Calcd for $C_{16}H_{22}N_2O_3S_2$: C, 54.21; H, 6.25; N, 7.90; S, 18.09. Found: C, 54.21; H, 6.33; N, 7.81; S, 17.93.

1,4-Dimethyl-3-[[(*tert*-butyldiphenylsilyl)oxy]methylene]-6-mercapto-6-benzyl-2,5-piperazinedione (16). To a stirred solution of **11** (3.50 g, 7.0 mmol, 1.0 equiv) in THF (60 mL) at −78 °C was added a solution of LDA (8.0 mmol, 1.15 equiv) in THF (7 mL). The resulting dark-colored enolate solution was stirred 30 s at −78 °C and added, via a cannula, to a solution of monoclinic elemental sulfur (0.4582 g, 14.0 mmol, 2.0 equiv) (vide infra) in THF (80 mL) at −78 °C. The mixture was stirred 20 min at −78 °C, quenched with 0.65 N HCl in MeOH (20 mL), warmed to room temperature, 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. The crude mercaptan was dissolved in EtOH (30 mL) and THF (10 mL) at 0 °C, and $NaBH_4$ (1.2737 g, 33.7 mmol, 4.8 eq) was added portionwise. The mixture was stirred 10 min at 0 °C, quenched with 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 3.7168 g of **16** (99%) as a brittle, white foam: ^{1}H NMR (90 MHz, $CDCl_3$) 1.10 (9 H, s), 3.07 (3 H, s), 3.22 (1 H, s), 3.37 (1 H, half an AB q, J = 14 Hz), 3.51 (3 H, s), 3.87 (1 H, half an AB q, J = 14 Hz), 6.94 (1 H, s), 6.98–7.35 (5 H, m), 7.35–7.80 (10 H, m); IR (KBr) 2550, 1675, 1620, 1495, 1390, 1360, 1185, 1160, 1110, 745, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 531 (M^+, 1.09), 498 (1.19), 135 (100), 91 (66).

Preparation of Elemental Sulfur for Sulfenylation of 11. A more THF-soluble form of elemental sulfur (S_8), believed to be the monoclinic allotropic modification,[11] was obtained by the following procedure. Sublimed orthorhombic sulfur (S_8, 0.4582 g) was placed in a reaction vessel and evacuated to ca. 0.1 mmHg. The sample was heated with a heat gun to ca. 100 °C until the color of the sulfur deepened slightly (application of heat should be done so as to prevent melting of the sulfur). The sulfur was allowed to cool to room temperature and then immediately dissolved in THF (80 mL). This solution was cooled to −78 °C immediately prior to enolate addition (prolonged cooling induces precipitation of S_8).

1,4-Dimethyl-3-(hydroxymethylene)-6-benzyl-6-(methyldithio)-2,5-piperazinedione (18). To a stirred solution of thiol **16** (1.122 g, 2.1 mmol, 1.0 equiv) in THF (5 mL) at −78 °C were added Et_3N (0.32 mL, 2.31 mmol, 1.1 equiv) and a solution of freshly prepared CH_3SCl[4] (0.227 g, 2.75 mmol, 1.3 equiv) in THF (5 mL). The resulting white suspension was stirred 20 min at −78 °C and 20 min at room temperature and filtered to remove Et_3N·HCl, and the solvent was evaporated to afford disulfide **17** as a brittle, pale yellow foam. Without further purification, **17** was dissolved in THF (10 mL)/1.6 N HCl in MeOH (20 mL)/6 N HCl (3 mL) and stirred at room temperature 18 h. The solution was poured into water 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 CH_2Cl_2) to afford 0.362 g of enolic disulfide **18** (51%) as an oil: ^{1}H NMR (60 MHz, $CDCl_3$) 2.30 (3 H, s), 3.08 (1 H, half an AB q, J = 14 Hz), 3.07 (3 H, s), 3.09 (3 H, s), 3.89 (1 H, half an AB q, J = 14 Hz), 6.90 (1 H, d, J = 12 Hz), 7.18 (5 H, m), 12.41 (1 H, d, D_2O exchangeable, J = 12 Hz); IR (neat, NaCl) 1660, 1605, 1500, 1420, 1395, 1250, 1195, 1145, 750, 705 cm^{-1}; mass spectrum, m/e (relative intensity) 337 (0.42), 292 (0.36), 259 (25.06), 91 (89.42), 42 (100).

(±)-Hyalodendrin (20). To a stirred solution of enolic methyl disulfide **18** (0.3516 g, 1.04 mmol, 1.0 equiv) in THF (10 mL) at −78 °C was added Et_3N (0.15 mL, 1.04 mmol, 1.0 equiv). To this solution was added triphenylmethyl chlorodisulfide[13] in THF (5 mL) over a 3-min period. The resulting white suspension was stirred 20 min at −78 °C, warmed to room temperature, and filtered, and the solvent was evaporated to afford 0.6762 g of aldehyde **19** (100%) as a brittle foam. Analysis of **19** by ^{1}H NMR ($CDCl_3$) indicated about a 2:1 anti/syn ratio of diastereomers (anti aldehyde proton at δ 8.2, syn aldehyde proton at δ 7.8).

To a stirred solution of diastereomers **19** (0.3272 g, 0.51 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was added sodium borohydride (0.1342 g, 3.55 mmol, 7.0 equiv). After the mixture was stirred 3 min at 0 °C, isopropyl alcohol (1 mL) was added. The mixture was warmed to room temperature, stirred 30 min, and then refluxed for 30 min. Stirring was continued for 1 h at room temperature, and an additional 7.0 equiv of sodium borohydride was added. The mixture was refluxed for 30 min and then stirred at room temperature 12 h. The mixture was acidified with 1 N HCl, saturated with NaCl, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was dissolved in isopropyl alcohol (20 mL) and THF (10 mL) at 0 °C, and sodium borohydride was added (0.1342 g, 3.55 mmol, 7.0 equiv).[24] The mixture was warmed to room temperature, stirred 12 h, acidified, and

(24) In a limited survey of reaction conditions this double reductive procedure gave better yields of (±)-hyalodendrin, though the procedure was not optimized. The conditions should epimerize the mixture of dithiols (see text).

extracted as above. The residue was dissolved in CH_2Cl_2 (15 mL) at 0 °C, and a 2.5% solution of KI_3 in pyridine was added dropwise until a faint iodine color persisted. The solution was filtered, and the CH_2Cl_2-soluble residue was separated on a preparative silica gel plate (eluted with 2% MeOH in CH_2Cl_2) to afford 0.0486 g of (±)-hyalodendrin (**20**, 29.4%) as pale yellow crystals: mp 128–131 °C (recrystallized from CH_2Cl_2/Et_2O); ^1H NMR (270 MHz, $CDCl_3$) 3.04 (3 H, s), 3.26 (3 H, s), 3.60 (1 H, dd, D_2O exchangeable, J_{ax} = 7.2 Hz, J_{bx} = 8.9 Hz), 3.69 (1 H, half an AB q, J = 16 Hz), 4.13 (1 H, half an AB q, J = 16 Hz), 4.33 (1 H, dd, J_{ab} = 14 Hz, J_{ax} = 7.2 Hz), 4.40 (1 H, dd, J_{ab} = 14 Hz, J_{bx} = 8.9 Hz), 7.35 (5 H, s); IR (KBr) 3500 (br), 1695, 1670, 1500, 1458 1423, 1360, 1255, 1245, 1220, 1085, 770, 718, 710 cm^{-1}; mass spectrum, m/e (relative intensity) 324 (M^+, 1.15), 259 (45.92), 231 (16.02), 214 (18.41), 91 (72.51), 42 (100); exact mass calcd for $C_{14}H_{16}N_2O_3S_2$ (M^+) m/e 324.06024, found 324.06096, calcd for $C_{14}H_{16}N_2O_3$ ($M^+ - S_2$) m/e 260.11609, found 260.11543.

1,4-Dimethyl-3-[[(*tert*-butyldiphenylsilyl)oxy]methylene]-6-benzyl-6-(trityltrithio)-2,5-piperazinedione (21). To a stirred solution of thiol **16** (0.5307 g, 1.0 mmol, 1.0 equiv) in THF (5 mL) at −78 °C was added Et_3N (0.14 mL, 1.0 mmol, 1.0 equiv). To this solution was added a solution of triphenylmethyl chlorodisulfide[13] (0.3429 g, 1.0 mmol, 1.0 equiv) in THF (5 mL). The mixture was stirred at −78 °C for 15 min, warmed to 0 °C, filtered, and evaporated. The oily residue was diluted with CH_2Cl_2 and washed with 0.1 N HCl. The organic extract was dried over anhydrous sodium sulfate, filtered, and evaporated to afford 0.5782 g of trisulfide **21** (69%) as white crystals: mp 172–174 °C (recrystallized from CH_2Cl_2/Et_2O); ^1H NMR (60 MHz, $CDCl_3$) 1.05 (9 H, s), 2.90 (3 H, s), 2.89 (1 H, half an AB q, J = 14 Hz), 3.50 (3 H, s), 3.76 (1 H, half an AB q, J = 14 Hz), 7.0–7.7 (31 H, m); IR (KBr) 1675, 1660, 1612, 1335, 1175, 1155, 735, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 495 (2.48), 438 (14.39), 243 (100), 164 (99.4).

1,4-Dimethyl-3-(hydroxymethylene)-6-benzyl-6-(trityltrithio)-2,5-piperazinedione (22). Silyl enol ether **21** (0.50 g, 0.6 mmol) was dissolved in THF (20 mL)/$CHCl_3$ (10 mL)/1.6 M HCl in MeOH (20 mL)/6 N HCl (2 mL) at room temperature. The mixture was stirred for 6 h, poured into water, and 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 CH_2Cl_2) to afford 0.1765 g of enolic trisulfide **22** (49%) as white crystals: mp 150–152 °C (recrystallized from CH_2Cl_2/Et_2O); ^1H NMR (60 MHz, $CDCl_3$) 2.92 (6 H, s), 2.86 (1 H, half an AB q, J = 14 Hz), 3.70 (1 H, half an AB q, J = 14 Hz), 6.78 (1 H, d, J = 11 Hz), 6.9–7.4 (20 H, m), 12.28 (1 H, d, D_2O exchangeable, J = 11 Hz); IR (KBr) 3460 (br), 1650, 1590, 1485, 1385, 1240, 1190, 1135, 745, 730, 695 cm^{-1}; mass spectrum, m/e (relative intensity) 258 (12.7), 243 (60.64), 165 (100), 91 (56.68).

1,4-Dimethyl-3-(trityldithio)-3-formyl-6-benzyl-6-(trityltrithio)-2,5-piperazinedione (23). To a stirred solution of **22** (0.7274 g, 1.2 mmol, 1.0 equiv) in THF (10 mL) at −78 °C was added Et_3N (0.17 mL, 1.2 mmol, 1.0 equiv). To this solution was added triphenylmethyl chlorodisulfide[13] (0.4171 g, 1.2 mmol, 1.0 equiv) in THF (5 mL). The resulting white suspension was stirred for 1 h at −78 °C, warmed to room temperature, filtered, and evaporated to afford 1.1727 g of **23** (100%) as a brittle, white foam: ^1H NMR (60 MHz, $CDCl_3$) 2.60 (3 H, s), 2.90 (3 H, s), 2.94 (1 H, half an AB q, J = 14 Hz), 3.25 (1 H, half an AB q, J = 14 Hz), 7.22 (35 H, s), 8.19 (1 H, s); IR (KBr) 1730, 1675, 1665, 1600, 1495, 1445, 1370, 740, 705 cm^{-1}; mass spectrum, m/e (relative intensity) 439 (0.34), 257 (18.92), 242 (66.24), 165 (100).

Reductive Methylation of 23. To a stirred solution of **23** (0.1308 g, 0.14 mmol, 1.0 equiv) in pyridine (0.23 mL) and methyl iodide (1.1 mL) at 0 °C was added an ice-cold solution of sodium borohydride (0.0378 g, 1.0 mmol, 7.0 equiv) in MeOH (1.1 mL). The mixture was allowed to stir 1 h at 0 °C and 4 h at room temperature. The solvents were evaporated, and the residue was partitioned between water and CH_2Cl_2. The aqueous layer was acidified with 1 N HCl to pH 3 and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. Analysis of the crude product by LC (Porasil, 1:1 CH_2Cl_2/EtOAc) revealed that the ratio of (±)-epigliovictin (**15**) to (±)-gliovictin (**9**) was greater than 10:1. This was confirmed by coinjection with authentic samples of **15** and **9**. Analysis by TLC (eluted with 2% MeOH in CH_2Cl_2, silica gel) confirmed (approximately) the ratio determined by LC.

Reductive Methylation of 23 with Epimerization. To a stirred solution of **23** (0.5135 g, 0.57 mmol, 1.0 equiv) in THF (10 mL) at 0 °C was added sodium borohydride (0.1503 g, 3.97 mmol, 7.0 equiv) portionwise. The mixture was stirred 3 min, and isopropyl alcohol (2 mL) was added. The solution was refluxed for 1 h and stirred at room temperature for 12 h. An additional 7.0 equiv of sodium borohydride was added, and stirring was continued for 12 h at room temperature. The mixture was acidified with 1 N HCl, saturated with sodium chloride, and extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was dissolved in pyridine (1 mL) at 0 °C, and methyl iodide (5 mL) was added. An ice-cold solution of sodium borohydride (0.10 g) in methanol (1 mL) was added and the mixture stirred 30 min at 0 °C. An additional 1 mL of methyl iodide was added and stirring continued for 3 h at room temperature. The solvents were evaporated, and the residue was partitioned between water and CH_2Cl_2. The pH of the aqueous phase was adjusted to 6 with 1 N HCl, and this was extracted thoroughly with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated. Analysis of the residue by LC (Porasil, 1:1 CH_2Cl_2/EtOAc) indicated an approximately 1:1 mixture of (±)-gliovictin (**9**) and (±)-epigliovictin (**15**). Separation of the residue by preparative silica gel TLC (eluted with 2% MeOH in CH_2Cl_2) afforded 0.0293 g of (±)-gliovictin (**9**, 14.5%) and 0.0411 g of (±)-epigliovictin (**15**, 20.4%) (see separate experiments for spectral data).

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Registry No. 2, 5076-82-4; **3**, 71742-24-0; (±)-**4**, 71742-25-1; (±)-**5**, 71742-26-2; (±)-**6**, 71771-24-9; (±)-*cis*-**7**, 73454-03-2; (±)-*trans*-**7**, 73454-04-3; (±)-**9**, 71772-59-3; **10**, 73454-05-4; (±)-**11**, 71742-28-4; (±)-**12**, 71742-29-5; (±)-**15**, 71772-60-6; (±)-**16**, 73454-06-5; (±)-**17**, 73454-07-6; (±)-**18**, 73454-08-7; (±)-*cis*-**19**, 73454-09-8; (±)-*trans*-**19**, 73454-10-1; (±)-**20**, 53777-19-8; (±)-**21**, 73454-11-2; (±)-**22**, 73454-12-3; (±)-**23**, 73454-13-4; *tert*-butyldimethylsilyl chloride, 18162-48-6; benzyl bromide, 100-39-0; *tert*-butyldiphenylsilyl chloride, 58479-61-1; sulfur, 7704-34-9; triphenylmethyl chlorodisulfide, 35572-83-9; (±)-*cis*-**14**, 73454-14-5; (±)-*trans*-**14**, 73454-15-6.