Divergent, Generalized Synthesis of Unsymmetrically Substituted 2,5-Piperazinediones

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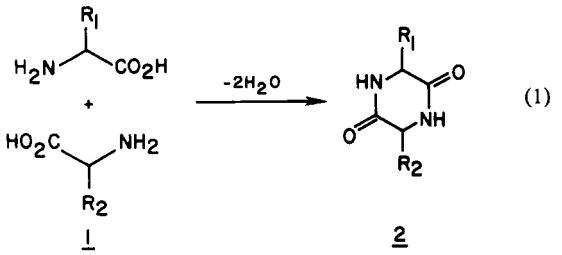
Abstract: N,N'-Disubstituted 2,5-piperazinediones (**12**) can be 3,6-dibrominated followed by displacement with sodium 2-mercaptopyridine to furnish syn-1,4-disubstituted 3,6-bis(2'-thiopyridyl)-2,5-piperazinediones (**8**) in high yield. Precomplexation of these sulfides with silver(I) triflate followed by addition of trimethylsilyl enol ethers leads to chemoselective C–C bond formation, furnishing the homologated piperazinediones **10**. The remaining sulfide functionality of **10** is relatively inert to a second substitution. These electrophilic 2,5-piperazinediones provide access to relatively inaccessible, unsymmetrical 2,5-piperazinediones and provide advantages over the corresponding well-known enolate anion approach. Substrates that contain *N*-*p*-methoxybenzyl residues can be deprotected to the lipophobic N,N'-unsubstituted 2,5-piperazinediones with aqueous ceric ammounium nitrate. The diastereoselectivity observed in the coupling reactions is discussed in the context of a single crystal X-ray structure determination of **20**.

Diketopiperazines (2,5-piperazinediones) constitute a large class of organic substances[1] that are derived by the net removal of two molecules of water from two amino acid residues (**1** → **2**, eq 1).



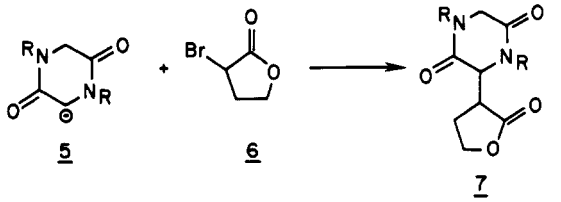
(1)

1 **2**

These cyclodipeptides occur widely in nature,[1,2] often being found in a high oxidation state relative to the derived amino acid residues. Diketopiperazines are also often formed during the synthesis, degradation, and manipulation of numerous peptides,[3] an often "unwelcome" occurrence. More recently, diketopiperazines have been used as versatile synthetic intermediates for the preparation of amino acids, amino acid derivatives, and, of course, natural products both containing[4] and ultimately lacking[5] the 2,5-piperazinedione ring system.

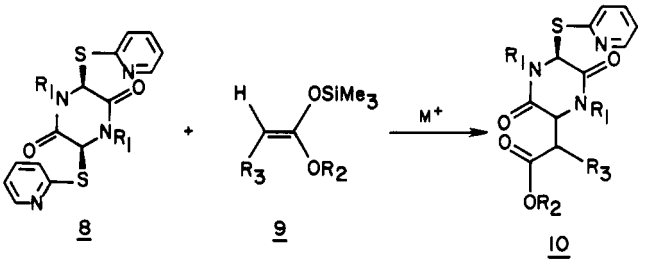
The two most common methods for preparing α-C-functionalized 2,5-piperazinediones involve (1) standard peptide coupling of two amino acids followed by cyclization[6] and (2) α-carbanion substitution of a pre-formed 2,5-piperazinedione which can be either racemic[7] or optically active.[8] Of the latter method, 2,5-piperazinedione enolate anions condense readily with aldehydes to produce dehydrocyclodipeptides[3] which can be hydrogenated (often stereospecifically) to give the α-C-functionalized piperazinediones;[9] the corresponding reaction with ketones, however, is much less general.[10] Thus, β,β-disubstituted 2,5-piperazinediones (**3**) are relatively inaccessible substances owing primarily to the poor nucleophilicity of the enolates toward more highly functionalized electrophiles and the paucity of naturally occurring or readily accessible α-amino acids bearing β substitution.

Scheme I

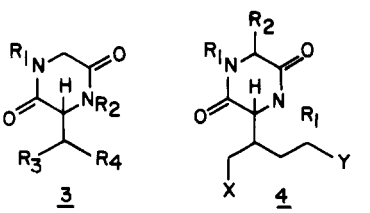


5 **6** **7**

Scheme II



8 **9** **10**



3 **4**

(1) For a review see: Sammes, P. G. *Fortschr. Chem. Org. Naturst.* **1975** *32*, 51.

(2) For examples, see: (a) Leigh, C.; Taylor, A. *Adv. Chem. Ser.* **1976**, *No. 149*, 228. (b) Marcuccio, S. M.; Elix, J. A. *Tetrahedron Lett.* **1983**, *24*, 1445. (c) Begg, W. R.; Elix, J. A.; Jones, A. J. *Ibid.* **1978**, 1047. (d) Battaini, F.; Peterkofsky, A. *Biochem. Biophys. Res. Commun.* **1980**, *94*, 240. (e) Miyoshi, T.; Miyairi, N.; Aoki, H.; Kohsaka, M.; Sakai, H.; Imanaka, H. *J. Antibiot.* **1972**, *25*, 569. (f) Cockrum, P. A.; Culvenor, C. C. J.; Edgar, J. A.; Payne, A. L. *J. Nat. Prod.* **1979**, *42*, 534.

(3) Schmidt, U.; Hausler, J.; Ohler, E.; Poisel, H. *Fortschr. Chem. Org. Naturst.* **1980**, *37*, 251.

(4) For several examples, see: (a) Fukuyama, T.; Nakatsuka, S.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045. (b) Nakatsuka, S.; Miyazaki, H.; Goto, T. *Tetrahedron Lett.* **1980**, *21*, 2817. (c) Fukuyama, T.; Frank, R. M.; Jewell, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 2122.

(5) For examples, see: (a) Shemyaskin, M. M.; Orchinnikov, Yu, A.; Antonov, V. K.; Kiryushkin, A. A.; Ivanov, V. T.; Shchelokov, V. I.; Shkrob, A. M. *Tetrahedron Lett.* **1964**, 47. (b) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957.

(6) Nitecki, D. E.; Halpern, B.; Westley, J. W. *J. Org. Chem.* **1968**, *33*, 864.

(7) (a) Gallina, C.; Liberatori, A. *Tetrahedron* **1974**, *30*, 667. (b) Williams, R. M.; Armstrong, R. W.; Josey, J.; Meyers, H.; Eriksson, C. *J. Am. Chem. Soc.* **1982**, *104*, 6092.

(8) Schollkopf, U.; Hartwig, W.; Pospischil, K.-H.; Kehne, H. *Synthesis* **1981**, 966 and references cited therein.

(9) Kanmera, T.; Lee, S.; Aoyagi, H.; Izumiya, N. *Tetrahedron Lett.* **1979**, 4483.

(10) For an exceptional case, see: Maag, H.; Blount, J. F.; Coffen, D. L.; Steppe, T. V.; Wong, F. *J. Am. Chem. Soc.* **1978**, *100*, 6786.

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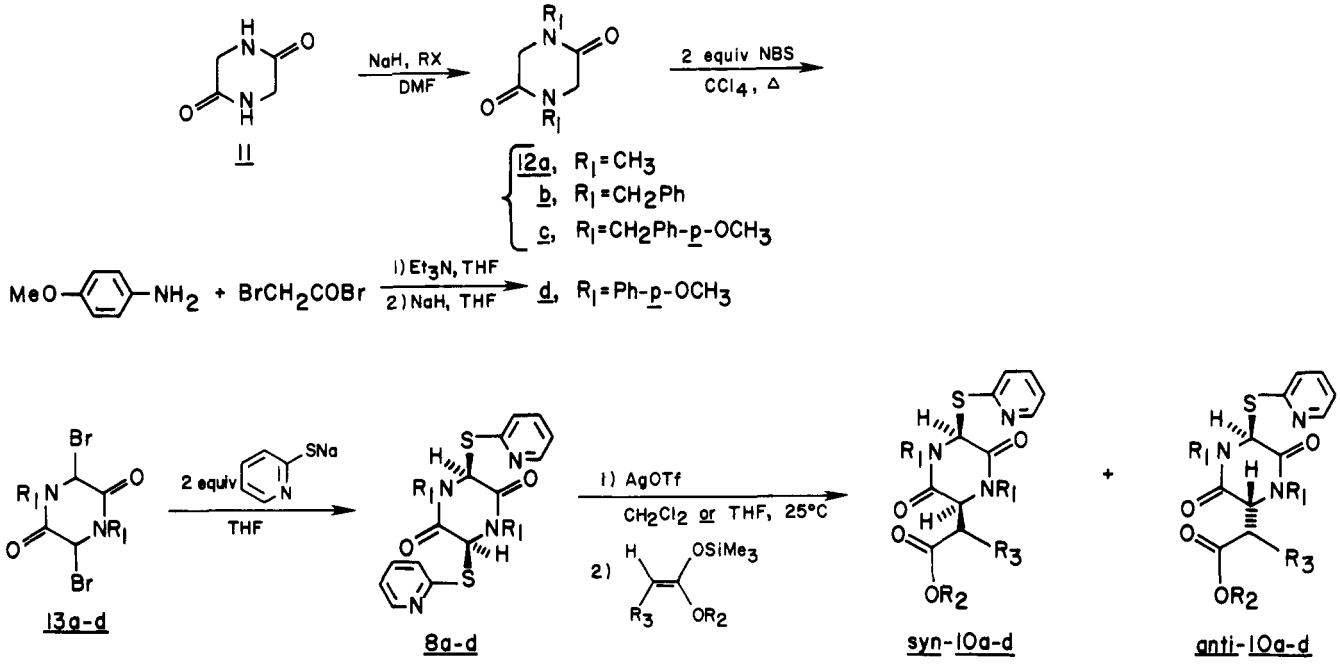
Scheme III



During the course of our investigations on the total synthesis of bicyclomycin,[11] we needed to prepare a suitably oxidized isoleucine derivative **4**. After many unsuccessful attempts to derivatize the 2,5-piperazinedione enolate[12] with numerous electrophiles, we finally realized the coupling of **5** (R = Me) and α-bromo-γ-butyrolactone (**6**) to afford the desired lactone **7** (Scheme I); the best yield obtained, however, was only 9% and a considerable array of unidentifiable side products accompanied the meager production of **7**. Thus, both the peptide coupling approach and the enolate functionalizations were found to be unsuitable.

In this paper, we wish to report a fundamentally new[11] and practical approach to α-C-functionalized 2,5-piperazinediones that features the *electrophilic* coupling of the *syn*-3,6-bis(2′-thiopyridyl)-2,5-piperazinediones **8** and ketene trimethylsilyl acetals (**9**) in the presence of thiophilic metal salts (Scheme II) to afford the α-C-functionalized 2,5-piperazinediones **10**.

Results and Discussion

Inexpensive, commercially available glycine anhydride (**11**) is efficiently alkylated in the presence of NaH and an alkyl halide (DMF, 25 °C) to afford the *N,N′*-dialkyl-2,5-piperazinediones (**12a–c**). The *N,N′*-diaryl substrate **12d** is prepared by dimerization of the condensation product of *p*-anisidine and bromoacetyl bromide (Scheme III). Bromination of **12** is accomplished by a modification (NBS, CCl_4 reflux) of the classical procedure first developed by Trown.[13] In almost every case, a single diastereomeric *syn*-dibromide is obtained. Reaction of dibromides **13a–d** with the sodium salt of 2-mercaptopyridine provides the crystalline *syn*-bis(sulfides) **8a–d** in high yields. In one instance (R_1 = CH_2Ph-*p*-OCH_3), we were able to prepare the corresponding *anti*-3,6-bis(sulfide) **14** from the *anti*-dibromide. A stereochemical assignment[14] (syn/anti) for both the bis(sulfides) and the resulting C-coupled products **10** is established through the chemical shift of the α-methine proton adjacent to sulfur at C-3 of the piperazinedione ring. For the *syn*-bis(sulfides) **8a–d**, the C-3 methine protons appear as a sharp singlet between δ 6.3 and 6.8. The anti diastereomer **14** exhibited this two-proton singlet at δ 5.44. Corroboration of this relationship was derived from the single-crystal X-ray analysis of the major syn-lactone **20** depicted in Figure 1. The C-3 methine proton of this compound exhibited a sharp singlet at δ 6.62; all diastereomers of **10** exhibiting this resonance between δ 6.6 and 6.9 were thus assigned the syn-relative configuration. The corresponding anti diastereomers of **10** exhibiting a C-3 methine resonance between δ 5.6 and 5.9 were easily distinguished.

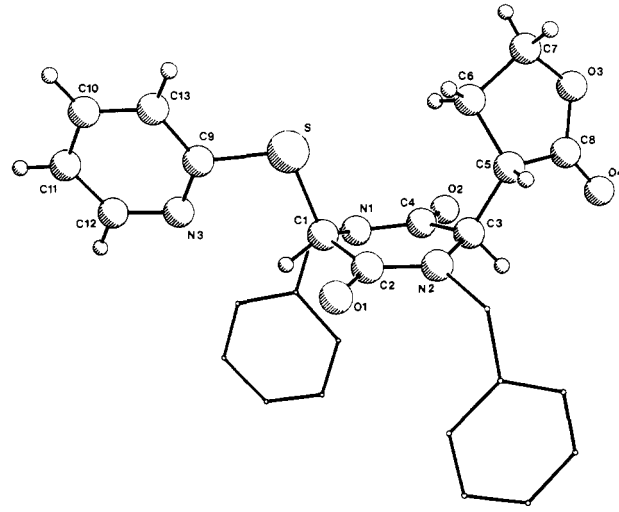


Figure 1. Molecular structure of **20**. Atoms are shown as spheres of fixed arbitrary radius.

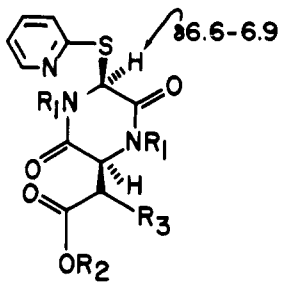
Before discussion of the diastereoselectivity in the coupling reactions, some comments regarding the experimental protocol are in order. Attempted couplings with the dibromides **13** were uniformly unsuccessful under a range of Lewis-acid conditions;

(11) (a) Armstrong, R. W.; Dung, J.-S.; Williams, R. M. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, WA Mar 1983; American Chemical Society: Washington, DC, 1983; ORGN 10. (b) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1984**, *106*, 5748. (c) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. "Abstracts of Papers", 188th National Meeting of the American Chemical Society, Philadelphia, PA, Aug 1984; American Chemical Society: Washington, DC, 1984; ORGN 92. (d) Williams, R. M.; Armstrong, R. W.; Dung, J. S., *J. Am. Chem. Soc.*, following paper in this issue.

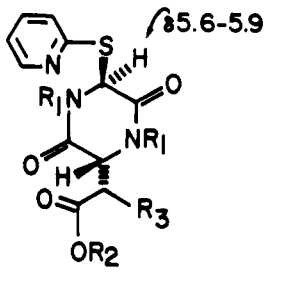
(12) A Michael-type approach to **4** has been reported but in our experience is limited to enolates of α-heteroatom-substituted 2,5-piperazinediones: Nakatsuka, S.; Yamada, K.; Yoshida, K.; Asano, O.; Murakami, Y.; Goto, T. *Tetrahedron Lett.* **1983**, *24*, 5627. See also: Yates, P.; Hoare, J. H. *Can. J. Chem.* **1983**, *61*, 1397 and references cited therein.

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

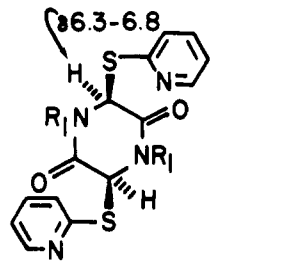
(14) Benedetti, E.; Marsh, R. E.; Goodman, M. *J. Am. Chem. Soc.* **1976**, *98*, 6676.



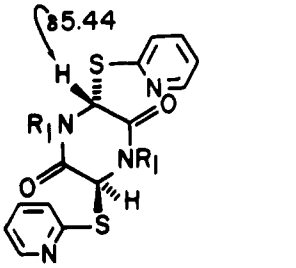
syn-10



anti-10



8



14, $R_1 = CH_2Ph\text{-}p\text{-}OCH_3$

decomposition and unisolable mixtures resulted. The typical procedure involves *precomplexation* of the bis(sulfide) **8** with silver(I) triflate at room temperature for ca. 10 min. This Ag^+ complex was found to be indefinitely stable in solution; no decomposition, hydrolysis, or other side products form. Upon addition of the ketene trimethylsilyl acetal,[15] the Ag^+ complex of **8** cleanly reacts over a 4-h period, producing the desired monocoupled products **10**. *In no case, even in the presence of excess silyl enol ether and AgOTf, were 3,6-bis-coupled products observed.* This result is very significant since a major competing side reaction for enolate functionalization of glycine anhydride derivatives (**12**) is 3,6-dialkylation. The complete *chemoselectivity* of the 3,6-bis(sulfides) **8** to couple *once* and the complete lack of reactivity of the thioacetal carbon in the products toward further nucleophilic substitution raise several interesting questions.

Considering that steric hindrance in the products might slow down any observable coupling, we prepared the corresponding 3-(2′-thiopyridyl)-2,5-piperazinediones (**16**) by careful monobromination of **12** (Scheme IV). Under the same, and even somewhat more vigorous, conditions, the monothiopyridyl derivatives **16** *were completely unreactive* toward nucleophilic substitution; unreacted starting material was recovered quantitatively.

However, if the *order* of addition of the silyl ketene acetal and silver salt are *reversed*, clean coupling to afford **17** can be realized. Thus, dissolution of **16** plus the silyl ketene acetal in CH_2Cl_2, followed by addition of silver(I) triflate, rapidly consumed **16** and afforded the desired product **17**. In the couplings of bis(sulfides) **8**, this *order* of addition failed to produce the products **10**; in every case examined, it turned out to be necessary to *precomplex* **8** with Ag^+. The monocoupled products **17** could also be prepared from **10** by Raney nickel desulfurization in ethanol at reflux temperature. It was of interest to note that the relative stereochemistry of the lactone α carbon and piperazinedione α carbon **17** (R_1 = CH_2Ph-*p*-OCH_3; R_2, R_3 = CH_2CH_2) obtained from **16** follows *inversely* from that obtained by Raney nickel reduction of the corresponding major diastereomer **10c**.

The diastereoselectivity exhibited by these substrates in the coupling reactions is unusual, in that the predominant configuration on the piperazinedione product nucleus (C-3, C-6) is syn.

(15) All trimethylsilyl ketene acetals were prepared according to literature procedures, see: Brownbridge, P. *Synthesis* **1983**, 1.

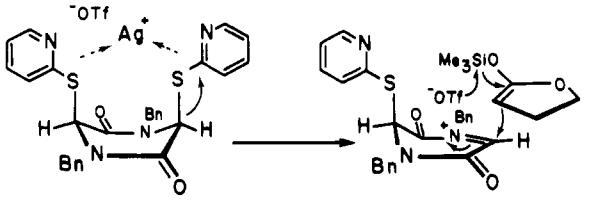
It is known from our experience[7b] on related substrates, that the syn diastereomers are thermodynamically more stable than the corresponding anti diastereomers. The stability for the syn configuration arises due to the known propensity[14] of N,N′-disubstituted diketopiperazines to adopt a "boat"-like conformation that places the 3- and 6-substitutents pseudoaxial to minimize steric compression with the substituents attached to the amide nitrogen atoms; inspection of Figure 1 makes this clear.

In addition to the syn/anti selectivity, there is significant diastereoselectivity observed between the lactone α carbon and C-6 of the 2,5-piperazinedione. In the butyrolactone series, Figure 1 illustrates the relative configuration of the major diastereoisomer produced. The anti diastereomers (**10**) can be readily epimerized with dilute base to the corresponding syn diastereomers (**10**). Under more forcing conditions, the stereochemistry between C-6 of the piperazinedione and the carbon α to the newly introduced carbonyl component can be scrambled, giving (in most cases) a 1:1 equilibrium mixture of the two syn diastereomers.

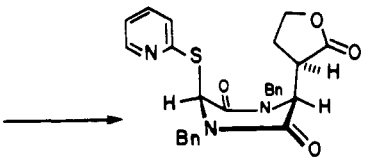
Table I provides the overall yields for coupling, the syn/anti ratio (relating the 3,6-positions of the piperazinedione), and the "major"/"minor" ratio (relating the stereochemistry at C-6 of the piperazinedione and the α carbon of the carbonyl component). For the purposes of the present discussion, "major" will refer to the stereorelationship defined by the lactone depicted in Figure 1 (C-5-(*S*), C-3-(*R*)/C-5-(*R*), C-3-(*S*) diastereomers).

The stereochemical results indicate that the initially formed Ag^+ complex **18** should produce the iminium species[16] **19** which is predominantly attacked from the *same face of the piperazinedione nucleus as the departing thiopyridyl residue.* In the case of the lactones, the predominant orientation of approach of the trimethylsilyl ketene acetal (vide infra) is depicted in structure **19**. Although the geometric and/or electronic interactions between the iminium species and the trimethylsilyl ketene acetal in the transition state cannot be clearly assessed at present, it is possible that the triflate counterion is spatially closer to the positively charged nitrogen atom and facilitates Si–O bond cleavage (cf., orientation depicted in **19**) as the new C–C bond is formed (eq 2).

The only anomalous behavior exhibited was the *N,N′-p*-methoxyphenyl substrate **8d** which gave a 1:1 syn/anti mixture (Table I, entry 7). This is in sharp contrast to the *N*-alkyl cases



18 19

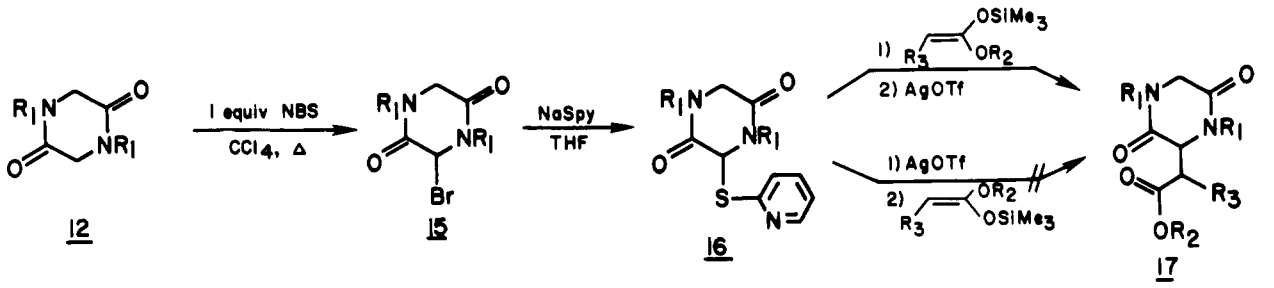


20 (2)

which all displayed a clear syn-diastereoselective preference. The *N*-aryl substrate **8d** is presumably conformationally and electronically quite different from the *N*-alkyl cases due to the pos-

(16) For some related trimethylsilyl enol ether additions to iminium species, see: (a) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056 and references cited therein. (b) Barrett, A. G.; Quayle, P. *J. Chem. Soc. Chem. Commun.* **1981**, 1076. (c) Reider, P. J. Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293. (d) Sera, A.; Itoh, K.; Yamada, H.; Aoki, R. *Heterocycles* **1984**, *22*, 713.

Scheme IV



Scheme V

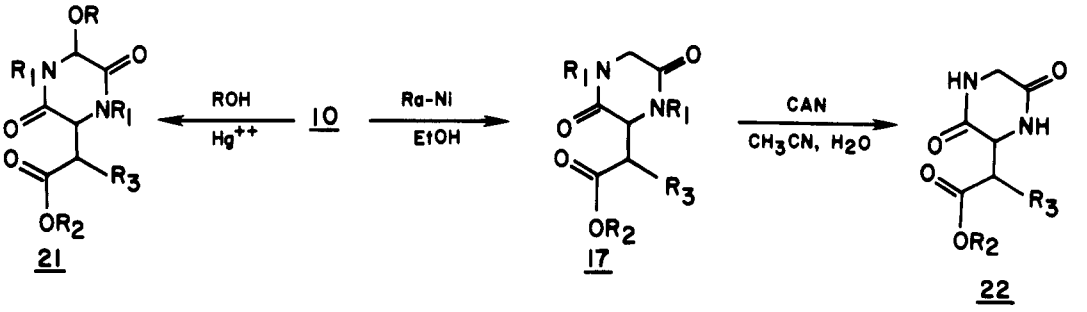
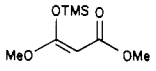
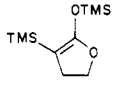


Table I. Coupling of 8 with Ketene Trimethylsilyl Acetals

entry	nucleophile	R_1	R_2	R_3	syn/anti ratio	major/minor ratio	yield, %
1		CH_3	$-CH_2-CH_2-$	$-CH_2-CH_2-$	3.8:1	3.8:1	60
2		CH_2Ph			1:0	2:1	68–70
3		CH_2Ph-*p*-OCH_3			1.37:1	2.3:1	71
4		CH_3	CH_3	CO_2CH_3	5.8:1		76
5		CH_2Ph			2.4:1		63
6		CH_2Ph-*p*-OCH_3			2:1		86
7		Ph-*p*-OCH_3			1:1		66
8		CH_3	$-CH_2CH_2CH_2-$	$-CH_2CH_2CH_2-$	2.5:1	1.6:1	62
9		CH_2Ph			3.5:1	1.8:1	70
10		CH_2Ph-*p*-OCH_3			2.9:1	2.2:1	44
11		CH_2Ph	CH_2-CH_2	CH_2-CH_2	1:0	3.3:1	99

sibility of resonance overlap of the *p*-methoxyphenyl rings and the amide π systems. It is possible that substitution of relatively electron-releasing groups on amide nitrogen might (relatively) destabilize the iminium species **19** resulting in a more reactive electrophile and, thus, poorer diastereoselectivity. Our data support such a hypothesis with an order of selectivity roughly following *N*-benzyl > *N*-methyl > *N*-*p*-methoxybenzyl > *N*-*p*-methoxyphenyl. We were initially interested in the *N*-*p*-methoxyphenyl series due to the possibility of removing this group from the amide nitrogens under oxidative conditions as modeled in the literature.[17] Unfortunately, under a range of conditions (O_3, DDQ, CAN, electrochemical oxidation, etc.) we were unable to cleanly deprotect both amides. Thus, due to the poor diastereoselectivity and protecting group properties displayed in this series, we have abandoned further studies with the *N*-*p*-methoxyphenyl substrates in favor of the *N*-benzyl and *N*-*p*-methoxybenzyl substrates. Fortunately, the *N*-*p*-methoxybenzyl series could be deprotected with ceric ammonium nitrate according to the excellent procedure of Yoshimura to afford the desired lipophobic derivatives **22** (Scheme V).

The substrates **10** could also be solvolyzed in the presence of Hg^{2+} to afford the ethers **21**. In each case we have examined, a single diastereomer is produced that is presumed to possess the syn configuration; an unambiguous stereochemical assignment, however, was not established.

The methodology described herein provides a new and practical approach to highly functionalized 2,5-piperazinediones. The use of these materials for the preparation of substituted piperazines and amino acid derivatives is under study in these laboratories and shall be reported on in due course. Additional experiments to expand the range of C-nucleophiles and further clarify the mechanistically and stereochemically intriguing aspects of these reactions are also under study.

Experimental Section

^1H NMR spectra were recorded on JEOL FX-100 (100 MHz), IBM/Bruker WP-270 (270 MHz), WP-200 (200 MHz), or Nicolet (360 MHz) spectrometers and are reported in δ values. Melting points were recorded on a Mel-Temp instrument in open capillaries and are uncorrected. Microanalyses are within ±0.3% of the calculated values. Infrared spectra were recorded on a Beckman 4240 spectrophotometer and are reported as λ_{max}. Low-resolution mass spectra were determined on a VG MM16F GC–mass spectrometer. Optical rotations were determined on a Perkin-Elmer Model 241 automatic polarimeter and are reported at the D line of Na°.

Thin-layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silica gel glass plates (60F-254) by using 5% phosphomolybdic acid in ethanol heat and/or UV light as a developing agent. Preparative-layer chromatography (PTLC) was carried out on glass-backed TLC plates with a fluorescent indicator on a Harrison Research

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

chromatotron by using 1.0-, 2.0-, or 4.0-mm layer thickness silica gel absorbents. Separations less than 50 mg were carried out on standard glass-backed E. Merck 0.25-mm silica gel plates; the separated products were eluted from the adsorbent with distilled THF. Flash column chromatography was performed by using Woelm silica gel 32–63.

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

The following abbreviations are used throughout: THF = tetrahydrofuran; Et_2O = diethyl ether; EtOAc = ethyl acetate; MeOH = methanol; LDA = lithium diisopropylamide; Et_3N = triethylamine; DMAP = dimethylaminopyridine.

General Procedure for the Preparation of *syn*-Bis(sulfides) 8. To a stirred solution of 1,4-disubstituted 2,5-piperazinedione **12** (1.0 equiv) in CCl_4 (0.1 M) was added *N*-bromosuccinimide (2.1 equiv) and a catalytic amount (1 mol %) of benzoyl peroxide. The mixture was brought to reflux temperature for 2 h, cooled to ambient temperature, filtered, and concentrated. The crude dibromide was recrystallized and stored under a nitrogen atmosphere in the dark.

To a stirred suspension of NaH (2.0 equiv) in THF (20:1 v/w) was added solid 2-mercaptopyridine (2.0 equiv) over a 30-min period. The resulting solution of the sodium thiolate was stirred 30 min at room temperature and transferred via cannula into a stirred solution of the dibromide (**13**) in THF (0.15 M). The mixture was allowed to stir for 30 min, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to afford the *syn*-sulfide **8** which was purified by recrystallization. Spectroscopic data are provided along with reaction scale in each specific case.

General Procedure for the Conversion of 8 → 10. To a stirred solution of the *syn*-bis(sulfide) **8** (1.0 equiv) in THF or CH_2Cl_2 (0.1 M) at room temperature was added recrystallized silver(I) triflate (1.05 equiv) in one portion. The mixture was allowed to stir for 10 min, resulting in a milky-white solution. To this complex was added the ketene trimethylsilyl acetal (1.0–3.0 equiv), and the mixture was allowed to stir at ambient temperature for 2 h. The reaction was diluted with CH_2Cl_2, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by silica gel chromatography. The solvent systems for chromatography are provided along with the reaction scale and spectroscopic data for each specific case. In some instances (as will be noted) an aqueous isolation/workup was omitted, and the crude reaction mixture was directly eluted on silica gel. All these reactions were performed in distilled, dry THF or CH_2Cl_2 under an atmosphere of nitrogen and were magnetically stirred. The ketene trimethylsilyl acetals were prepared according to literature procedures.

1,4-Dimethyl-3,6-bis(2′-mercaptopyridyl)-2,5-piperazinedione (8a). From 1.04 g (3.5 mmol) of dibromide **13a** was obtained 643 mg (51%; two-step yield) of the *syn*-bis(sulfide) **8a**: mp 175–178 °C dec (recryst CH_2Cl_2/MeOH); ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 3.08 (6 H, s) 6.66 (2 H, s), 7.11 (2 H, m), 7.27 (2 H, m), 7.58 (2 H, s), 8.51 (2 H, m); IR (KBr pellet) 1695, 1578, 1562, 1462, 1415, 1400, 1300, 1253, 1118, 1015, 770, 715, 635 cm^{-1}. Anal. ($C_{16}H_{16}N_4O_2S_2$) C, H, N, S.

1,4-Dibenzyl-3,6-bis(2′-thiopyridyl)-2,5-piperazinedione (8b). From 4.6 g (15.8 mmol) of **12b** was obtained 6.98 g (98%) of dibromide **13b** (oil): ^{1}H NMR (100 MHz) ($CDCl_3$) δ TMS 4.04 (2 H, $^1/_2$ABq, *J* = 14.5 Hz), 5.36 (2 H, $^1/_2$ABq, *J* = 14.5 Hz), 5.89 (2 H, s), 7.16–7.50 (10 H, m); IR (NaCl, neat) 2990, 1670, 1395, 710 cm^{-1}; mass spectrum, *m/e* 371 (0.8), 292 (4.4), 99 (91), 56.2 (100).

From 7.2 g (15.9 mmol) of **13b** was obtained 7.67 g (94%) of the *syn*-bis(sulfide) **8b**: mp 149–151 °C (recryst CH_2Cl_2/hexanes); ^{1}H NMR (100 MHz) ($CDCl_3$ δ TMS 4.22 (2 H, $^1/_2$ABq, *J* = 14.6 Hz), 5.23 (2 H, $^1/_2$ABq, *J* = 14.6 Hz), 6.8 (2 H, s), 6.95–7.53 (16 H, m), 8.4 (2 H, d, *J* = 4.1 Hz); IR (NaCl, neat) 2910, 1670, 1450, 1150 cm^{-1}, mass spectrum, *m/e* 402 (0.6), 292 (0.2), 111 (60.7), 91 (12), 49 (100). Anal. ($C_{28}H_{24}N_4O_2S_2$) C, H, N, S.

1,4-Bis(*p*-methoxybenzyl)-3,6-bis(2′-thiopyridyl)-2,5-piperazinedione (8c). From 24 g (67.8 mmol) of **12c** was obtained 31.2 g (90.2%) of dibromide **13c**: mp 164–165 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 4.23 (6 H, s), 4.46 (2 H, $^1/_2$ABq, *J* = 13.5 Hz), 5.64 (2 H, $^1/_2$ABq, *J* = 13.5 Hz), 6.37 (2 H, s), 7.36 (4 H, d, *J* = 8.7 Hz), 7.68 (4 H, d, *J* = 8.7 Hz); IR (NaCl, neat) 1695, 1520 cm^{-1}.

From 37.0 g (72.5 mmol) of dibromide **13c** was obtained 34.2 g (86%) of the *syn*-bis(sulfide) **8c**: mp 174–175 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 3.80 (6 H, s), 4.14 (2 H, $^1/_2$ABq, *J* = 14.5 Hz), 5.15 (2 H, $^1/_2$ABq, *J* = 14.5 Hz), 6.62 (2 H, s), 6.84 (4 H, d, *J* = 8.6 Hz), 7.12 (2 H, m), 7.26 (4 H, d, *J* = 8.6 Hz), 7.27 (2 H, m), 7.56 (2 H, m), 8.52 (2 H, d, *J* = 4.8 Hz); IR (NaCl, neat) 1670, 1505, 1405, 1240 cm^{-1}; mass spectrum, *m/e* 592 ($M^+ + H_3O^+$, 0.4), 574 ($M^+ + 1$, 0.4), 543 (0.5), 219 (8.0), 121 (29.6), 111 (84.4), 57 (100). Anal. ($C_{30}H_{28}N_4O_4S_2$) C, H, N, S.

1,4-Bis(*p*-methoxyphenyl)-3,6-bis(2′-thiopyridyl)-2,5-piperazinedione (8d). From 57 mg (0.17 mmol) of **12d** was obtained 108 mg (93%) of the dibromide **13d**: ^{1}H NMR (60 MHz) ($CDCl_3$) δ TMS 3.87 (6 H, s), 6.33 (2 H, s), 6.97 (4 H, d, *J* = 9 Hz), 7.33 (4 H, d, *J* = 7.3 Hz); mass spectrum, *m/e* 484 (0.2), 405 (1.7), 403 (2.0), 377 (1.1), 375 (1.1), 364 (0.9), 324 (2.5), 296 (2.3), 163 (1.6), 149 (100), 134 (90.3), 106 (32.4), 78 (20.8).

From 120 mg (0.22 mmol) of **13d** was obtained 110 mg (92.4%) of the *syn*-bis(sulfide) **8d**: mp 240–241 °C (recryst CH_2Cl_2/Et_2O); ^{1}H NMR (100 MHz) ($CDCl_3$) δ TMS 3.76 (6 H, s), 6.82 (4 H, d, *J* = 9.0 Hz), 7.01 (2 H, s), 7.32 (4 H, d, *J* = 9.0 Hz), 6.80–8.24 (8 H, m); IR (NaCl, neat) 1690, 1650, 1610, 1580, 1510, 1410, 1245, 1115, 905, 725 cm^{-1}. Anal. ($C_{28}H_{24}N_4O_4S_2$) C, H, N, S.

1,4-Dimethyl-3-(2′-thiopyridyl)-6-(2″-γ-butyrolactonyl)-2,5-piperazinedione (10a, R_1 = CH_3; R_2, R_3 = CH_2CH_2). From 25 mg (0.069 mmol) of **8a**, 17.8 mg (0.069 mmol, 1.0 equiv) of AgOTF, and 16 mg of (0.1 mmol, 1.5 equiv) of TMS enol ether in CH_2Cl_2 (1.0 mL) was obtained 14 mg (60%) of the lactone **10a** as a mixture of syn and anti diastereomers (14:6:13:1, syn-major/anti-major/syn-minor/anti-minor diasteromers) (syn/anti, 3.8:1) (isolated by flash column silica gel, eluted with EtOAc).

Major *syn*-10a: mp 159.5–160.5 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$ δ TMS 2.19–2.28 (1 H, m), 2.43–2.51 (1 H, m), 3.04 (3 H, s), 3.13 (3 H, s), 3.74 (1 H, t, *J* = 6.3 Hz), 4.24–4.44 (2 H, m), 4.56 (1 H, d, *J* = 3.6 Hz), 6.67 (1 H, s), 7.11–7.15 (1 H, m), 7.22–7.29 (1 H, m), 7.56–7.62 (1 H, m), 8.48–8.50 (1 H, m); IR (NaCl, neat) 3050, 2980, 2930, 1770, 1670, 1575, 1560, 1025, 755 cm^{-1}. Anal. ($C_{15}H_{17}N_3O_4S$) C, H, N, S.

Minor *anti*-10a: mp 160–161 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.14–2.28 (2 H, m), 2.92 (3 H, s), 3.05 (3 H, s), 3.68 (1 H, dd, *J* = 10.2, 11.5 Hz), 4.23–4.33 (1 H, m), 4.44–4.52 (1 H, m), 4.62 (1 H, s), 5.70 (1 H, s), 7.08–7.12 (1 H, m), 7.20–7.26 (1 H, m), 7.56 (1 H, dd, *J* = 5.08, 7.2 Hz), 8.44 (1 H, d, *J* = 5.00 Hz).

Minor *syn*-10a: mp 148–149.5 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.17–2.50 (2 H, m), 2.97 (3 H, s), 3.05 (3 H, s), 3.30–3.44 (1 H, m), 4.26–4.33 (1 H, m), 4.48–4.55 (1 H, m), 4.74 (1 H, s), 6.73 (1 H, s), 7.10–7.14 (1 H, m), 7.20–7.27 (1 H, m), 7.55–7.61 (1 H, m), 8.48–8.51 (1 H, m); IR (NaCl, neat) 3030, 2910, 2840, 1765, 1665, 1570, 1550, 1010, 750 cm^{-1}. Anal. ($C_{15}H_{17}N_3O_4S$) C, H, N, S.

Major *anti*-10a: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.97–2.40 (2 H, m), 3.06 (3 H, s), 3.08 (3 H, s), 3.18–3.22 (1 H, m), 4.29–4.47 (2 H, m), 4.77 (1 H, d, *J* = 3.0 Hz), 5.96 (1 H, s), 7.10–7.14 (1 H, m), 7.21–7.27 (1 H, m), 7.54–7.57 (1 H, m), 8.45–8.48 (1 H, m); IR (NaCl, neat) 1770, 1675, 1580, 1560, 1300, 1025, 760 cm^{-1}.

Epimerization of the anti-minor isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH at 25 °C for 48 h resulted in a 2:1:2 ratio of syn-major/anti-major/syn-minor isomers.

1,4-Dimethyl-3-(2′-thiopyridyl)-6-(dimethylmalonyl)-2,5-piperazinedione (10a, R_1 = CH_3; R_2 = CH_3; R_3 = CO_2CH_3). From 25 mg (0.07 mmol) of **8a**, 28 mg (0.138 mmol, 2.0 equiv) of carbomethoxy ketene methyl trimethylsilyl acetal, and 17.8 mg (0.07 mmol, 1.0 equiv) of AgOTf in CH_2Cl_2 (1.5 mL) was obtained 20 mg (76%) of the product **10a** as a 5.8:1 syn/anti mixture (isolated on PTLC silica gel, eluted with 33% hexanes in EtOAc).

Syn Isomer 10a: mp 144.5–145 °C (recryst EtOAc/hexanes); ^{1}H NMr (270 MHz) ($CDCl_3$) δ TMS 3.05 (6 H, s), 3.84 (3 H, s), 3.85 (3 H, s), 4.05 (1 H, d, *J* = 4.7 Hz), 4.72 (1 H, d, *J* = 4.7 Hz), 6.87 (1 H, s), 7.05–7.10 (1 H, m), 7.24–7.28 (1 H, m), 7.52–7.59 (1 H, m), 8.45–8.47 (1 H, m); IR (NaCl, neat) 2950, 1750, 1675, 1580, 1560, 905, 730 cm^{-1}. Anal. ($C_{16}H_{19}N_3O_6S$) C, H, N, S.

Anti Isomer 10a: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS (3.02 (3 H, s), 3.09 (3 H, s), 3.79 (3 H, s), 3.83 (3 H, s), 4.15 (1 H, d, *J* = 3.6 Hz), 4.73 (1 H, d, *J* = 3.6 Hz), 5.72 (1 H, s), 7.06–7.09 (1 H, m), 7.20–7.26 (1 H, m), 7.54 (1 H, m), 8.41 (1 H, m); IR (NaCl, neat) 2950, 1750, 1675, 1580, 1560, 1250, 760, 720 cm^{-1}.

Epimerization of the anti isomer to a mixture of syn/anti isomers was carried out by treatment of the anti isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH for 2.5 h at 25 °C. Evaporation of the solvent produced a 1.5:1 syn/anti mixture.

1,4-Dimethyl-3-(2′-thiopyridyl)-6-(2″-δ-valerolactonyl)-2,5-piperazinedione (10a, R_1 = CH_3; R_2, R_3 = $CH_2CH_2CH_2$). From 25 mg (0.07 mmol, 1.0 equiv) of **8a**, 17.8 mg (0.07 mmol, 1.0 eqiv) of AgOTf, and 18 mg (0.1 mmol, 1.5 equiv) of the trimethylsilyl ketene acetal of δ-valerolactone in CH_2Cl_2 (1.0 mL) was obtained 15 mg (62%) of the valerolactone products **10a** (1.6:1, major/minor ratio) (2.2:1 syn/anti

ratio) isolated by PTLC silica gel (eluted with EtOAc).

Major *syn*-10a: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.80–2.19 (4 H, m), 2.95 (1 H, m), 3.04 (3 H, s), 3.10 (3 H, s), 4.27–4.50 (2 H, m), 4.94 (1 H, d, J = 3.2 Hz), 6.70 (1 H, s), 7.09–7.12 (1 H, m), 7.22–7.27 (1 H, m), 7.55–7.67 (1 H, m), 8.49 (1 H, m); IR (NaCl, neat) 1727, 1672, 1578, 1450, 1399, 1250, 1165, 1118, 754, 715 cm^{-1}.

Minor *syn*-10a: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.03–2.10 (4 H, m), 2.98 (3 H, s), 3.05 (3 H, s), 3.20–3.31 (1 H, m), 4.31–4.37 (1 H, m), 4.42–4.50 (1 H, m), 4.97 (1 H, s), 6.78 (1 H, s), 7.08–7.18 (1 H, m), 7.20–7.38 (1 H, m), 7.54–7.65 (1 H, m), 8.47–8.49 (1 H, m); IR (NaCl, neat) 1731, 1672, 1579, 1560, 1265, 1162, 892, 728 cm^{-1}.

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-(2″-γ-butyrolactonyl)-2,5-piperazinedione (10b, R_1 = CH_2Ph; R_2, R_3 = CH_2CH_2). From 4.0 g (7.81 mmol) of **8b**, 1.36 mL (8.6 mmol, 1.1 equiv) of TMS enol ether, and 2.0 g (7.81 mmol) of AgOTf in THF (0.22 M) was obtained 2.59 g (68%) of the syn lactones **10b** (2:1, major/minor ratio).

Major *syn*-10b: mp 184–185 °C (recryst CH_2Cl_2/hexanes); ^{1}H NMR (360 MHz) ($CDCl_3$) δ TMS 2.25–2.35 (1 H, m), 2.35–2.50 (1 H, m), 3.02 (1 H, ddd, J = 10.3 H, 9.3, 4.3 Hz), 4.08 (1 H, $^1/_2$ABq, J = 14.57 Hz), 4.20 (1 H, m), 4.36 (1 H, m), 4.58 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.60 (1 H, d, J = 4.3 Hz), 5.24 (1 H, $^1/_2$ABq, J = 14.6 Hz), 6.58 (1 H, s), 7.16–7.20 (1 H, m), 7.2–7.4 (11 H, m); 7.58–7.62 (1 H, m), 8.46–8.48 (1 H, m); ^{13}C NMR (25 MHz) ($CDCl_3$) δ $CHCl_3$ 23.75 (t), 43.02 (d), 46.99 (t), 48.39 (t), 58.72 (d), 60.42 (d), 66.31 (t), 121.19 (d) 122.48 (d), 127.85 (d), 128.50 (d), 135.03 (s), 136.84 (d), 149.28 (d), 154.59 (s), 164.34 (s), 165.57 (s), 176.37 (s); IR (NaCl, neat) 2905, 1770, 1670, 1450, 1150, 1020 cm^{-1}; mass spectrum, m/e 487 (M$^+$, 2.1), 396 (1.2), 477 (1.0), 91 (100), 85 (27). Anal. ($C_{27}H_{25}N_3O_4S$) C, H, N, S. A single crystal X-ray determination of this substance was perfomred; see experimental description and supplementary material.

Minor *syn*-10b: ^{1}H NMR (100 MHz) ($CDCl_3$) δ $CHCl_3$ 1.76–2.16 (1 H, m), 2.40–2.88 (2 H, m), 3.99–4.42 (2 H, m), 4.03 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.05 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.77 (1 H, s), 4.97 (1 H, $^1/_2$ABq, J = 15.0 Hz), 5.19 (1 H, $^1/_2$ABq, J = 15.0 Hz), 6.62 (1 H, s), 6.96–7.62 (13 H, m), 8.30–8.42 (1 H, m); IR (NaCl, neat) 1770, 1670, 1450, 1150 cm^{-1}; mass spectrum, m/e 487 (M$^+$, 2.2), 402 (0.2), 396 (2.0), 377 (5.4) 111 (18.7), 91 (100). Treatment of the minor *syn*-**10b** with (0.1 N) NaOH/THF at 25 °C afforded an equilibrium mixture of major *syn*-**10b** and minor *syn*-**10b** (1:1 ratio).

The overall yield of coupling in this instance could be considerably improved by using the α-(trimethylsilyl)trimethylsilyl ketene acetal of γ-butyrolactone as follows: From 1.44 g (2.8 mmol) of **8b**, 0.66 mL (2.94 mmol, 1.05 equiv) of α-(trimethylsilyl)trimethylsilyl ketene acetal of γ-butyrolactone, and 0.72 g (2.8 mmol, 1.0 equiv) of AgOTf in THF (150 mL) was obtained 1.312 g (76%) of the major *syn*-**10b** plus 399 mg (23%) of the minor *syn*-**10b** (99% combined yield).

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-(dimethylmalonyl)-2,5-piperazinedione (10b, R_1 = CH_2Ph; R_2 = CH_3; R_3 = CO_2CH_3). From 25 mg (0.048 mmol) of **8b**, 20 mg (0.096 mmol, 2.0 equiv) of carbomethoxy ketene methyl trimethylsilyl acetal and 12.5 mg (0.048 mmol, 1.0 equiv) of AgOTf in CH_2Cl_2 (2.0 mL) was obtained 16.4 mg (63%) of the product **10b** as a 2.4:1 syn/anti mixture (isolated on PTLC silica gel, eluted with 20% EtOAc in benzene).

Syn Isomer 10b: mp 136–137 °C (recryst CH_2Cl_2/Et_2O/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.73 (3 H, s), 3.77 (3 H, s), 3.96 (1 H, d, J = 5.2 Hz), 4.09 (1 H, $^1/_2$ABq, J = 14.6 Hz), 4.55 (1 H, $^1/_2$ABq, J = 15.4 Hz), 4.79 (1 H, d, J = 5.2 Hz), 4.82 (1 H, $^1/_2$ABq, J = 15.4 Hz), 5.32 (1 H, $^1/_2$ABq, J = 14.6 Hz), 6.81 (1 H, s), 7.05–7.09 (1 H, m), 7.21–7.34 (11 H, m), 7.52–7.59 (1 H, m), 8.39–8.41 (1 H, m); IR (NaCl, neat) 1745, 1672, 1572, 1445, 1263, 882, 725, 690 cm^{-1}. Anal. ($C_{28}H_{27}N_3O_6S$) C, H, N, S.

Anti Isomer 10b: mp 150 °C dec (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.63 (3 H, s), 3.77 (3 H, s), 4.10 (1 H, d, J = 3.5 Hz), 4.13 (1 H, $^1/_2$ABq, J = 14.8 Hz), 4.34 (1 H, $^1/_2$ABq, J = 15.6 Hz), 4.91 (1 H, d, J = 3.5 Hz), 5.11 (1 H, $^1/_2$ABq, J = 15.6 Hz), 5.44 (1 H, s), 5.52 (1 H, $^1/_2$ABq, J = 14.8 Hz), 6.99–7.02 (1 H, m), 7.19–7.55 (12 H, m), 8.09 (1 H, d, J = 4.1 Hz); IR (NaCl, neat) 1750, 1672, 1580, 1432, 1355, 1165, 755, 725, 695 cm^{-1}.

Epimerization of the anti isomer to a mixture of syn/anti isomers was carried out by treatment of the anti isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH at 25 °C for 12 h. Evaporation of the solvent produced a 1.8:1 syn/anti mixture.

1,4-Dibenzyl-3-(2′-thiopyridyl)-6-(2″-δ-valerolactonyl)-2,5-piperazinedione (10b, R_1 = CH_2Ph; R_2, R_3 = $CH_2CH_2CH_2$). From 26 mg (0.05 mmol, 1.0 equiv) of **8b**, 13 mg (0.05 mmol, 1.0 equiv) of AgOTf and 13 mg (0.076 mmol, 1.5 equiv) of the TMS enol ether of δ-valerolactone in THF (0.5 mL) was obtained 14 mg (70% based on recovered **8b**) of the valerolactone product **10b** as a 3.5:1 syn/anti mixture (1.8:1 major:minor ratio) (isolated by PTLC silica gel, eluted with 20% EtOAc in hexanes).

Major *syn*-10b: mp 166–167 °C (recryst EtOAc/hexanes); ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.40–2.15 (4 H, m), 2.89–2.95 (1 H, m), 4.05 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.23–4.30 (1 H, m), 4.30–4.38 (1 H, m), 4.63 (1 H, $^1/_2$ABq, J = 14.9 Hz), 4.81 (1 H, $^1/_2$ABq, J = 14.9 Hz), 5.02 (1 H, d, J = 3.8 Hz), 5.30 (1 H, $^1/_2$ABq, J = 14.5 Hz), 6.59 (1 H, s), 7.15–7.8 (1 H, m), 7.18–7.37 (1 H, m), 7.56–7.62 (1 H, m), 8.46–8.49 (1 H, m); IR (NaCl, neat) 1730, 1665, 1450, 1260, 1160 cm^{-1}; mass spectrum, m/e 501 (M$^+$, 0.3), 391 (2.7), 299 (1.5), 292 (1.7), 91 (100). Anal. ($C_{28}H_{27}N_3O_4S$) C, H, N, S.

Minor *syn*-10b: mp 181–183 °C (recryst EtOAc/hexanes); ^{1}H NMR (360 MHz) ($CDCl_3$) δ $CHCl_3$ 1.45–2.10 (5 H, m), 3.16–3.22 (1 H, m), 3.55–3.62 (1 H, m), 4.05 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.59 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.69 (1 H, $^1/_2$ABq, J = 15.0 Hz), 5.05 (1 H, d, J = 1.5 Hz), 5.29 (1 H, $^1/_2$ABq, J = 14.3 Hz), 6.74 (1 H, s), 7.14–7.18 (1 H, m), 7.18–7.41 (11 H, m), 7.54–7.62 (1 H, m), 8.42–8.45 (1 H, m); IR (NaCl, neat) 1730, 1665, 1450, 1260, 1160 cm^{-1}. mass spectrum, m/e 501 (M$^+$, 0.3), 391 (2.7), 299 (1.5), 292 (1.7), 91 (100). Anal. ($C_{28}H_{27}N_3O_4S$) C, H, N, S.

1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-(2″-γ-butyrolactonyl)-2,5-piperazinedione (10c, R_1 = CH_2Ph-*p*-OCH_3; R_2, R_3 = CH_2CH_2). From 1.117 g (1.95 mmol, 1.0 equiv) of **8c**, 0.46 g (2.93 mmol, 1.5 equiv) of TMS enol ether, and 0.6 g (2.34 mmol, 1.2 equiv) of AgOTf in THF (15 mL) was obtained 0.53 g (49.5%) of *syn*-**10c** (major/minor ratio = 1.11:1) plus 0.23 g (21.4%) of *anti*-**10c** (major/mino ratio = 2.3:1) (overall yield 70.9%, syn/anti ratio = 2.3:1).

Major *syn*-10c: mp 178–180 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 1.80–2.10 (2 H, m), 3.14 (1 H, ddd, J = 4.0, 10.8, 10.8 Hz), 3.91 (3 H, s), 3.92 (3 H, s), 4.12 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.25–4.32 (1 H, m), 4.50 (1 H, ddd, J = 14.3, 9.8, 9.8 Hz), 4.59 (1 H, $^1/_2$ABq, J = 14.8 Hz), 4.73 (1 H, d, J = 4.1 Hz), 5.07 (1 H, $^1/_2$ABq, J = 14.8 Hz), 5.29 (1 H, $^1/_2$ABq, J = 14.3 Hz), 6.67 (1 H, s), 6.92 (2 H, d, J = 8.9 Hz), 6.96 (2 H, d, J = 8.9 Hz), 7.27–7.40 (2 H, m), 7.31 (2 H, d, J = 8.9 Hz), 7.32 (2 H, d, J = 8.9 Hz), 7.72 (1 H, m), 8.63 (1 H, d, J = 4.2 Hz); IR (NaCl, neat) 1772, 1672, 1513, 1265, 1025 cm^{-1}; mass spectrum, m/e 438 (0.2), 316 (0.2), 163 (3.9), 136 (5.5), 121 (100), 111 (12.3).

Major *anti*-10c: mp 168–168.5 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.80–2.05 (2 H, m), 3.19 (1 H, dd, J, J = 8.1 Hz) 3.77 (3 H, s), 3.81 (3 H, s), 4.08 (1 H, $^1/_2$ABq, J = 14.5 Hz), 4.20–4.40 (3 H, m), 4.85 (1 H, s), 5.09 (1 H, $^1/_2$ABq, J = 15.4 Hz), 5.28 (1 H, $^1/_2$ABq, J = 14.5 Hz), 5.86 (1 H, s), 6.82 (2 H, d, J = 8.4 Hz), 6.84 (2 H, d, J = 8.7 Hz), 7.06 (1 H, t), 7.17 (2 H, d, J = 8.4 Hz), 7.17–7.20 (1 H, m), 7.19 (2 H, d, J = 8.7 Hz), 7.56 (1 H, t, J = 6.4 Hz), 8.27 (1 H, d, J = 3.9 Hz); IR (NaCl, neat) 1765, 1670, 1512, 1245, 1025 cm^{-1}; mass spectrum, m/e 467 (0.9), 347 (3.4), 257 (5.8), 167 (7.1), 121 (5.5), 111 (19.1), 57 (100). Anal. ($C_{29}H_{29}N_3O_6S$) C, H, N, S.

Minor *syn*-10c: mp 194–195 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 2.30–2.44 (2 H, m), 3.31 (1 H, dd, J, J = 10.9 Hz), 3.80 (6 H, s) 3.99 (2 H, twice $^1/_2$ABq, J = 14.5 Hz), 4.17–4.27 (1 H, m), 4.34 (1 H, dd, J, J = 8.6 Hz), 4.81 (1 H, s), 4.99 (1 H, $^1/_2$ABq, J = 14.6 Hz), 5.28 (1 H, $^1/_2$ABq, J = 14.5 Hz), 6.64 (1 H, s), 6.80 (2 H, d, J = 7.6 Hz), 6.83 (2 H, d, J = 7.4 Hz), 7.15 (2 H, d, J = 7.4 Hz), 7.26 (2 H, d, J = 7.6 Hz), 7.20–7.30 (2 H, m), 7.59 (1 H, t, J = 7.7 Hz, 8.48 (1 H, d, J = 4.2 Hz); IR (NaCl, neat) 1768, 1670, 1512, 1450, 1242, 1020 cm^{-1}.

Minor *anti*-10c: mp 136–138 °C (recryst EtOAc/hexanes); ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 1.20–1.40 (1 H, m), 1.80–1.90 (1 H, m), 3.75–3.98 (2 H, m), 3.78 (3 H, s), 3.80 (3 H, s), 4.17 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.28 (1 H, $^1/_2$ABq, J = 13.9 Hz), 4.32 (1 H, d, J = 2.3 Hz), 5.14 (1 H, d, J = 2.3 Hz), 5.23 (1 H, $^1/_2$ABq, J = 13.9 Hz), 5.28 (1 H, $^1/_2$ABq, J = 14.3 Hz), 5.62 (1 H, s), 6.68 (2 H, d, J = 8.6 Hz), 6.76 (2 H, d, J = 8.6 Hz), 6.88–6.94 (1 H, m), 7.12–7.16 (1 H, m), 7.24 (2 H, d, J = 8.6 Hz), 7.29 (2 H, d, J = 8.6 Hz), 7.49 (1 H, t), 7.87 (1 H, d, J = 4.2 Hz); IR (NaCl, neat) 1770, 1678, 1520, 1251, 1031 cm^{-1}; mass spectrum, m/e 400 (0.3), 368 (0.7), 191 (3.1), 149 (13.8), 121 (27.4), 91 (4.9), 57 (100).

1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-(dimethylmalonyl)-2,5-piperazinedione (10c, R_1 = CH_2Ph-*p*-OCH_3; R_2 = CH_3; R_3 = CO_2CH_3). From 50 mg (0.087 mmol, 1.0 equiv) of **8c**, 1.8 μL (0.013 mmol, 0.15 equiv) of triethylamine, 22.4 mg (0.087 mmol, 1.0 equiv) of AgOTf, and 35 mg (0.174 mmol, 2.0 equiv) of the trimethylsilyl ketene acetal of dimethylmalonate was otained 44.6 mg (86%) of product **10c** as a 2:1 syn/anti mixture (isolated on PTLC silica gel, eluted with 15% EtOAc/benzene.

***anti*-10c**: ^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS 3.66 (3 H, s), 3.78 (3 H, s), 3.79 (3 H, s), 3.82 (3 H, s), 4.04 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.13 (1 H, d, J = 3.8 Hz), 4.18 (1 H, $^1/_2$ABq, J = 15.3 Hz), 4.86 (1 H, d, J = 3.8 Hz), 5.13 (1 H, $^1/_2$ABq, J = 15.3 Hz), 5.39 (1 H, s), 5.46 (1 H, $^1/_2$ABq, J = 14.4 Hz), 6.79 (2 H, d, J = 8.6 Hz), 6.87 (2 H, d, J = 8.6 Hz), 6.95–7.01 (1 H, m), 7.16–7.21 (3 H, m), 7.36 (2 H, d, J = 8.6

Hz), 7.48–7.54 (1 H, m), 8.05–8.07 (1 H, m); IR (NaCl, neat) 1740, 1665, 1610, 1575, 1511, 1433, 1243, 1165, 1025 cm^{-1}; mass spectrum, *m/e* 592.9 (0.1), 481.9 (0.8), 121.0 (96.9), 111.0 (25.8).

***syn*-10c**: ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 3.76 (3 H, s), 3.79 (6 H, s), 3.81 (3 H, s), 4.01 (1 H, d, J = 5.1 Hz), 4.03 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.40 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.77 (1 H, d, J = 5.1 Hz), 4.85 (1 H, $^1/_2$ABq, J = 15.0 Hz), 5.26 (1 H, $^1/_2$ABq, J = 14.3 Hz), 6.78 (2 H, d, J = 8.6 Hz), 6.79 (1 H, s), 6.85 (2 H, d, J = 8.6 Hz), 7.08–7.12 (1 H, m), 7.16 (2 H, d, J = 3.2 Hz), 7.19 (2 H, d, J = 3.2 Hz), 7.29 (1 H, t, J = 7.8 Hz), 7.57 (1 H, d of t, J = 1.7, 7.8 Hz), 8.44–8.46 (1 H, m); IR (NaCl, neat) 1740, 1662, 1610, 1575, 1508, 1440, 1240, 1160, 1115, 1025, 722, 692, cm^{-1}; mass spectrum, *m/e* 593.2 (0.2), 482 (1.6), 111.0 (44.9), 121.1 (100.0); exact mass ($M^+ - C_5H_5NS$) calcd for $C_{25}H_{26}N_2O_8$ 482.168 98, found 482.168 93.

Epimerization of the anti isomer to a mixture of syn/anti isomers was carried out by treatment of the minor anti isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH at 25 °C under N_2 for 12 h. Evaporation of the solvent yielded a 5.7:1 mixture (syn/anti).

1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-6-(2″-δ-valerolactonyl)-2,5-piperazinedione (10c, R_1 = CH_2Ph-*p*-OCH_3; R_2, R_3 = $CH_2CH_2CH_2$). From 25 mg (0.043 mmol, 1.0 equiv) of **8c**, 15 mg (0.058 mmol, 1.3 equiv) of AgOTf, and 9.8 mg (0.056 mmol, 1.3 equiv) of the trimethylsilyl ketene acetal of δ-valerolactone in CH_2Cl_2 (0.5 mL) was obtained 10.7 mg (44%) of the product as a mixture of diastereomers (1.7:1.0:1.2, syn-major/anti-major/syn-minor) (syn/anti = 2.9:1) (isolated by PTLC eluted with 2:1 EtOAc/hexanes).

Minor *syn*-10c: mp 148.5–150.5 °C (recryst EtOAc/hexanes); ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 1.85–2.01 (4 H, m), 3.17–3.24 (1 H, m), 3.58–3.65 (1 H, m), 3.80 (3 H, s), 3.81 (3 H, s), 3.98 (1 H, d, $^1/_2$ABq, J = 14.4 Hz), 4.20–4.24 (1 H, m), 4.54 (1 H, d, $^1/_2$ABq, J = 14.8 Hz), 4.61 (1 H, $^1/_2$ABq, J = 14.8 Hz), 5.06 (1 H, s), 5.26 (1 H, $^1/_2$ABq, J = 14.4 Hz), 6.72 (1 H, s), 6.80–6.86 (4 H, m), 7.12–7.36 (6 H, m), 7.57–7.64 (1 H, m), 8.49–8.50 (1 H, m); IR (NaCl, neat) 1715, 1650, 1503, 1444, 1297, 1241, 1155, 1020, 750 cm^{-1}.

Major *syn*-10c: mp 158.5–159 °C; ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 1.68–2.09 (4 H, m), 2.95 (1 H, m), 3.80 (6 H, s), 3.98 (1 H, d, $^1/_2$ABq, J = 14.3 Hz), 4.23–4.42 (2 H, m), 4.51 (1 H, d, $^1/_2$ABq, J = 14.7 Hz), 4.81 (1 H, d, $^1/_2$ABq, J = 14.7 Hz), 5.04 (1 H, d, J = 3.5 Hz), 5.26 (1 H, d, $^1/_2$ABq, J = 14.3 Hz), 6.58 (1 H, s), 6.80 (2 H, d, J = 8.6 Hz), 6.84 (2 H, d, J = 8.6 Hz), 7.13–7.31 (6 H, m), 7.57–7.64 (1 H, m), 8.51–8.53 (1 H, m); IR (NaCl, neat) 1720, 1665, 1508, 1448, 1244, 1155, 1112, 1082, 1023, 738 cm^{-1}. Anal. ($C_{30}H_{31}N_3O_6S$) C, H, N, S.

Major *anti*-10c: mp 153–155 °C (recryst EtOAc/hexanes); ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 1.39–1.88 (4 H, m), 3.12 (1 H, m), 3.79 (3 H, s), 3.81 (3 H, s), 4.02 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.07 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.24–4.41 (2 H, m), 5.12 (1 H, d, J = 2.76 Hz), 5.21 (1 H, $^1/_2$ABq, J = 15.0 Hz), 5.34 (1 H, d, $^1/_2$ABq, J = 14.4 Hz), 5.71 (1 H, s), 6.79 (2 H, d, J = 8.6 Hz), 6.85 (2 H, d, J = 8.7 Hz), 6.98–7.03 (1 H, m), 7.18–7.26 (5 H, m), 7.49–7.52 (1 H, m), 8.15–8.17 (1 H, m); IR (NaCl, neat) 1715, 1655, 1503, 1410, 1297, 1242, 1170, 1080, 1020 cm^{-1}. Epimerization of the anti isomer was carried out by treatment of the anti isomer in 50% THF/MeOH with 0.1 N NaOMe in MeOH at 25 °C under N_2 for 16 h. Evaporation of the solvent yielded the syn isomers.

1,4-Bis(*p*-methoxyphenyl)-3-(2′-thiopyridyl)-6-(dimethylmalonyl)-2,5-piperazinedione (10d, R_1 = Ph-*p*-OCH_3; R_2 = CH_3; R_3 = CO_2CH_3). From 25 mg (0.046 mmol, 1.0 equiv) of **8d**, 12 mg (0.046 mmol, 1.0 equiv) of AgOTf, 1 μL of Et_3N, and 18 mg (0.092 mmol, 2.0 equiv) of carbomethoxy ketene methyltrimethylsilyl acetal in CH_2Cl_2 (2.0 mL) was obtained 17.1 mg (66%) of the product **10d** as a 1.1:1 syn/anti mixture (isolated by PTLC silica gel, eluted with 33% hexanes in EtOAc, three elutions). (Epimerization of the anti isomer was carried out by treatment with 0.1 N NaOMe in 50% THF/MeOH at 25 °C for 24 h. Evaporation of the solvent afforded a 1:3, syn/anti mixture).

***syn*-10d**: mp 175–177 °C (recryst, THF/hexanes); ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 3.68 (3 H, s), 3.73 (3 H, s), 3.83 (3 H, s), 3.89 (3 H, s), 3.94 (1 H, d, J = 4.7 Hz), 5.24 (1 H, d, J = 4.7 Hz), 6.79–7.39 (12 H, m), 8.20 (1 H, d, J = 4.0 Hz); IR (NaCl, neat) 1735, 1675, 1602, 1574, 1505, 1295, 1240, 1020, 820, 790, 750, 722 cm^{-1}. Anal. ($C_{28}H_{27}N_3O_8S$) C, H, N.

***anti*-10d**: mp 164–165 °C (recryst, EtOAc/hexanes); ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 3.71 (3 H, s), 3.76 (1 H, d, J = 3.8 Hz), 3.79 (3 H, s), 3.82 (3 H, s), 5.44 (1 H, d, J = 3.8 Hz), 5.84 (1 H, s), 6.88–7.36 (10 H, m), 7.55 (1 H, m), 8.60 (1 H, d, J = 4.1 Hz); IR (NaCl, neat) 1735, 1670, 1600, 1570, 1502, 1350, 1240, 1020, 820, 790, 747, 720 cm^{-1}.

1,4-Bis(*p*-methoxybenzyl)-3-bromo-2,5-piperazinedione. To a stirred solution of **12c** (1.0 g, 2.82 mmol, 1.0 equiv) in CCl_4 (100 mL) was added *N*-bromosuccinimide (251 mg, 1.41 mmol, 0.5 equiv) and 5 mg of benzoyl peroxide at room temperature. The mixture was refluxed for 1 h, cooled to 0 °C, filtered, concentrated, and separated by PTLC silica gel (eluted with $CHCl_3$) to afford 405 mg (33% or 66% based on consumed **12c**) of the monobromide as white crystals, mp 158 °C dec (recryst EtOAc/hexanes).

1,4-Bis(*p*-methoxybenzyl)-3-(2′-thiopyridyl)-2,5-piperazinedione (16, R_1 = CH_2Ph-*p*-OCH_3). A solution of sodium 2-mercaptopyridine was prepared by adding a solution of 2-mercaptopyridine (141 mg, 1.27 mmol, 1.1 equiv) in THF (35 mL) to a suspension of NaH (51 mg, 1.27 mmol, 1.1 equiv) in THF (50 mL). After stirring 30 min, this solution was transferred via cannula to a stirred solution of 1,4-bis(*p*-methoxybenzyl)-3-bromo-2,5-piperazinedione (500 mg, 1.15 mg, 1.0 equiv) in THF (30 mL) at 25 °C. After stirring for 10 min, the solution was diluted with CH_2Cl_2, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and crystallized from EtOAc/hexanes to afford 492 mg (93%) of **16**; mp 132–132.5 °C; ^1H NMR (60 MHz) ($CDCl_3$) δ TMS 3.82 (6 H, s), 3.88 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.08 (1 H, $^1/_2$ABq, J = 15.0 Hz), 4.22 (2 H, $^1/_2$ABq, J = 14.0 Hz), 4.97 (1 H, $^1/_2$ABq, J = 14.0 Hz), 5.42 (1 H, $^1/_2$Abq, J = 14.0 Hz), 5.79 (1 H, s), 6.88 (2 H, d, J = 9.0 Hz), 6.90 (2 H, d, J = 9.0 Hz), 7.25 (3 H, m), 7.34 (2 H, d, J = 9.0 Hz), 7.40 (2 H, d, J = 9.0 Hz), 8.3 (1 H, br d, J = 4.0 Hz); IR (NaCl, neat) 1670, 1450, 1245 cm^{-1}. Anal. ($C_{25}H_{25}N_3O_4S$) C, H, N, S.

1,4-Bis(*p*-methoxybenzyl)-3-(2′-γ-butyrolactonyl)-2,5-piperazinedione (17, R_1 = CH_2Ph-*p*-OCH_3; R_2, R_3 = CH_2CH_2). To a stirred solution of **16** (45 mg, 0.1 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added the trimethyl silyl ketene acetal of mL) (23 mg, 0.126 mmol, 1.3 equiv) at room temperature. To this solution was added AgOTf (32 mg, 0.146 mmol, 1.5 equiv) in one portion. The resulting milky-white suspension was stirred for 30 min, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with EtOAc) to afford 13 mg (30.5%) of a major diastereoisomer (mp 202–203 °C, recryst CH_2Cl_2/Et_2O) and 8 mg (18.8%) of a minor diastereoisomer (mp 190–192 °C, recryst EtOAc/hexanes). The major/minor stereochemical relationship follows *inversely* from that for **10c** as evidenced by Raney nickel conversions of minor **10c** to major **17** (see below).

Major Diastereomer: ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ (2.2 (1 H, m), 2.41 (1 H, m), 3.14 (1 H, dd, J_{vic} = J_{vic} = 10.2 Hz), 3.80 (6 H, s), 3.83 (1 H, $^1/_2$ABq, J = 17.4 Hz), 3.97 (1 H, $^1/_2$ABq, J = 14.8 Hz), 4.04 (1 H, $^1/_2$ABq, J = 17.4 Hz), 4.19 (1 H, m), 4.35 (1 H, $^1/_2$ABq, J = 14.4 Hz), 4.38 (1 H, m), 4.42 (1 H, d, J = 1.0 Hz), 4.63 (1 H, $^1/_2$ABq, J = 14.4 Hz), 5.16 (1 H, $^1/_2$ABq, J = 14.8 Hz), 6.86 (4 H, d, J = 8.9 Hz), 7.15 (2 H, d, J = 8.9 Hz), 7.23 (2 H, d, J = 8.9 Hz); IR (NaCl, neat) 1780, 1670, 1420, 1270 cm^{-1}. Anal. ($C_{24}H_{26}N_2O_6$) C, H, N.

Minor Diastereomer: ^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$ 1.85 (1 H, m), 2.02 (1 H, m), 2.99 (1 H, dd, J_{vic} = 4.2 Hz, J_{vic} = 10.2 Hz), 3.86 (3 H, s), 3.87 (3 H, s), 3.91 (1 H, $^1/_2$ABq, J = 17.0 Hz), 4.02 (1 H, $^1/_2$ABq, J = 17.0 Hz), 4.16 (1 H, m), 4.21 (1 H, m), 4.35 (1 H, $^1/_2$ABq, J = 14.9 Hz), 4.38 (1 H, $^1/_2$ABq, J = 14.64 Hz), 4.58 (1 H, d, J = 4.2 Hz), 4.68 (1 H, $^1/_2$ABq, J = 14.9 Hz), 4.95 (1 H, $^1/_2$ABq, J = 14.6 Hz), 6.84 (2 H, d, J = 6.7 Hz), 6.85 (2 H, d, J = 6.7 Hz), 7.19 (2 H, d, J = 6.7 Hz), 7.22 (2 H, d, J = 6.7 Hz); IR (NaCl, neat) 1778, 1670, 1420, 1270 cm^{-1}.

Raney Nickel Reduction of 10c. To a stirred solution of minor *syn-10c* (10 mg, 0.02 mmol, 1.0 equiv) in THF (1 mL) was added 10 mL of ethanol followed by excess Raney nickel. The system was flushed with H_2, refluxed for 2 h, filtered, concentrated and separated on PTLC silica gel (eluted with 33% hexanes in EtOAc) to afford 4.8 mg (60%) of the lactone corresponding to the major diastereomer **17**.

1,4-Dibenzyl-3-methoxy-6-(dimethylmalonyl)-2,5-piperazinedione (21, R_1 = CH_2Ph; R, R_2 = CH_3; R_3 = CO_2CH_3). To a stirred solution of **10b** (R_1 = CH_2Ph; R_2 = CH_3; R_3 = CO_2CH_3) (150 mg, 0.28 mmol, 1.0 equiv) in MeOH (35 mL) was added $Hg(OAc)_2$ (98 mg, 0.31 mmol, 1.1 equiv) at 25 °C. The mixture was stirred for 12 h, evaporated, 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, concentrated, and separated on PTLC silica gel (eluted with 25% EtOAc in hexanes) to afford 75 mg (59%) of **21** as a clear oil: ^1H NMR (270 MHz) ($CDCl_3$) δ TMS 3.39 (3 H, s), 3.57 (3 H, s), 3.73 (3 H, s), 3.97 (1 H, d, J = 3.7 Hz), 4.21 (1 H, $^1/_2$ABq, J = 14.3 Hz), 4.33 (1 H, $^1/_2$ABq, J = 15.4 Hz), 4.72 (1 H, d, J = 3.7 Hz), 4.85 (1 H, s), 5.03 (1 H, $^1/_2$ABq, J = 15.4 Hz), 5.22 (1 H, $^1/_2$ABq, J = 14.3 Hz), 7.20–7.44 (10 H, m).

3-(2′-γ-Butyrolactonyl)-2,5-piperazinedione (22, R_2, R_3 = CH_2CH_2). To a stirred, room-temperature suspension of lactone **17** (9 mg, 0.02 mmol, 1 equiv) in CH_3CN/H_2O (0.3 mL, 2:1 by v/v) was added CAN (60 mg, 0.1 mmol, 5 equiv). The reaction mixture was stirred for 45 min and directly separated on PTLC silica gel (eluted with 20% MeOH in

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

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

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

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

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

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

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

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

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

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

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

‡ NIH Research Career Development Awardee 1984–1989.

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

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